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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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Keywords:	HIV, ART, mortality, attrition, viral load, adherence

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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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Authors' contributions: RK, LL, HC, YR, WY were responsible for study design and planning. RK, LL, HC, QZ, JZ, ZS, GL, ZT, YS, YR, WY contributed to data collection and analysis. RK, LL, HX, YS, YR, WY contributed to interpretation of data. RK, YS, YR, WY contributed to writing the manuscript. All authors read and approved the final version of the manuscript.

#### 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  $\geq 18$  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  $\geq$  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.<sup>1,2</sup> In 2005, the recommended first-line regimen in China was zidovudine (AZT) or stavudine (D4T) with lamivudine (3TC) and nevirapine (NVP),<sup>2,3</sup> 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<sup>3</sup>, WHO-defined stage III/IV clinical conditions, or willingness to receive ART regardless of meeting the first two criteria.<sup>4</sup> The regimen was adjusted again and D4T was gradually replaced by AZT or tenofovir (TDF).<sup>4</sup> 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.<sup>5</sup> 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.<sup>5</sup> To achieve the UNAIDS "90-90-90" target,<sup>6</sup> 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<sup>7</sup> 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

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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)  $\geq$  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  $\leq$  0.05. All statistical analyses were performed using SAS 9.1<sup>TM</sup> 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  $\ge 40$  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<sup>3</sup> and  $\ge 350$  cells/mm<sup>3</sup> 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 versus initial ART regimen including AZT or TDF versus initial ART regimen including LPV/r versus initial ART regimen including AZT or TDF 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  $\geq$  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  $\geq$  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  $\geq$  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 or TDF (p = 0.89).

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# 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.<sup>8-10</sup> 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.<sup>11</sup> 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.<sup>10</sup>

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.<sup>12</sup> 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.<sup>13</sup> In 2010, the WHO recommended to reduce or to abandon D4T,<sup>14,15</sup> and in 2013 indicated that D4T should definitely be discontinued for use in first-line regimens due to its well-recognized metabolic toxicities.<sup>16</sup>

Previous studies have shown that regimens that include LPV/r had better virological efficacy or immunological outcome.<sup>17-20</sup> 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.<sup>21,22</sup> However, our study showed that initial ART regimens that included LPV/r were inferior to regimens including AZT or TDF. Both gastrointestinal

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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.<sup>23</sup> 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.<sup>24</sup> 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.<sup>25</sup> 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.<sup>26</sup>

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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Cable 1. Characteristics of HIV patients who initi           Variable	ated ART between 2011 and Number	2013 in Guangx
Total	25789	100.0
	23789	100.0
Age (years)	10215	40.0
18-40	10315	40.0
<u>≥40</u>	15474	60.0
Sex	1717(	
Male	17176	66.6
Female	8613	33.4
Marital status	10111	70.2
Married	18111	70.2
Other	7678	29.8
Route of HIV infection	22020	
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 <sup>3</sup> )		
<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	Deaths/100	AHR <sