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Treatment outcomes of initial differential antiretroviral regimens among HIV patients in southwest China: comparison from an observational cohort study

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Abstract

Objective China has continued to expand antiretroviral therapy (ART) services and optimize ART guidelines in an effort to significantly reduce and prevent mortality and transmission rates among HIV patients. However, there has been no study worldwide that compared treatment outcomes of initial differential antiretroviral regimens among HIV patients in the real world setting. This study aimed to compare the effect of different ART regimens on treatment outcomes among adults.

Design Observational cohort study.

Setting Data from 2011 to 2013 in Guangxi, China.

Participants Patients aged ≥ 18 years (n = 25789) were selected.

Results A total of 25789 patients were included in this study. The average mortality and attrition rate was 2.65 and 4.99, respectively, per 100 person-years among all patients. There were differences in adjusted hazard ratio (aHR) for death between initial ART regimes: zidovudine (AZT) or tenofovir (TDF) versus stavudine (D4T) was 0.72 (95% CI: 0.65-0.79), and lopinavir-ritonavir (LPV/r) versus D4T was 1.44 (95% CI: 1.26-1.66). There were also differences for attrition: AZT or TDF versus D4T (aHR = 0.83; 95% CI: 0.76-0.90), LPV/r versus D4T (aHR = 1.45; 95% CI: 1.30-1.61), and LPV/r versus AZT or TDF (aHR = 1.75; 95% CI: 1.60-1.91). The proportion of patients with viral load ≥ 1000 copies/ml at 12 months of ART was 4.4%. High gastrointestinal reactions and poor adherence were observed among HIV patients whose initial ART included LPV/r.

Conclusions Our study found that the treatment outcomes of initial ART that included AZT or TDF were better than those of D4T and LPV/r. Initial ART regimens that included LPV/r were associated with higher gastrointestinal reactions and poorer adherence than other regimens.

Key words: HIV; ART; mortality; attrition; viral load; adherence

Strengths and limitations of this study：

Our study was conducted on a observational cohort study in Guangxi, China.

This study included 25789 patients and had the strong evidence to support our study results.

There are several limitations worth noting in our study. They were described in detail in the discussion part.

Introduction

Highly active antiretroviral therapy (HAART) has been an available treatment for people living with HIV for more than three decades. In China, ART regimens are applied according to World Health Organization (WHO) guidelines. As the WHO guidelines change, ART criteria and regimens have been appropriately adjusted. The National Free Antiretroviral Treatment Program (NFATP) was initiated in China among former plasma donors as a pilot project in Henan province in 2002, and fully performed nationally in 2003.[1,2] In 2005, the recommended first-line regimen in China was zidovudine (AZT) or stavudine (D4T) with lamivudine (3TC) and nevirapine (NVP),[2,3] as recommended by the WHO. In the beginning of 2008, the Chinese national criteria for receiving ART treatment were revised as follows: CD4 cell count < 350/mm^3, WHO-defined stage III/IV clinical conditions, or willingness to receive ART regardless of meeting the first two criteria.[4] The regimen was adjusted again and D4T was gradually replaced by AZT or tenofovir (TDF).[4] To date, all individuals infected with HIV who are eligible for treatment have been treated in all 31 provinces, autonomous regions, and municipalities in China.[5] Current first-line ART regimens include TDF or AZT with 3TC and EFV or NVP. Second-line ART regimens include lopinavir-ritonavir (LPV/r) or TDF with 3TC and EFV.[5] To achieve the UNAIDS "90-90-90" target,[6] regimens that include LPV/r have been gradually and widely implemented as initial ART treatment in China. However, despite recommendations to initiate ART among all individuals infected with HIV, there exists limited understanding about the effects of different initial regimens on the mortality and attrition rates in real-world settings in China.

Guangxi Zhuang Autonomous Region (Guangxi) is located in southwest China, and borders the drug trafficking route known as the "Golden Triangle". By the end of 2017, Guangxi was ranked fourth among all provinces in China for number of newly-reported HIV cases[7] and thus plays a critical role in the country's HIV prevention and treatment campaign. This study was conducted in Guangxi, with the objective of comparing the effects of different initial ART regimens on death, attrition, death and attrition, and viral load among HIV patients, using the database of a large ART treatment cohort.

Materials and Methods

Study design and study participants

This HIV antiretroviral treatment observational cohort study was conducted in Guangxi, an autonomous region in rural southwest China. The study participants included HIV patients who initiated free ART between 2011 and 2013 through the Chinese National Free Antiretroviral Treatment Program (NFATP). The date censored was April 30, 2016. Individuals who initiated free ART were at least 18 years old at the time of ART initiation, and eligible patients provided informed consent to participate in this study. The study protocol was approved by the institutional review board (IRB) of the Guangxi Center for Disease Control and Prevention. All research methods in this study were carried out in accordance with the approved guidelines.

Data collection

The baseline variables of all patients included demographics such as age, sex, marital status, route of HIV infection, laboratory results of CD4 cell counts before ART, WHO clinical stage before ART, initial ART regimen, current ART regimen, date of ART initiation, date of discontinuing ART, and reasons for treatment discontinuation. Follow-up status variables included: treatment continuation, loss to follow-up, survival status, transferals to another clinic, and stopped ART. The follow up visits occurred at 0.5, one, two, and three months following ART initiation, and then every three months thereafter. Loss to follow-up was

defined as not having a visit for more than 90 days after the last date seen in clinic.

Statistical analysis

In this study, treatment outcomes included death and attrition. Attrition was defined as stopped ART or loss to follow-up as reported through the database. Time zero was defined as the date of ART initiation, and data were censored at April 30, 2016. Survival time was calculated from the date of ART initiation to date of death or the last follow-up. Mortality rates, attrition rates, and death and attrition rates with their 95% confidence intervals (CI) were analyzed with incidence density rate per 100 person-years of follow-up.

We used Cox proportional hazard models to estimate crude hazard ratio (HR) and adjusted hazard ratio (aHR) to compare the effects of initial ART regimens on death, attrition, and death and attrition. We used multivariate logistic regression models to estimate the differences of viral load (VL) ≥ 1000 copies/ml, adverse events, gastrointestinal reactions, and adherence among different initial ART regimens. In the adjusted model, the following baseline covariates were adjusted to control for potential confounding factors: age, sex, marital status, route of HIV infection, WHO clinical stage before ART, initial ART regimen, and year initiated ART. Statistical significance was determined using a 2-tailed p-value ≤ 0.05. All statistical analyses were performed using SAS 9.1^{TM} for Windows (SAS Institute Inc., Cary, NC, USA).

Results

General characteristics of the study population

A total of 25862 HIV patients began to receive ART between 2011 and 2013 in Guangxi, China. Forty-six of these patients were less than 18 years old, and five of whom were more than 12 months on the first visit. Patients were excluded whose initial ART included either none or more than one of D4T, AZT, or TDF (n = 22). A final total of 25789 patients were included in this study. The baseline characteristics of the 25789 patients are provided in Table 1. The majority of patients (n = 15474; 60.0%) were ≥ 40 years old. The majority of patients (n = 17176; 66.6%) were male, and 18111 patients (70.2%) were married. The main route of HIV infection was heterosexual intercourse (88.9%), followed by injection drug use (7.5%), homosexual intercourse (1.3%), and other routes of transmission (2.3%). Before ART initiation, the number of patients with CD4 counts < 350 cells/mm^3 and ≥ 350 cells/mm^3 were 22511 (87.3%) and 2760 (10.7%), respectively. An additional 518 (2.0%) patients had unknown CD4 counts before ART initiation. Patients who were WHO-defined clinical stage III/IV before ART accounted for 41.8% of the study population. Patients with initial ART regimens of D4T, AZT or TDF and LPV/r accounted for 21.3%, 67.5% and 11.2%, respectively. The number of patients being treated with the current first-line ART regimen was 20230 (78.4%). The proportion of patients who initiated ART in 2011, 2012 and 2013 was 30.0%, 35.7% and 34.3%, respectively.

Mortality rates

Among 25789 patients who initiated ART between 2011 and 2013 in Guangxi, 2071 deaths were observed. In the first, second, third, fourth, and fifth year of ART initiation, 1167, 433, 273, 153, and 45 patients died, respectively. The mortality rates and 95% CI for these years were 4.90 (4.61-5.19), 1.99 (1.80-2.18), 1.50 (1.32-1.68), 1.43 (1.20-1.65) and 1.21 (0.86-1.56), respectively. The average mortality rate was 2.65 deaths per 100 person-years among all patients (95% CI: 2.53-2.76) (Supplementary Table 1).

Attrition rates

Among 25789 patients, 3905 attritions were observed: 2541 patients were lost to follow-up, and 1364 patients stopped ART. Of these, poor adherence was the reason for stopping ART among 805 patients, while

204 patients stopped ART because of adverse events. The number of attrition in the first, second, third, fourth, and fifth year of ART initiation was 3115, 1139, 728, 342, and 124 patients, respectively. In these years, the attrition rates and 95% CI were 13.09 (12.63-13.55), 5.24 (4.93-5.54), 4.00 (3.71-4.29), 3.19 (2.85-3.53) and 3.34 (2.75-3.92), respectively. The average attrition rate in the study period was 4.99 attritions per 100 person-years among all patients (95% CI: was 4.83-5.15) (Supplementary Table 2).

Death and attrition rates

Among 25789 patients, 5976 deaths and attritions were observed. A total of 4282, 1572, 1001, 495, and 169 patients in the first, second, third, fourth, and fifth year of ART initiation, respectively. The average death and attrition rate was 7.63 attritions per 100 person-years among all patients (95% CI: 7.44-7.83) (Supplementary Table 3).

Effects of initial ART regimen on death

The deaths per 100 person-years of initial ART regimen that included D4T, initial ART regimen that included AZT or TDF, and initial ART regimen that included LPV/r were 3.77 (95% CI: 3.49-4.06), 2.05 (95% CI: 1.93-2.17) and 4.09 (95% CI: 3.74-4.65), respectively (Table 2). The aHR for death of initial ART regimen including AZT or TDF versus those including D4T was 0.72 (95% CI: 0.65-0.79), and initial ART regimen including LPV/r versus D4T was 1.44 (95% CI: 1.26-1.66). The aHR for death of initial ART regimens that included LPV/r versus initial ART regimen including AZT or TDF was 2.01 (95% CI: 1.77-2.28).

Effects of initial ART regimen on attrition

The attritions per 100 person-years of initial ART regimen including D4T, initial ART regimen including AZT or TDF, and initial ART regimen including LPV/r were 5.04 (95% CI: 4.71-5.38), 3.19 (95% CI: 3.03-3.34) and 7.87 (95% CI: 7.25-8.50), respectively (Table 3). The aHR for attrition of initial ART regimen including AZT or TDF and initial ART regimen including LPV/r versus initial ART regimen including D4T was 0.83 (95% CI: 0.76-0.90) versus 1.45 (95% CI:1.30-1.61). The aHR for attrition of initial ART regimen that included LPV/r versus initial ART regimen including AZT or TDF was 1.75 (95% CI: 1.60-1.91).

Effects of initial ART regimen on death and attrition

The aHR for death and attrition of initial ART regimen including AZT or TDF and initial ART regimen including LPV/r versus initial ART regimen including D4T were 0.78 (95% CI: 0.73-0.83) and 1.44 (95% CI:1.32-1.56), respectively. The aHR for death and attrition of initial ART regimens that included LPV/r versus initial ART regimens that included AZT or TDF was 1.84 (95% CI: 1.71-1.98) (Supplementary Table 4).

Viral load at 12 months of ART

During 12 months of ART, 1167 patients died and 3115 patients were lost to attrition, with a remaining total of 21507 patients. The proportion of patients with VL ≥ 1000 copies/ml was 4.4% (Table 4). The number of patients whose initial ART included LPV/r, D4T, and AZT or TDF was 2220, 4393 and 14894, respectively, and the respective proportion of VL ≥ 1000 copies/ml in these groups was 4.4%, 4.4% and 4.5%. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinical stage before ART, and year initiated ART, differences in VL ≥ 1000 copies/ml were not statistically significant between initial ART including LPV/r and initial ART including D4T (p = 0.74) or between initial ART including LPV/r and initial ART including AZT or TDF (p = 0.89).

Adverse events and adherence

Information for adverse events during the first three months was available for 24600 patients (Table 5). A total of 6993 (28.4%) patients had adverse events, and the proportion of patients that had adverse events among those who initiated ART including LPV/r, D4T, and AZT or TDF were 27.9%, 27.3%, and 28.9%, respectively. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinical stage before ART, and year initiated ART, differences in adverse events were marginally statistically significant between initial ART including LPV/r and initial ART including D4T (p = 0.05) but were statistically significant between initial ART including LPV/r and initial ART including AZT or TDF (p = 0.04).

A total of 4211 (17.2%) patients had gastrointestinal reactions. Among those who initiated ART that included LPV/r, D4T, and AZT or TDF, the percentage of patients with gastrointestinal reactions were 23.1%, 15.1%, and 16.8%, respectively. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinical stage before ART, and year initiated ART, differences in gastrointestinal reactions were statistically significant between those who initiated ART including D4T, AZT or TDF compared with those who initiated ART including LPV/r (p < 0.001).

Among all patients in the first three months, 2698 of 24600 (11.0%) patients reported having missed doses in the past seven days. Among those who initiated ART including LPV/r, D4T, and AZT or TDF, 14.0%, 11.2%, and 10.4% of patients reported having missed doses in the past seven days, respectively. There were significant differences among the study groups (Table 5).

Discussion

In this three-year observational cohort study among HIV patients in Guangxi, China, the total mortality rate was 2.65 per 100 person-years, which was higher than that in developed countries and lower than rates in resource-limited settings.[8-10] The total attrition rate was 4.99 per 100 person-years. EuroSIDA, an international, multicenter observational study in Europe, Israel, and Argentina, showed that the incidence of loss to follow-up was 3.72 per 100 person-years.[11] A Kenyan cohort study reported the total loss to follow-up rate (which included death and drop-out for other reasons) as 43.2 per 100 person-years, and the drop-out rate in that study was 24.0 per 100 person-years.[10]

In our study, initial ART regimens that included AZT or TDF were significantly more superior to those that included D4T. Beginning in 2008, D4T was gradually replaced by AZT or TDF in China. A prospective cohort study in South Africa found the aHR for mortality and loss-from-care of initial ART including D4T compared with TDF was 2.7 (95% CI: 2.0-3.5) and 1.4 (95% CI: 1.3-1.5), respectively, and that TDF performed better than D4T overall.[12] A three-year randomized trial in South Africa, Europe and the United States showed that a regimen of TDF, 3TC, and EFV was highly effective and had less toxicity than a regimen that included D4T, 3TC, and EFV through 144 weeks.[13] In 2010, the WHO recommended to reduce or to abandon D4T,[14,15] and in 2013 indicated that D4T should definitely be discontinued for use in first-line regimens due to its well-recognized metabolic toxicities.[16]

Previous studies have shown that regimens that include LPV/r had better virological efficacy or immunological outcome.[17-20] Additionally, some studies comparing protease inhibitors (PIs) demonstrated that a combination regimen including LPV/r was well tolerated and superior to regimens containing nelfinavir (NFV) for the initial ART of adults infected with HIV. [21,22] However, our study showed that initial ART regimens that included LPV/r were inferior to regimens including AZT or TDF. Both gastrointestinal

reactions and self-report missed dose in the past seven days were highest among patients in our study who initiated ART with LPV/r. Gastrointestinal reactions can induce discomfort and lead to missed doses or complete discontinuation of ART. Other studies have shown similar results to our findings. For example, the EuroSIDA study found that, due to toxicity or patient choice, patients on LPV/r had a significantly higher discontinuation rate compared with patients on NVP.[23] Another study demonstrated that at week 96, the proportion of patients with virological failure in receiving a regimen of LPV/r plus two nucleoside reverse-transcriptase inhibitors (NRTIs) was higher than those receiving EFV plus two NRTIs.[24] In the FHDH-ANRS CO4 cohort study, TDF/emtricitabine (FTC) plus LPV/r were less durable than TDF/FTC with a third drug; furthermore, TDF/FTC plus LPV/r had a higher risk of non-AIDS morbidity.[25] In the ART Cohort Collaboration study (ART-CC), the odds of virological failure (HIV-1 RNA level > 200 copies/ml) at 48 weeks were higher for LPV/r compared with EFV in ART-CC.[26]

There are several limitations worth noting in our study. First, our study included only subjects who initiated ART, but subjects who were infected with HIV but not receiving ART were not included. Second, in this study, we used all-cause mortality and did not separate AIDS-defining death and non-AIDS-defining death, which may have an effect on the evaluation of treatment effects. Third, this study was conducted only in Guangxi, and thus might not be representative of other regions in China.

In summary, among the patients included in Guangxi, initial ART regimens that included AZT or TDF were found to have better treatment effects than initial ART that included D4T or LPV/r. Patients that initiated ART including LPV/r had higher rates of gastrointestinal reaction and self-reported missed dose in the past seven days. Thus, it is important to improve the current training for HIV care among treatment staff and enhance patient education on ART adherence and future research is needed to assess the treatment effects after these changes.

Supplementary materials

This study also showed the number of patients lost to death, attrition and death and attrition at the first year, second year, third year, fourth year and fifth year of ART initiation (Supplementary Table 1 - 3). The effect of different initial ART regimens on death and attrition was shown in Supplementary Table 4.

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Table 1. Characteristics of HIV patients who initiated ART between 2011 and 2013 in Guangxi, China

Variable	Number	%
Total	25789	100.0
Age (years)		
18-40	10315	40.0
≥40	15474	60.0
Sex		
Male	17176	66.6
Female	8613	33.4
Marital status		
Married	18111	70.2
Other	7678	29.8
Route of HIV infection		
Heterosexual intercourse	22930	88.9
Homosexual intercourse	322	1.3
Intravenous drug use	1936	7.5
Other	601	2.3
CD4 count before ART (cells/mm^3)		
<350	22511	87.3
≥350	2760	10.7
Missing	518	2.0
WHO clinic stage before ART		
I/II	15009	58.2
III/IV	10780	41.8
Initial ART regimen		
The initial ART including D4T	5493	21.3
The initial ART including AZT or TDF	17409	67.5
The initial ART including LPV/r	2887	11.2
Current ART regimen		
The initial ART	20230	78.4
The second-line ART	5559	21.6
Year of ART initiation		
2011	7734	30.0
2012	9203	35.7
2013	8852	34.3

Table 2. Effects of initial ART regimen on death among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Deaths	Person years	Deaths/100 person-years (95% CI)	AHR* (95%CI)	P-value	aHR* (95%CI)	P-value
Total	25789	2071	78273.01	2.65(2.53-2.76)				
Initial ART regimen								
The initial ART including D4T	5493	657	17405.58	3.77(3.49-4.06)	Reference			
The initial ART including AZT or TDF	17409	1089	53118.81	2.05(1.93-2.17)	0.72(0.65-0.79)	<0.001	Reference	
The initial ART including LPV/r	2887	325	7748.62	4.19(3.74-4.65)	1.44(1.26-1.66)	<0.001	2.01(1.77-2.28)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART, year initiated ART.

Table 3. Effects of initial ART regimen on attrition on attrition among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Attritions	Person years	Attritions/100 person-years (95% CI)	AHR* (95%CI)	P-value	aHR* (95%CI)	P-value
Total	25789	3905	78273.01	4.99(4.83-5.15)				
Initial ART regimen								
The initial ART including D4T	5493	878	17405.58	5.04(4.71-5.38)	Reference			
The initial ART including AZT or TDF	17409	1692	53118.81	3.19(3.03-3.34)	0.83(0.76-0.90)	<0.001	Reference	
The initial ART including LPV/r	2887	610	7748.62	7.87(7.25-8.50)	1.45(1.30-1.61)	<0.001	1.75(1.60-1.91)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART, year initiated ART.

Table 4. Viral load at 12 months of ART among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	N	VL(copies/ml)* ≥1000	%	OR	P	aOR*	P*
Total	21507	957	4.4				
Initial ART regimen							
The initial ART including LPV/r	2220	98	4.4	Reference		Reference	
The initial ART including D4T	4393	192	4.4	1.01(0.79-1.30)	0.94	1.04(0.81-1.35)	0.74
The initial ART including AZT or TDF	14894	667	4.5	0.99(0.79-1.22)	0.89	1.02(0.82-1.27)	0.89

*Adjusted for multivariate logistic regression: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART, year initiated ART.

Table 5. Adverse events, gastrointestinal reaction and adherence during the first 3 months of ART among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Adverse events	%	P*	Gastrointestinal reaction	%	P*	Missed dose in the past seven days	%	P*
Total	24600	6993	28.4		4221	17.2		2698	11.0	
Initial ART regimen										
The initial ART including LPV/r	2708	756	27.9	Reference	625	23.1	Reference	377	14.0	Reference
The initial ART including D4T	5143	1402	27.3	0.05	776	15.1	<0.001	576	11.2	<0.001
The initial ART including AZT or TDF	16749	4835	28.9	0.04	2821	16.8	<0.001	1745	10.4	<0.001

*Adjusted for multivariate logistic regression: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART, year initiated ART.

Supplementary table 1. Mortality rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Deaths	Person years	Deaths/100 person-years (95% CI)
Overall	25789	2071	78273.01	2.65(2.53-2.76)
Year post-ART initiation				
First year	25789	1167	23796.06	4.90(4.62-5.19)
Second year	22056	433	21751.83	1.99(1.80-2.18)
Third year	20887	273	18213.06	1.50(1.32-1.68)
Fourth year	13886	153	10709.62	1.43(1.20-1.65)
Fifth year	6512	45	3717.61	1.21(0.86-1.56)

Supplementary table 2. Attrition rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Attritions	Person years	Attritions /100 person-years (95% CI)
Overall	25789	3905	78273.01	4.99(4.83-5.15)
Year post-ART initiation				
First year	25789	3115	23796.06	13.09(12.63-13.55)
Second year	22056	1139	21751.83	5.24(4.93-5.54)
Third year	20887	728	18213.06	4.00(3.71-4.29)
Fourth year	13886	342	10709.62	3.19(2.85-3.53)
Fifth year	6512	124	3717.61	3.34(2.75-3.92)

Supplementary table 3. Death and attrition rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Deaths and attritions	Person years	Deaths and attritions /100 person-years (95% CI)
Overall	25789	5976	78273.01	7.63(7.44-7.83)
Year post-ART initiation				
First year	25789	4282	23796.06	17.99(17.46-18.53)
Second year	22056	1572	21751.83	7.23(6.87-7.58)
Third year	20887	1001	18213.06	5.50(5.16-5.84)
Fourth year	13886	495	10709.62	4.62(4.21-5.03)
Fifth year	6512	169	3717.61	4.55(3.86-5.23)

Supplementary table 4. Effects of initial ART regiment on death and attrition in HIV-infected patients who started ART between 2011 and 2013 in Guangxi, China

Variable	Number	Deaths and attritions	Person years	Deaths and attritions /100 person-years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25789	5976	78273.01	7.63(7.44-7.83)				
Initial ART regimen								
The initial ART including D4T	5493	1535	17405.58	8.82(8.38-9.26)	Reference			
The initial ART including AZT or TDF	12030	2387	38740.85	6.16(5.91-6.41)	0.78(0.73-0.83)	<0.001	Reference	
The initial ART including LPV/r	2887	935	7748.62	12.07(11.29-12.84)	1.44(1.32-1.56)	<0.001	1.84(1.71-1.98)	<0.001

* HR=hazard ratio; AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART, year initiated ART.

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Treatment outcomes of initial differential antiretroviral regimens among HIV patients in southwest China: comparison from an observational cohort study

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Abstract

Objective China has continued to expand antiretroviral therapy (ART) services and optimize ART guidelines in an effort to significantly reduce and prevent mortality and transmission rates among HIV patients. However, no study worldwide has compared treatment outcomes of initial differential antiretroviral regimens among HIV patients in a real-world setting in China. This study aimed to compare the effect of different ART regimens on treatment outcomes among adults.

Design Observational retrospective cohort study.

Setting Data from 2011 to 2013 in Guangxi, China.

Participants Patients aged ≥ 18 years (n = 25732) were selected.

Results A total of 25732 patients were included in this study. The average mortality and attrition rate were 2.64 and 4.98, respectively, per 100 person-years. Using Cox proportional hazard models, zidovudine-based (AZT-based) regimen versus stavudine-based (D4T-based) regimen had an adjusted hazard ratio (AHR) for death of 0.65 (95% CI: 0.58-0.73); tenofovir-based (TDF-based) versus D4T-based regimen was 0.81 (95% CI: 0.71-0.92), and lopinavir-ritonavir-based (LPV/r-based) versus D4T-based regimen was 1.19 (95% CI: 1.04-1.37). AZT-based versus D4T-based regimen had an AHR for drop-out of 0.89 (95% CI: 0.81-0.97); TDF-based versus D4T-based regimen (AHR = 0.88; 95% CI: 0.80-0.98), and the LPV/r-based versus D4T-based regimen (AHR = 1.42; 95% CI: 1.27-1.58). AZT-based and TDF-based regimens had a lower risk compared to D4T-based regimens, while LPV/r-based regimens had a higher risk. High gastrointestinal reactions and poor adherence were observed among HIV patients whose initial ART regimen was an LPV/r-based.

Conclusions Our study found that the treatment outcomes of initial ART regimens that AZT-based or TDF-based were better than those of D4T-based and LPV/r-based regimens. This finding could be related to the higher rates of gastrointestinal reactions and poorer adherence associated with the LPV/r-based regimens compared to other initial ART regimens.

Key words: HIV; ART; mortality; attrition; viral load; adherence

Strengths and limitations of this study:

Our study was conducted as an observational retrospective cohort study in Guangxi, China, using the data of 25732 patients.

The large sample size provides the strong evidence in support of our study results.

However, there are several limitations to our study that should be noted. The study population included only subjects who initiated ART; but subjects who were infected with HIV but not receiving ART were not included. Additionally, this study might not be representative of the whole country.

Introduction

Highly active antiretroviral therapy (HAART) has been an available treatment for people living with HIV for more than three decades. In China, ART regimens are applied according to World Health Organization (WHO) guidelines. As the WHO guidelines change, ART criteria and regimens have been appropriately adjusted. The National Free Antiretroviral Treatment Program (NFATP) was initiated in China among former plasma donors as a pilot project in Henan province in 2002, and fully performed nationally in 2003.[1,2] In 2005, the recommended first-line regimen in China was zidovudine (AZT) or stavudine (D4T) with lamivudine (3TC) and nevirapine (NVP),[2,3] as recommended by the WHO. In the beginning of 2008, the Chinese national criteria for receiving ART treatment were revised as follows: CD4 cell count < 350/mm^3, WHO-defined stage III/IV clinical conditions, or willingness to receive ART regardless of meeting the first two criteria.[4] The regimen was adjusted again and D4T was gradually replaced by AZT or tenofovir (TDF).[4] To date, all individuals infected with HIV who are eligible for treatment have been treated in all 31 provinces, autonomous regions, and municipalities in China.[5] Current first-line ART regimens include TDF or AZT with 3TC and efavirenz (EFV) or NVP. Second-line ART regimens include lopinavir-ritonavir (LPV/r) with 3TC and AZT or TDF.[5] To achieve the UNAIDS "90-90-90" target,[6] regimens that include LPV/r have been gradually and widely implemented as initial ART treatment in China. However, despite recommendations to initiate ART among all individuals infected with HIV, there exists limited understanding about the effects of different initial regimens on the mortality and attrition rates in real-world settings in China.

Guangxi Zhuang Autonomous Region (Guangxi) is located in southwest China, and borders the drug trafficking route known as the "Golden Triangle". By the end of 2017, Guangxi was ranked fourth among all provinces in China for number of newly-reported HIV cases, and patients with HIV/AIDS in Guangxi accounted for 10% of the entire HIV/AIDS population in China.[7] Thus Guangxi plays a critical role in the country's HIV prevention and treatment campaign. The objective of this study was to estimate the treatment effects of different initial ART regimens (including D4T-based regimen (D4T+3TC+EFV/NVP), AZT-based regimen (AZT+3TC+EFV/NVP), TDF-based regimen (TDF+3TC+EFV/NVP) and LPV/r-based regimen (LPV/r+3TC+D4T/AZT/TDF)) on death, drop-out, death and drop-out, and viral load among HIV patients, using the database of a large ART treatment cohort.

Materials and Methods

Patient and public involvement

The study being retrospective, patients or the public were not involved in the design or in the conduct of the study.

Study design and study participants

This retrospective observational cohort study of HIV antiretroviral treatment was conducted in Guangxi, an autonomous region in rural southwest China. The study participants included HIV patients who initiated free ART between 2011 and 2013 through the Chinese National Free Antiretroviral Treatment Program (NFATP). The date censored was April 30, 2016. Eligibility criteria of individuals included those: initiated free ART between 2011 and 2013 through the NFATP in Guangxi, those who were at least 18 years old at the time of ART initiation, those who provided informed consent to participate in this study, and those whose initial ART regimen (including D4T-based regimen, AZT-based regimen, TDF-based regimen and LPV/r-based regimen. The study protocol was approved by the institutional review board (IRB) of the Guangxi Center for Disease Control and Prevention. All research methods in this study were carried out in accordance with the approved guidelines.

Data collection

The baseline variables of all patients included age, sex, marital status, route of HIV infection, laboratory results of CD4 cell counts before ART, WHO clinical stage before ART, initial ART regimen, current ART regimen, date of ART initiation, date of discontinuing ART, and reasons for treatment discontinuation. Follow-up status variables included: treatment continuation, loss to follow-up, survival status, transferals to another clinic, and stopped ART. The follow up visits occurred at 0.5, one, two, and three months following ART initiation, and then every three months thereafter.[8] Loss to follow-up was defined as not having a visit for more than 90 days after the last date seen in clinic.

Statistical analysis

In this study, treatment outcomes included death and drop out from follow-up. Drop-out included stopped ART or loss to follow-up as reported through the database. Time zero was defined as the date of ART initiation, and data were censored at April 30, 2016. Survival time was calculated from the date of ART initiation to date of death or the last follow-up. Person-years were the unit of measure for incidence rates Mortality rates, drop-out rates, and death and drop-out rates with their 95% confidence intervals (CI) were analyzed with incidence density rate per 100 person-years of follow-up. We used Cox proportional hazard models to estimate hazard ratio (HR) to compare the effects of initial ART regimens on death, drop out, and death and drop out.

We also collected viral load (VL) at 12 months of ART, adverse events, gastrointestinal reactions, and adherence during the first three months. Self-reported adherence variables included missed doses in the past seven days during the first three months. We used multivariate logistic regression models to estimate the differences of viral load (VL) < 50 copies/ml at 12 months of ART, adverse events during the first three months, gastrointestinal reactions during the first three months, and adherence among different initial ART regimens.

In the adjusted model, the following baseline covariates were adjusted to control for potential confounding factors: age, sex, marital status, route of HIV infection, and WHO clinical stage before ART. Statistical significance was determined using a two-tailed p-value < 0.05. All statistical analyses were performed using SAS 9.1™ for Windows (SAS Institute Inc., Cary, NC, USA).

Results

General characteristics of the study population

A total of 25862 HIV/AIDS patients initiated ART between 2011 and 2013 in Guangxi, China. One hundred and thirty patients were excluded: forty-six of them were less than 18 years old, five of whom were visited more than 12 months on the first visit, and seventy-nine of them whose initial ART regimen that was not D4T-based, AZT-based, TDF-based or LPV/r-based. (Supplementary figure 1) A final total of 25732 patients were included in this study. The baseline characteristics of these 25732 patients are provided in Table 1. Patient ages were categorized into 18-29 years, 30-49 years and ≥ 50 years; these age groups accounted for 13.7%, 47.4% and 39.0%, respectively, of the study population. The majority of patients (n = 17139; 66.6%) were male, and 18074 patients (70.2%) were married. The main route of HIV infection was heterosexual intercourse (88.9%), followed by injection drug use (7.5%), homosexual intercourse (1.3%), and other routes of transmission (2.3%). The number of patients with CD4 counts before ART < 350 cells/mm^3 and ⩾ 350 cells/mm^3 were 22458 (87.3%) and 2756 (10.7%), respectively. An additional 518 (2.0%) patients had unknown CD4 counts before ART initiation. Patients who were WHO-defined clinical stage III/IV before ART accounted for 41.8% of the study population. Patients with initial ART regimens of D4T-based, AZT-

based, TDF-based and LPV/r-based accounted for 21.3%, 47.2%, 21.0 and 11.2%, respectively. The number of patients being treated with the current first-line ART regimen was 20194 (78.5%). The proportion of patients who initiated ART in 2011, 2012 and 2013 was 30.0%, 35.7% and 34.3%, respectively.

Mortality rates

Among 25732 patients who initiated ART between 2011 and 2013 in Guangxi, 2062 deaths were observed. In the first, second, third, fourth, and fifth year of ART initiation, 1164, 427, 273, 153, and 45 patients died, respectively. The mortality rates and 95% CI for these years were 4.90 (95% CI: 4.62 – 5.18), 1.97 (95% CI: 1.78 – 2.15), 1.50 (95% CI: 1.32 – 1.68), 1.43 (95% CI: 1.20 – 1.66) and 1.21 (95% CI: 0.86 – 1.57) per 100 person-years, respectively. The average mortality rate was 2.64 deaths per 100 person-years among all patients (95% CI: 2.53 – 2.75) (Supplementary Table 1).

Drop-out rates

Among 25732 patients, 3893 dropped out from follow up. Of these, 2531 patients were lost to follow-up, and 1362 patients stopped ART. The number of patients who dropped-out in the first, second, third, fourth, and fifth year of ART initiation was 3105, 1136, 727, 342, and 124 patients, respectively. In these years, the drop-out rates and 95% CI were 13.08 (95% CI: 12.62 – 13.54), 5.23 (95% CI: 4.91 – 5.52), 4.00 (3.71 – 4.29), 3.20 (95% CI: 2.86 – 3.54) and 3.34 (95% CI: 2.75 – 3.93) per 100 person-years, respectively. The average drop-out rate in the study period was 4.98 per 100 person-years among all patients (95% CI: was 4.83-5.15) (Supplementary Table 2).

Death and drop-out rates

Among 25732 patients, 5955 deaths and drop-out were observed. A total of 4269, 1563, 1000, 495, and 169 patients died or dropped out in the first, second, third, fourth, and fifth year of ART initiation, respectively. The average death and drop-out rate was 7.62 per 100 person-years among all patients (95% CI: 7.43 – 7.81) (Supplementary Table 3).

Effects of initial ART regimen on death

The deaths per 100 person-years for initial ART regimen that D4T-based, AZT-based, TDF-based, and LPV/r-based were 3.77 (95% CI: 3.48 – 4.06), 1.80 (95% CI: 1.66 – 1.93), 2.71 (95% CI: 2.44 – 2.98) and 4.18 (95% CI: 3.72 – 4.63), respectively (Table 2). After adjustment of Cox proportional hazards models, the AHR for death of patients on AZT-based regimens versusD4T-based was 0.65 (95% CI: 0.58 – 0.73), the AHR for TDF-based regimen r versus D4T-based was 0.81 (95% CI: 0.71 – 0.92), and the AHR for LPV/r-based regimen versus D4T was 1.19 (95% CI: 1.04 – 1.37). After adjustment, the AHR for death of initial ART regimen that LPV/r-based versus AZT-based was 1.83 (95% CI: 1.60 – 2.10).

Effects of initial ART regimen on drop-out

The drop-out per 100 person-years of initial ART regimen that D4T-based, AZT-based, TDF-based, and LPV/r-based were 5.03 (95% CI: 4.70 – 5.37), 4.37 (95% CI: 4.16 – 4.57), 5.04 (95% CI: 4.67 – 5.40) and 7.85 (95% CI: 7.23 – 8.48), respectively (Table 3). The AHR for drop-out of initial ART regimen that AZT-based, TDF-based, and LPV/r-based versus D4T-based was 0.89 (95% CI: 0.81 – 0.97),0.88 (95% CI: 0.80-0.98) and 1.42 (95% CI: 1.27 – 1.58). After adjustment, the AHR for drop-out of initial ART regimen that LPV/r-based versus AZT-based was 1.60 (95% CI: 1.45 – 1.76).

Effects of initial ART regimen on death and drop-out

After adjustment, the AHR for death and drop out of initial ART regimen that AZT-based, TDF-based, and LPV/r-based versus D4T-basedwas 0.79 (95% CI: 0.74 – 0.85), 0.85 (95% CI: 0.78 – 0.92) and 1.32 (95% CI:

1.22 – 1.44), respectively. After adjustment, the AHR for death and drop-out of initial ART regimen of LPV/r-based versus ART-based was 1.67 (95% CI: 1.54 – 1.81) (Supplementary Table 4).

Viral load at 12 months of ART

During 12 months of ART, 1164 patients died and 3105 patients dropped out, with a remaining total of 21463 patients. The proportion of patients with VL< 50 copies/ml was 75.0% (Table 4). The number of patients whose initial ART regimen of LPV/r-based, D4T-based, AZT-based, and TDF-based was 2220, 4393, 10293 and 4601 respectively, and the respective proportion of VL < 50 copies/ml in these groups was 73.7%, 72.5%, 75.3% and 77.6%. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, and WHO clinical stage before ART, differences in VL< 50 copies/ml were not statistically significant between LPV/r-based regimen and D4T-based regimen (p = 0.32) or between LPV/r-based regimen and AZT-based regimen (p = 0.33), but were statistically significant between LPV/r-based regimen and TDF-based regimen ($p < 0.001$).

Adverse events and adherence

Information for adverse events during the first three months was available for 24517 patients (Table 5). A total of 6966 (28.4%) patients had adverse events, and the proportion of patients that had adverse events among those who initiated ART regimen that was LPV/r-based, D4T-based, AZT-based, and TDF-based was 27.6%, 27.3%, 31.6%, and 22.7%, respectively. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, and WHO clinical stage before ART, differences in adverse events were not statistically significant between LPV/r-based regimen and D4T-based regimen (p = 0.26), but were statistically significant between LPV/r-based regimen and AZT-based regimen ($p < 0.001$) and between LPV/r-based regimen and TDF-based regimen ($p < 0.001$).

A total of 4203 (17.1%) patients had gastrointestinal reactions (Table 5). Among those who initiated ART regimen that was LPV/r-based, D4T-based, AZT-based and TDF-based, the percentage of patients with gastrointestinal reactions was 22.9%, 15.1%, 19.3%, and 11.4%, respectively. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, and WHO clinical stage before ART, differences in gastrointestinal reactions were statistically significant between those who initiated ART regimen that D4T-based, AZT-based and TDF-based compared with LPV/r-based regimen ($p < 0.005$).

Among all patients in the first three months, 2673 of 24517 (10.9%) patients reported having missed doses (Table 5). Among those who initiated an LPV/r-based, D4T-based, AZT-based and TDF-based regimen, 13.4%, 11.2%, 11.4%, and 8.1% of patients respectively, reported adherence. There were significant differences among the study groups.

Discussion

In this three-year observational cohort study among HIV patients in Guangxi, China, the total mortality rate was 2.62 per 100 person-years and the total drop-out rate was 4.98 per 100 person-years. The mortality rate was higher than that in developed countries and lower than previously reported rates in resource-limited settings.[9-11] The total drop-out rate was higher than an international, multicenter observational study in Europe, Israel, and Argentina,[12] but was lower than that of a Kenyan cohort study.[11]

In our study, initial ART regimens that were AZT-based or TDF-based were significantly superior to those that were D4T-based. Beginning in 2008, D4T was gradually replaced by AZT or TDF in China. A prospective cohort study in South Africa found that initial ART including TDF performed better than D4T overall.[13] A

three-year randomized trial in South Africa, Europe and the United States showed that a regimen of TDF, 3TC, and EFV was highly effective and had less toxicity than a regimen that included D4T, 3TC, and EFV over 144 weeks.[14] In 2010, the WHO recommended heath providers to reduce or abandon D4T,[15,16] and in 2013 indicated that D4T should definitely be discontinued for use in first-line regimens due to its well-recognized metabolic toxicities.[17]

Previous studies have shown that LPV/r-based regimen had better virological efficacy or immunological outcome.[18-21] Additionally, some studies comparing protease inhibitors (PIs) demonstrated that a combination regimen including LPV/r was well tolerated and superior to regimens containing nelfinavir (NFV) for the initial ART of adults infected with HIV. [22,23] However, our study showed that initial ART regimens that were LPV/r-based were inferior to AZT-based and TDF-based regimens. Gastrointestinal reactions and self-reported missed dose in the past seven days were both highest among patients in our study who initiated ART with LPV/r. Gastrointestinal reactions can induce discomfort and lead to missed doses or complete discontinuation of ART. Other studies have shown similar results to our findings. For example, the EuroSIDA study found that, due to toxicity or patient choice, patients on LPV/r had a significantly higher discontinuation rate compared with patients on NVP.[24] Another study demonstrated that at week 96, the proportion of patients with virological failure who were in receiving a regimen of LPV/r plus two nucleoside reverse-transcriptase inhibitors (NRTIs) was higher than those receiving EFV plus two NRTIs.[25] In the FHDH-ANRS CO4 cohort study, TDF/emtricitabine (FTC) plus LPV/r was less durable than TDF/FTC with a third drug; furthermore, TDF/FTC plus LPV/r had a higher risk of non-AIDS morbidity.[26] In the ART Cohort Collaboration study (ART-CC), the odds of virological failure (HIV-1 RNA level > 200 copies/ml) at 48 weeks were higher for LPV/r compared with EFV in ART-CC.[27]

There are several limitations in our study. First, our study included only subjects who initiated ART, but subjects who were infected with HIV but not receiving ART were not included. Second, in this study, we used all-cause mortality and did not separate AIDS-defining death and non-AIDS-defining death, which may have an effect on the evaluation of treatment effects. Third, this study was conducted only in Guangxi, and thus might not be representative of other regions in China. Fourth, only patients who received China's free ART regimen were included in the study, and integrase inhibitors are not free in China. Thus, we could not estimate the treatment effects of integrase inhibitors.

In summary, among the patients included in Guangxi, initial ART regimens that included AZT or TDF were found to have better treatment effects than initial ART that included D4T or LPV/r. Patients that initiated ART including LPV/r had higher rates of gastrointestinal reaction and self-reported missed dose in the past seven days. Thus, it is important to improve the current training for HIV care among treatment staff and enhance patient education regarding ART adherence and future research is needed to assess the treatment effects after these improvements.

Supplementary materials

This study also showed the number of patients lost to death, drop-out and death and drop-out at the first year, second year, third year, fourth year and fifth year of ART initiation (Supplementary Table 1 - 3). The effect of different initial ART regimens on death and drop-out is shown in Supplementary Table 4.

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Table 1. Characteristics of HIV patients who initiated ART between 2011 and 2013 in Guangxi, China

Variable	Number	%
Total	25732	100.0
Age (years)		
18-29	3513	13.7
30-49	12186	47.4
⩾50	10033	39.0
Sex		
Male	17139	66.6
Female	8593	33.4
Marital status		
Married	18074	70.2
Other	7658	29.8
Route of HIV infection		
Heterosexual intercourse	22882	88.9
Homosexual intercourse	321	1.3
Intravenous drug use	1931	7.5
Other	598	2.3
CD4 count before ART (cells/mm^3)		
<350	22458	87.3
≥350	2756	10.7
Missing	518	2.0
WHO clinic stage before ART		
I/II	14985	58.2
III/IV	10747	41.8
Initial ART regimen		
D4T-based regimen	5483	21.3
AZT-based regimen	12018	46.7
TDF-based regimen	5352	20.8
LPV/r-based regimen	2879	11.2
Current ART regimen		
The first-line ART	20194	78.5
The second-line ART	5538	21.5
Year of ART initiation		
2011	7722	30.0
2012	9178	35.7
2013	8832	34.3

Table 2. Effects of initial ART regimen on death among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Deaths	Person years	Deaths/100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	2062	78137.47	2.64(2.53-2.75)				
Initial ART regimen								
D4T-based regimen	5483	656	17384.21	3.77(3.48-4.06)	Reference			
AZT-based regimen	12018	695	38705.61	1.80(1.66-1.93)	0.65(0.58-0.73)	<0.001	Reference	
TDF-based regimen	5352	388	14315.82	2.71(2.44-2.98)	0.81(0.71-0.92)	0.001	1.24(1.10-1.41)	<0.001
LPV/r-based regimen	2879	323	7731.82	4.18(3.72-4.63)	1.19(1.04-1.37)	0.01	1.83(1.60-2.10)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Table 3. Effects of initial ART regimen on drop-out among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Attritions	Person years	drop-out/100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	3893	78137.47	4.98(4.83-5.14)				
Initial ART regimen								
D4T-based regimen	5483	875	17384.21	5.03(4.70-5.37)	Reference			
AZT-based regimen	12018	1690	38705.61	4.37(4.16-4.57)	0.89(0.81-0.97)	0.005	Reference	
TDF-based regimen	5352	721	14315.82	5.04(4.67-5.40)	0.88(0.80-0.98)	0.02	1.00(0.91-1.09)	0.93
LPV/r-based regimen	2879	607	7731.82	7.85(7.23-8.48)	1.42(1.27-1.58)	<0.001	1.60(1.45-1.76)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Table 4. Viral load at 12 months of ART among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

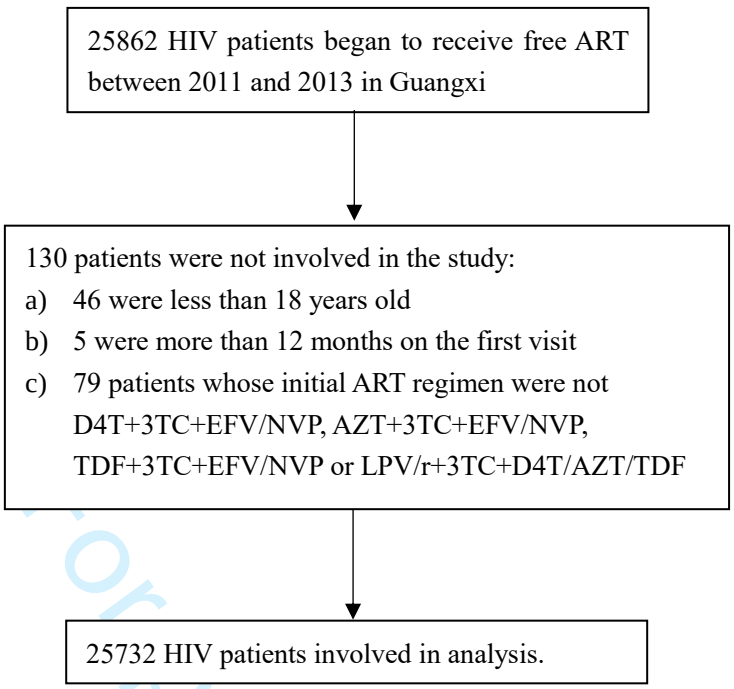
Variable	N	VL (copies/ml)* <50	%	OR	P	AOR*	P*
Total	21463	16139	75.0				
Initial ART regimen							
LPV/r-based regimen	2220	1633	73.7	Reference		Reference	
D4T-based regimen	4393	3180	72.5	0.94(0.84-1.06)	0.29	0.94(0.83-1.06)	0.32
AZT-based regimen	10293	7741	75.3	1.09(0.98-1.21)	0.13	1.05(0.94-1.18)	0.33
TDF-based regimen	4601	3553	77.6	1.23(1.10-1.39)	<0.001	1.25(1.11-1.41)	<0.001

*Adjusted for multivariate logistic regression: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Table 5. Adverse event, gastrointestinal reaction and adherence during the first 3 months of ART among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Adverse event	%	P*	Gastrointestinal reaction	%	P*	Adherence	%	P*
Total	24517	6966	28.4		4203	17.1		2673	10.9	
Initial ART regimen										
LPV/r-based regimen	2672	737	27.6	Reference	613	22.9	Reference	359	13.4	Reference
D4T-based regimen	5133	1400	27.3	0.26	774	15.1	<0.001	574	11.2	0.01
AZT-based regimen	11587	3666	31.6	<0.001	2231	19.3	0.004	1324	11.4	0.16
TDF-based regimen	5125	1163	22.7	<0.001	585	11.4	<0.001	416	8.1	<0.001

*Adjusted for multivariate logistic regression: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.



Supplementary figure 1. Flow chart of exclusion in this observational cohort study.

Supplementary table 1. Mortality rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Deaths	Person years	Deaths/100 person years (95% CI)
Overall	25732	2062	78137.47	2.64(2.53-2.75)
Year post-ART initiation				
First year	25732	1164	23746.03	4.90(4.62-5.18)
Second year	22012	427	21711.84	1.97(1.78-2.15)
Third year	20852	273	18183.13	1.50(1.32-1.68)
Fourth year	13867	153	10697.61	1.43(1.20-1.66)
Fifth year	6505	45	3714.04	1.21(0.86-1.57)

Supplementary table 2. Attrition rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Attritions	Person years	Attritions /100 person year (95% CI)
Overall	25732	3893	78137.47	4.98(4.83-5.15)
Year post-ART initiation				
First year	25732	3105	23746.03	13.08(12.62-13.54)
Second year	22012	1136	21711.84	5.23(4.93-5.54)
Third year	20852	727	18183.13	4.00(3.71-4.29)
Fourth year	13867	342	10697.61	3.20(2.86-3.54)
Fifth year	6505	124	3714.04	3.34(2.75-3.93)

Supplementary table 3. Death + attrition rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Deaths + attritions	Person years	Deaths + attritions /100 person years (95% CI)
Overall	25732	5955	78137.47	7.62(7.43-7.81)
Year post-ART initiation				
First year	25732	4269	23746.03	17.98(17.44-18.52)
Second year	22012	1563	21711.84	7.20(6.84-7.56)
Third year	20852	1000	18183.13	5.50(5.16-5.84)
Fourth year	13867	495	10697.61	4.63(4.22-5.03)
Fifth year	6505	169	3714.04	4.55(3.86-5.24)

Supplementary table 4. Effects of initial ART regiment on death + drop-out in HIV-infected patients who started ART between 2011 and 2013 in Guangxi, China

Variable	Number	Deaths+ drop-out	Person years	Deaths + drop-out /100 person years (95% CI)	HR* (95%CI)	P-value	HR* (95%CI)	P-value
Total	25732	5955	78137.47	7.62(7.43-7.81)				
Initial ART regimen								
D4T-based regimen	5483	1531	17384.21	8.81(8.37-9.25)	Reference			
AZT-based regimen	12018	2385	38705.61	6.16(5.91-6.41)	0.79(0.74-0.85)	<0.001	Reference	
TDF-based regimen	5352	1109	14315.82	7.75(7.29-8.20)	0.85(0.78-0.92)	<0.001	1.07(1.00-1.15)	0.06
LPV/r-based regimen	2879	930	7731.82	12.03(11.26-12.80)	1.32(1.22-1.44)	<0.001	1.67(1.54-1.81)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P.3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P.4
Objectives	3	State specific objectives, including any prespecified hypotheses	P.4
Methods			
Study design	4	Present key elements of study design early in the paper	P.4-P.5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P.4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P.4-P.5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	No
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P.5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P.5
Bias	9	Describe any efforts to address potential sources of bias	P.5
Study size	10	Explain how the study size was arrived at	P.5-P.6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P.5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P.5
		(*b*) Describe any methods used to examine subgroups and interactions	P.5
		(*c*) Explain how missing data were addressed	P.5
		(*d*) If applicable, explain how loss to follow-up was addressed	P.5
		(*e*) Describe any sensitivity analyses	No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P.5-P.6
		(b) Give reasons for non-participation at each stage	Table 1
		(c) Consider use of a flow diagram	Supplementary figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1

		(c) Summarise follow-up time (eg, average and total amount)	Supplementary table 1-table 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-table 5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2-table 5
		(*b*) Report category boundaries when continuous variables were categorized	Table 2-table 5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	No
Discussion			
Key results	18	Summarise key results with reference to study objectives	P.9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P.8-P.9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P.8-P.9
Generalisability	21	Discuss the generalisability (external validity) of the study results	P.8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P.2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Treatment outcomes of initial differential antiretroviral regimens among HIV patients in southwest China: comparison from an observational cohort study

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Secondary Subject Heading:	HIV/AIDS
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Treatment outcomes of initial differential antiretroviral regimens among HIV patients in southwest China: comparison from an observational cohort study

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Ethics approval: The institutional review board (IRB) of the NCAIDS, China CDC approved this study.

Data sharing statement: No additional data are available.

Abstract

Objectives China has continued to expand antiretroviral therapy (ART) services and optimize ART guidelines in an effort to significantly reduce and prevent mortality and transmission rates among HIV patients. However, no study to date has compared treatment outcomes of initial differential antiretroviral regimens among HIV patients in a real-world setting in China. This study aimed to compare the effects of different ART regimens on treatment outcomes among adults.

Design Observational retrospective cohort study.

Setting Data from 2011 to 2013 in Guangxi, China.

Participants Patients aged ≥ 18 years (n = 25732) were selected.

Results A total of 25732 patients were included in this study. The average mortality and attrition rate were 2.64 and 4.98, respectively, per 100 person-years. Using Cox proportional hazard models, zidovudine-based (AZT-based) regimen versus stavudine-based (D4T-based) regimen had an adjusted hazard ratio (AHR) for death of 0.65 (95% CI: 0.58–0.73); the AHR of tenofovir-based (TDF-based) versus D4T-based regimens was 0.81 (95% CI: 0.71–0.92), and of lopinavir-ritonavir-based (LPV/r-based) versus D4T-based regimens, 1.19 (95% CI: 1.04–1.37). AZT-based versus D4T-based regimens had an AHR for drop-out of 0.89 (95% CI: 0.81–0.97); this ratio for TDF-based versus D4T-based regimens was 0.88 (95% CI: 0.80–0.98), and for LPV/r-based versus D4T-based regimens, 1.42 (95% CI: 1.27–1.58). AZT-based and TDF-based regimens had a lower risk compared to D4T-based regimens, while LPV/r-based regimens had a higher risk. High gastrointestinal reactions and poor adherence were observed among HIV patients whose initial ART regimen was LPV/r-based.

Conclusions Our study found that the treatment outcomes of initial ART regimens that were AZT-based or TDF-based were significantly better than D4T-based or LPV/r-based regimens. This finding could be related to the higher rates of gastrointestinal reactions and poorer adherence associated with the LPV/r-based regimens compared to other initial ART regimens.

Key words: HIV; ART; mortality; attrition; viral load; adherence

Strengths and limitations of this study:

- Our study was conducted as an observational retrospective cohort study in Guangxi, China, using the data of 25732 patients.
- The large sample size provides the strong evidence in support of our study results.
- The study population included only subjects who initiated ART; but subjects who were infected with HIV but not receiving ART were not included.
- This study might not be representative of all patients living with HIV in China.

Introduction

Highly active antiretroviral therapy (HAART) has been an available treatment for people living with HIV for more than three decades. In China, ART regimens are applied according to World Health Organization (WHO) guidelines. As the WHO guidelines change, ART criteria and regimens have been appropriately adjusted. The National Free Antiretroviral Treatment Program (NFATP) was initiated in China among former plasma donors as a pilot project in Henan province in 2002, and fully performed nationally in 2003.[1,2] In 2005, the recommended first-line regimen in China was zidovudine (AZT) or stavudine (D4T) with lamivudine (3TC) and nevirapine (NVP),[2,3] as recommended by the WHO. In the beginning of 2008, the Chinese national criteria for receiving ART treatment were revised as follows: CD4 cell count < 350/mm^3, WHO-defined stage III/IV clinical conditions, or willingness to receive ART regardless of meeting the first two criteria.[4] The regimen was adjusted again and D4T was gradually replaced by AZT or tenofovir (TDF).[4] To date, all individuals infected with HIV who are eligible for treatment have been treated in all 31 provinces, autonomous regions, and municipalities in China.[5] Current first-line ART regimens include TDF or AZT with 3TC and efavirenz (EFV) or NVP. Second-line ART regimens include lopinavir-ritonavir (LPV/r) with 3TC and AZT or TDF.[5] To achieve the UNAIDS "90-90-90" target,[6] regimens that include LPV/r have been gradually and widely implemented as initial ART treatment in China. However, despite recommendations to initiate ART among all individuals infected with HIV, there exists limited understanding about the effects of different initial regimens on the mortality and attrition rates in real-world settings in China.

Guangxi Zhuang Autonomous Region (Guangxi) is located in southwest China, and borders the drug trafficking route known as the "Golden Triangle". By the end of 2017, Guangxi was ranked fourth among all provinces in China for number of newly-reported HIV cases, and patients with HIV/AIDS in Guangxi accounted for 10% of the entire HIV/AIDS population in China.[7] Thus Guangxi plays a critical role in the country's HIV prevention and treatment campaign.

The objective of this study was to estimate the treatment effects of different initial ART regimens (including D4T-based regimen (D4T+3TC+EFV/NVP), AZT-based regimen (AZT+3TC+EFV/NVP), TDF-based regimen (TDF+3TC+EFV/NVP) and LPV/r-based regimen (LPV/r+3TC+D4T/AZT/TDF)) on death, drop-out, death and drop-out, and viral load among HIV patients, using the database of a large ART treatment cohort.

Materials and Methods

Patient and public involvement

The study being retrospective, patients or the public were not involved in the design or in the conduct of the study.

Study design and study participants

This retrospective observational cohort study of HIV antiretroviral treatment was conducted in Guangxi, an autonomous region in rural southwest China. The study participants included HIV patients who initiated free ART between 2011 and 2013 through the Chinese National Free Antiretroviral Treatment Program (NFATP). The date censored was April 30, 2016. Eligibility criteria of individuals included those who initiated free ART between 2011 and 2013 through the NFATP in Guangxi, those who were at least 18 years old at the time of ART initiation, those who provided informed consent to participate in this study, and those whose initial ART regimen was D4T-based, AZT-based, TDF-based , or LPV/r-based. The study protocol was approved by the institutional review board (IRB) of the Guangxi Center for Disease Control and Prevention. All research

methods in this study were carried out in accordance with the approved guidelines.

Data collection

The baseline variables of all patients included age, sex, marital status, route of HIV infection, laboratory results of CD4 cell counts before ART, WHO clinical stage before ART, initial ART regimen, current ART regimen, date of ART initiation, date of discontinuing ART, and reasons for treatment discontinuation. Follow-up status variables included: treatment continuation, loss to follow-up, survival status, transferals to another clinic, and stopped ART. The follow up visits occurred at 0.5, one, two, and three months following ART initiation, and then every three months thereafter.[8] Loss to follow-up was defined as not having a visit for more than 90 days after the last date seen in clinic.

Statistical analysis

In this study, treatment outcomes included death and drop out from follow-up. Drop-out included stopped ART or loss to follow-up as reported through the database. Time zero was defined as the date of ART initiation, and data were censored at April 30, 2016. Survival time was calculated from the date of ART initiation to date of death or the last follow-up. Person-years were the unit of measure for incidence rates Mortality rates, drop-out rates, and death and drop-out rates with their 95% confidence intervals (CI) were analyzed with incidence density rate per 100 person-years of follow-up. We used Cox proportional hazard models to estimate hazard ratio (HR) to compare the effects of initial ART regimens on death, drop out, and death and drop out.

We also collected data regarding viral load (VL) at 12 months of ART, adverse events, gastrointestinal reactions, and adherence during the first three months. Self-reported adherence variables included missed doses in the past seven days during the first three months. We used multivariate logistic regression models to estimate the differences of VL < 50 copies/ml at 12 months of ART, adverse events during the first three months, gastrointestinal reactions during the first three months, and adherence among different initial ART regimens.

In the adjusted model, the following baseline covariates were adjusted to control for potential confounding factors: age, sex, marital status, route of HIV infection, and WHO clinical stage before ART. Statistical significance was determined using a two-tailed p-value < 0.05. All statistical analyses were performed using SAS 9.1™ for Windows (SAS Institute Inc., Cary, NC, USA).

Results

General characteristics of the study population

A total of 25862 HIV/AIDS patients initiated ART between 2011 and 2013 in Guangxi, China. One hundred and thirty patients were excluded: forty-six of them were less than 18 years old, five were visited more than 12 months after the first visit, and seventy-nine had an initial ART regimen that was not D4T-based, AZT-based, TDF-based, or LPV/r-based (Supplementary Figure 1). A final total of 25732 patients were included in this study. The baseline characteristics of these 25732 patients are provided in Table 1. Patient ages were categorized into 18-29 years, 30-49 years and ≥ 50 years; these age groups accounted for 13.7%, 47.4%, and 39.0%, respectively, of the study population. The majority of patients (n = 17139; 66.6%) were male, and 18074 patients (70.2%) were married. The main route of HIV infection was heterosexual intercourse (88.9%), followed by injection drug use (7.5%), homosexual intercourse (1.3%), and other routes of transmission (2.3%). The number of patients with CD4 counts before ART < 350 cells/mm^3 and ⩾ 350 cells/mm^3 were 22458 (87.3%) and 2756 (10.7%), respectively. An additional 518 (2.0%) patients had unknown CD4 counts before ART initiation. Patients who were WHO-defined clinical stage III/IV before ART accounted for 41.8%

of the study population. Patients with initial ART regimens of D4T-based, AZT-based, TDF-based, and LPV/r-based accounted for 21.3%, 47.2%, 21.0, and 11.2%, respectively. The number of patients being treated with the current first-line ART regimen was 20194 (78.5%). The proportion of patients who initiated ART in 2011, 2012, and 2013 was 30.0%, 35.7%, and 34.3%, respectively.

Mortality rates

Among 25732 patients who initiated ART between 2011 and 2013 in Guangxi, 2062 deaths were observed. In the first, second, third, fourth, and fifth year of ART initiation, 1164, 427, 273, 153, and 45 patients died, respectively. The mortality rates and 95% CI for these years were 4.90 (95% CI: 4.62 – 5.18), 1.97 (95% CI: 1.78 – 2.15), 1.50 (95% CI: 1.32 – 1.68), 1.43 (95% CI: 1.20 – 1.66), and 1.21 (95% CI: 0.86 – 1.57) per 100 person-years, respectively. The average mortality rate was 2.64 deaths per 100 person-years among all patients (95% CI: 2.53 – 2.75) (Supplementary Table 1).

Drop-out rates

Among 25732 patients, 3893 dropped out from follow up. Of these, 2531 patients were lost to follow-up, and 1362 patients stopped ART. The number of patients who dropped out in the first, second, third, fourth, and fifth year of ART initiation was 3105, 1136, 727, 342, and 124, respectively. In these years, the drop-out rates and 95% CI were 13.08 (95% CI: 12.62 – 13.54), 5.23 (95% CI: 4.91 – 5.52), 4.00 (3.71 – 4.29), 3.20 (95% CI: 2.86 – 3.54), and 3.34 (95% CI: 2.75 – 3.93) per 100 person-years, respectively. The average drop-out rate in the study period was 4.98 per 100 person-years among all patients (95% CI: was 4.83 – 5.15) (Supplementary Table 2).

Death and drop-out rates

Among 25732 patients, 5955 deaths and drop-outs were observed. A total of 4269, 1563, 1000, 495, and 169 patients died or dropped out in the first, second, third, fourth, and fifth year of ART initiation, respectively. The average death and drop-out rate was 7.62 per 100 person-years among all patients (95% CI: 7.43 – 7.81) (Supplementary Table 3).

Effects of initial ART regimen on death

The deaths per 100 person-years for D4T-based, AZT-based, TDF-based, and LPV/r-based initial ART regimens was 3.77 (95% CI: 3.48 – 4.06), 1.80 (95% CI: 1.66 – 1.93), 2.71 (95% CI: 2.44 – 2.98) and 4.18 (95% CI: 3.72 – 4.63), respectively (Table 2). After adjustment with Cox proportional hazards models, the AHR for death of patients on AZT-based versus D4T-based regimens was 0.65 (95% CI: 0.58 – 0.73), the AHR for TDF-based versus D4T-based regimens was 0.81 (95% CI: 0.71 – 0.92), and the AHR for LPV/r-based versus D4T-based regimens was 1.19 (95% CI: 1.04 – 1.37). After adjustment, the AHR for death of LPV/r-based versus AZT-based initial ART regimen was 1.83 (95% CI: 1.60 – 2.10).

Effects of initial ART regimen on drop-out

The drop-out per 100 person-years for D4T-based, AZT-based, TDF-based, and LPV/r-based initial ART regimen was 5.03 (95% CI: 4.70 – 5.37), 4.37 (95% CI: 4.16 – 4.57), 5.04 (95% CI: 4.67 – 5.40), and 7.85 (95% CI: 7.23 – 8.48), respectively (Table 3). The AHR for drop-out of initial ART regimen that was AZT-based, TDF-based, and LPV/r-based versus D4T-based was 0.89 (95% CI: 0.81 – 0.97),0.88 (95% CI: 0.80 – 0.98), and 1.42 (95% CI: 1.27 – 1.58), respectively. After adjustment, the AHR for drop-out of initial ART regimen that was LPV/r-based versus AZT-based was 1.60 (95% CI: 1.45 – 1.76).

Effects of initial ART regimen on death and drop-out

After adjustment, the AHR for death and drop out of AZT-based, TDF-based, and LPV/r-based versus D4T-

based initial ART regimen was 0.79 (95% CI: 0.74 – 0.85), 0.85 (95% CI: 0.78 – 0.92), and 1.32 (95% CI: 1.22 – 1.44), respectively. After adjustment, the AHR for death and drop-out of LPV/r-based versus ART-based initial ART regimen was 1.67 (95% CI: 1.54 – 1.81) (Supplementary Table 4).

Viral load at 12 months of ART

During 12 months of ART, 1164 patients died and 3105 patients dropped out, with a remaining total of 21463 patients. The proportion of patients with VL< 50 copies/ml was 75.0% (Table 4). The number of patients whose initial ART regimen was LPV/r-based, D4T-based, AZT-based, and TDF-based was 2220, 4393, 10293, and 4601, respectively, and the respective proportion of VL < 50 copies/ml in these groups was 73.7%, 72.5%, 75.3%, and 77.6%. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, and WHO clinical stage before ART, differences in VL < 50 copies/ml were not statistically significant between LPV/r-based and D4T-based regimens ($p = 0.32$) or between LPV/r-based and AZT-based regimens ($p = 0.33$), but were statistically significant between LPV/r-based and TDF-based regimens ($p < 0.001$).

Adverse events and adherence

Information for adverse events during the first three months was available for 24517 patients (Table 5). A total of 6966 (28.4%) patients had adverse events, and the proportion of patients that had adverse events among those whose initial ART regimen was LPV/r-based, D4T-based, AZT-based, and TDF-based was 27.6%, 27.3%, 31.6%, and 22.7%, respectively. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, and WHO clinical stage before ART, differences in adverse events were not statistically significant between LPV/r-based and D4T-based regimens ($p = 0.26$), but were statistically significant between LPV/r-based and AZT-based regimens ($p < 0.001$) and between LPV/r-based and TDF-based regimens ($p < 0.001$).

A total of 4203 (17.1%) patients had gastrointestinal reactions (Table 5). Among those who initiated an ART regimen that was LPV/r-based, D4T-based, AZT-based, or TDF-based, the percentage of patients with gastrointestinal reactions was 22.9%, 15.1%, 19.3%, and 11.4%, respectively. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART, and WHO clinical stage before ART, differences in gastrointestinal reactions were statistically significant between those who initiated an ART regimen that was D4T-based, AZT-based and TDF-based compared with those whose initial ART regimen was LPV/r-based ($p < 0.005$).

Among all patients in the first three months, 2673 of 24517 (10.9%) patients reported having missed doses (Table 5). Among those who initiated an LPV/r-based, D4T-based, AZT-based, or TDF-based regimen, 13.4%, 11.2%, 11.4%, and 8.1% of patients respectively, reported adherence. There were significant differences between the study groups.

Discussion

In this three-year observational cohort study among HIV patients in Guangxi, China, the total mortality rate was 2.62 per 100 person-years and the total drop-out rate was 4.98 per 100 person-years. The mortality rate was higher than that in developed countries and lower than previously reported rates in resource-limited settings.[9-11] The total drop-out rate was higher than an international, multicenter observational study in Europe, Israel, and Argentina,[12] but was lower than that of a Kenyan cohort study.[11]

In our study, initial ART regimens that were AZT-based or TDF-based were significantly superior to those

that were D4T-based. Beginning in 2008, D4T was gradually replaced by AZT or TDF in China. A prospective cohort study in South Africa found that initial ART including TDF performed better than D4T overall.[13] A three-year randomized trial in South Africa, Europe, and the United States showed that a regimen of TDF, 3TC, and EFV was highly effective and had less toxicity than a regimen that included D4T, 3TC, and EFV over 144 weeks.[14] In 2010, the WHO recommended heatlh providers to reduce or abandon D4T,[15,16] and in 2013 indicated that D4T should definitely be discontinued for use in first-line regimens due to its well-recognized metabolic toxicities.[17]

Previous studies have shown that LPV/r-based regimens had better virological efficacy or immunological outcome.[18-21] Additionally, some studies comparing protease inhibitors (PIs) demonstrated that a combination regimen including LPV/r was well-tolerated and superior to regimens containing nelfinavir (NFV) for the initial ART of adults infected with HIV. [22,23] However, our study showed that initial ART regimens that were LPV/r-based were inferior to AZT-based and TDF-based regimens. Gastrointestinal reactions and self-reported missed dose in the past seven days were both highest among patients in our study who initiated ART with LPV/r. Gastrointestinal reactions can induce discomfort and lead to missed doses or complete discontinuation of ART. Other studies have shown similar results to our findings. For example, the EuroSIDA study found that, due to toxicity or patient choice, patients on LPV/r had a significantly higher discontinuation rate compared with patients on NVP.[24] Another study demonstrated that at week 96, the proportion of patients with virological failure who were in receiving a regimen of LPV/r plus two nucleoside reverse-transcriptase inhibitors (NRTIs) was higher than those receiving EFV plus two NRTIs.[25] In the FHDH-ANRS CO4 cohort study, TDF/emtricitabine (FTC) plus LPV/r was less durable than TDF/FTC with a third drug; furthermore, TDF/FTC plus LPV/r had a higher risk of non-AIDS morbidity.[26] In the ART Cohort Collaboration study (ART-CC), the odds of virological failure (HIV-1 RNA level > 200 copies/ml) at 48 weeks were higher for LPV/r compared with EFV in ART-CC.[27]

There are several limitations of our study. First, our study included only subjects who initiated ART, but subjects who were infected with HIV but not receiving ART were not included. Second, in this study, we used all-cause mortality and did not separate AIDS-defining death and non-AIDS-defining death, which may have an effect on the evaluation of treatment effects. Third, this study was conducted only in Guangxi, and thus might not be representative of other regions in China. Fourth, only patients who received China's free ART regimen were included in the study, and integrase inhibitors are not free in China. Thus, we could not estimate the treatment effects of integrase inhibitors.

In summary, among the patients included in Guangxi, initial ART regimens that included AZT or TDF were found to have better treatment effects than initial ART that included D4T or LPV/r. Patients that initiated an ART regiment that included LPV/r had higher rates of gastrointestinal reaction and self-reported missed doses in the past seven days. Thus, it is important to improve the current training for HIV care among treatment staff and enhance patient education regarding ART adherence. Future research is needed to assess the treatment effects after such improvements have been implemented.

Supplementary materials

This study also showed the number of patients lost to death, drop-out and death and drop-out at the first year, second year, third year, fourth year and fifth year of ART initiation (Supplementary Table 1 - 3). The effect of different initial ART regimens on death and drop-out is shown in Supplementary Table 4. Additionally, the effect of initial ART which included NNRTI-based regimen (D4T-based regimen, AZT-based regimen, and TDF-based regimen) and PI-based regimen (LPV/r+3TC+D4T/AZT/TDF) is shown in Supplementary Table 5 - 7.

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Table 1. Characteristics of HIV patients who initiated ART between 2011 and 2013 in Guangxi, China

Variable	Number	%
Total	25732	100.0
Age (years)		
18-29	3513	13.7
30-49	12186	47.4
⩾50	10033	39.0
Sex		
Male	17139	66.6
Female	8593	33.4
Marital status		
Married	18074	70.2
Other	7658	29.8
Route of HIV infection		
Heterosexual intercourse	22882	88.9
Homosexual intercourse	321	1.3
Intravenous drug use	1931	7.5
Other	598	2.3
CD4 count before ART (cells/mm^3)		
<350	22458	87.3
≥350	2756	10.7
Missing	518	2.0
WHO clinic stage before ART		
I/II	14985	58.2
III/IV	10747	41.8
Initial ART regimen		
D4T-based regimen	5483	21.3
AZT-based regimen	12018	46.7
TDF-based regimen	5352	20.8
LPV/r-based regimen	2879	11.2
Current ART regimen		
The first-line ART	20194	78.5
The second-line ART	5538	21.5
Year of ART initiation		
2011	7722	30.0
2012	9178	35.7
2013	8832	34.3

Table 2. Effects of initial ART regimen on death among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Deaths	Person years	Deaths/100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	2062	78137.47	2.64(2.53-2.75)				
Initial ART regimen								
D4T-based regimen	5483	656	17384.21	3.77(3.48-4.06)	Reference			
AZT-based regimen	12018	695	38705.61	1.80(1.66-1.93)	0.65(0.58-0.73)	<0.001	Reference	
TDF-based regimen	5352	388	14315.82	2.71(2.44-2.98)	0.81(0.71-0.92)	0.001	1.24(1.10-1.41)	<0.001
LPV/r-based regimen	2879	323	7731.82	4.18(3.72-4.63)	1.19(1.04-1.37)	0.01	1.83(1.60-2.10)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Table 3. Effects of initial ART regimen on drop-out among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Drop-out	Person years	drop-out/100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	3893	78137.47	4.98(4.83-5.14)				
Initial ART regimen								
D4T-based regimen	5483	875	17384.21	5.03(4.70-5.37)	Reference			
AZT-based regimen	12018	1690	38705.61	4.37(4.16-4.57)	0.89(0.81-0.97)	0.005	Reference	
TDF-based regimen	5352	721	14315.82	5.04(4.67-5.40)	0.88(0.80-0.98)	0.02	1.00(0.91-1.09)	0.93
LPV/r-based regimen	2879	607	7731.82	7.85(7.23-8.48)	1.42(1.27-1.58)	<0.001	1.60(1.45-1.76)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Table 4. Viral load at 12 months of ART among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

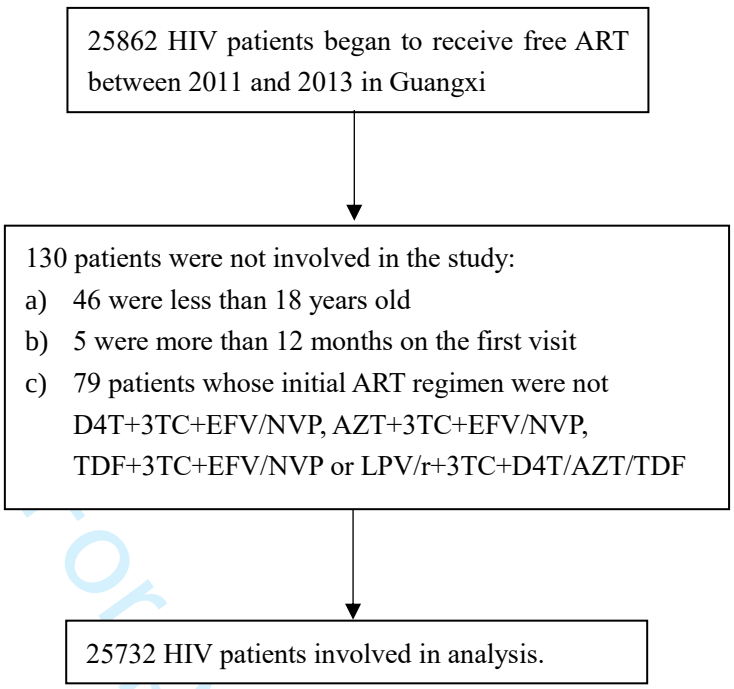
Variable	Number	VL (copies/ml)* <50	%	OR	P	AOR*	P*
Total	21463	16139	75.0				
Initial ART regimen							
LPV/r-based regimen	2220	1633	73.7	Reference		Reference	
D4T-based regimen	4393	3180	72.5	0.94(0.84-1.06)	0.29	0.94(0.83-1.06)	0.32
AZT-based regimen	10293	7741	75.3	1.09(0.98-1.21)	0.13	1.05(0.93-1.18)	0.33
TDF-based regimen	4601	3553	77.6	1.23(1.10-1.39)	<0.001	1.25(1.11-1.41)	<0.001

*Adjusted for multivariate logistic regression: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Table 5. Adverse event, gastrointestinal reaction and adherence during the first 3 months of ART among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by initial ART regimen

Variable	Number	Adverse event	%	P*	Gastrointestinal reaction	%	P*	Adherence	%	P*
Total	24517	6966	28.4		4203	17.1		2673	10.9	
Initial ART regimen										
LPV/r-based regimen	2672	737	27.6	Reference	613	22.9	Reference	359	13.4	Reference
D4T-based regimen	5133	1400	27.3	0.26	774	15.1	<0.001	574	11.2	0.01
AZT-based regimen	11587	3666	31.6	<0.001	2231	19.3	0.004	1324	11.4	0.16
TDF-based regimen	5125	1163	22.7	<0.001	585	11.4	<0.001	416	8.1	<0.001

*Adjusted for multivariate logistic regression: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.



Supplementary figure 1. Flow chart of exclusion in this observational cohort study.

Supplementary table 1. Mortality rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Deaths	Person years	Deaths/100 person years (95% CI)
Overall	25732	2062	78137.47	2.64(2.53-2.75)
Year post-ART initiation				
First year	25732	1164	23746.03	4.90(4.62-5.18)
Second year	22012	427	21711.84	1.97(1.78-2.15)
Third year	20852	273	18183.13	1.50(1.32-1.68)
Fourth year	13867	153	10697.61	1.43(1.20-1.66)
Fifth year	6505	45	3714.04	1.21(0.86-1.57)

Supplementary table 2. Attrition rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Attritions	Person years	Attritions /100 person year (95% CI)
Overall	25732	3893	78137.47	4.98(4.83-5.15)
Year post-ART initiation				
First year	25732	3105	23746.03	13.08(12.62-13.54)
Second year	22012	1136	21711.84	5.23(4.93-5.54)
Third year	20852	727	18183.13	4.00(3.71-4.29)
Fourth year	13867	342	10697.61	3.20(2.86-3.54)
Fifth year	6505	124	3714.04	3.34(2.75-3.93)

Supplementary table 3. Death + drop-out rates among HIV patients who initiated ART between 2011 and 2013 in Guangxi, China, by year post-ART initiation

Variable	Number of HIV patients	Deaths + drop-out	Person years	Deaths + drop-out /100 person years (95% CI)
Overall	25732	5955	78137.47	7.62(7.43-7.81)
Year post-ART initiation				
First year	25732	4269	23746.03	17.98(17.44-18.52)
Second year	22012	1563	21711.84	7.20(6.84-7.56)
Third year	20852	1000	18183.13	5.50(5.16-5.84)
Fourth year	13867	495	10697.61	4.63(4.22-5.03)
Fifth year	6505	169	3714.04	4.55(3.86-5.24)

Supplementary table 4. Effects of initial ART regimen on death + drop-out in HIV-infected patients who started ART between 2011 and 2013 in Guangxi, China

Variable	Number	Deaths+ drop-out	Person years	Deaths + drop-out /100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	5955	78137.47	7.62(7.43-7.81)				
Initial ART regimen								
D4T-based regimen	5483	1531	17384.21	8.81(8.37-9.25)	Reference			
AZT-based regimen	12018	2385	38705.61	6.16(5.91-6.41)	0.79(0.74-0.85)	<0.001	Reference	
TDF-based regimen	5352	1109	14315.82	7.75(7.29-8.20)	0.85(0.78-0.92)	<0.001	1.07(1.00-1.15)	0.06
LPV/r-based regimen	2879	930	7731.82	12.03(11.26-12.80)	1.32(1.22-1.44)	<0.001	1.67(1.54-1.81)	<0.001

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Supplementary table 5. Effects of initial ART regimen on death in HIV-infected patients who started ART between 2011 and 2013 in Guangxi, China

Variable	Number	Deaths	Person years	Deaths /100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	2062	78137.47	2.64(2.53-2.75)				
Initial ART regimen								
NNRTI-based regimen	22853	1739	70405.65	2.47(2.35-2.59)	Reference			
PI-based regimen	2879	323	7731.82	4.18(3.72-4.63)	1.51(1.33-1.71)	<0.001		
NNRTI-based regimen								
D4T-based regimen	5483	656	17384.21	3.77(3.48-4.06)	Reference			
AZT-based regimen	12018	695	38705.61	1.80(1.66-1.93)	0.64(0.57-0.71)	<0.001	Reference	
TDF-based regimen	5352	388	14315.82	2.71(2.44-2.98)	0.79(0.70-0.90)	<0.001	1.24(1.09-1.41)	<0.001
PI-based regimen								
LPV/r+3TC+D4T	280	45	717.04	6.28(4.44-8.11)	Reference			
LPV/r+3TC+AZT	863	39	2471.79	1.58(1.08-2.07)	0.62(0.40-0.97)	0.03	Reference	
LPV/r+3TC+TDF	1736	239	4542.99	5.26(4.59-5.93)	0.96(0.70-1.32)	0.81	1.54(1.09-2.48)	0.01

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Supplementary table 6. Effects of initial ART regimen on drop-out in HIV-infected patients who started ART between 2011 and 2013 in Guangxi, China

Variable	Number	Drop-out	Person years	Drop-out /100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	3893	78137.47	4.98(4.83-5.14)				
Initial ART regimen								
NNRTI-based regimen	22853	3286	70405.65	4.67(4.51-4.83)	Reference			
PI-based regimen	2879	607	7731.82	7.85(7.23-8.48)	1.55(1.42-1.70)	<0.001		
NNRTI-based regimen								
D4T-based regimen	5483	875	17384.21	5.03(4.70-5.37)	Reference			
AZT-based regimen	12018	1690	38705.61	4.37(4.16-4.57)	0.88(0.80-0.95)	<0.001	Reference	

TDF-based regimen	5352	721	14315.82	5.04(4.67-5.40)	0.88(0.79-0.97)	0.001	1.00(1.05-1.24)	0.002
PI-based regimen								
LPV/r+3TC+D4T	280	71	717.04	9.90(7.60-12.21)	Reference			
LPV/r+3TC+AZT	863	163	2471.79	6.59(5.58-7.61)	1.00(0.74-1.33)	0.97	Reference	
LPV/r+3TC+TDF	1736	373	4542.99	8.21(7.38-9.04)	0.85(0.66-1.09)	0.20	1.00(0.92-1.09)	0.99

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

Supplementary table 7. Effects of initial ART regimen on death and drop-out in HIV-infected patients who started ART between 2011 and 2013 in Guangxi, China

Variable	Number	Deaths + drop-out	Person years	Deaths + drop-out /100 person years (95% CI)	AHR* (95%CI)	P-value	AHR* (95%CI)	P-value
Total	25732	5955	78137.47	7.62(7.43-7.81)				
Initial ART regimen								
NNRTI-based regimen	22853	5025	70405.65	7.14(6.94-7.33)	Reference			
PI-based regimen	2879	930	7731.82	12.03(11.26-12.80)	1.54(1.44-1.66)	0.001		
NNRTI-based regimen								
D4T-based regimen	5483	1531	17384.21	8.81(8.37-9.25)	Reference			
AZT-based regimen	12018	2385	38705.61	6.16(5.91-6.41)	0.78(0.73-0.83)	0.001	Reference	
TDF-based regimen	5352	1109	14315.82	7.75(7.29-8.20)	0.84(0.77-0.91)	0.001	1.07(1.00-1.15)	0.06
PI-based regimen								
LPV/r+3TC+D4T	280	116	717.04	16.18(13.23-19.12)	Reference			
LPV/r+3TC+AZT	863	202	2471.79	8.17(7.05-9.30)	0.89(0.70-1.13)	0.32	Reference	
LPV/r+3TC+TDF	1736	612	4542.99	13.47(12.40-14.54)	0.89(0.73-1.09)	0.25	1.00(0.85-1.19)	0.97

* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 count before ART, WHO clinic stage before ART.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P.3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P.4
Objectives	3	State specific objectives, including any prespecified hypotheses	P.4
Methods			
Study design	4	Present key elements of study design early in the paper	P.4-P.5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P.4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P.4-P.5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	No
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P.5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P.5
Bias	9	Describe any efforts to address potential sources of bias	P.5
Study size	10	Explain how the study size was arrived at	P.5-P.6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P.5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P.5
		(*b*) Describe any methods used to examine subgroups and interactions	P.5
		(*c*) Explain how missing data were addressed	P.5
		(*d*) If applicable, explain how loss to follow-up was addressed	P.5
		(*e*) Describe any sensitivity analyses	No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P.5-P.6
		(b) Give reasons for non-participation at each stage	Table 1
		(c) Consider use of a flow diagram	Supplementary figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1

		(c) Summarise follow-up time (eg, average and total amount)	Supplementary table 1-table 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-table 5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2-table 5
		(*b*) Report category boundaries when continuous variables were categorized	Table 2-table 5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	No
Discussion			
Key results	18	Summarise key results with reference to study objectives	P.9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P.8-P.9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P.8-P.9
Generalisability	21	Discuss the generalisability (external validity) of the study results	P.8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P.2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.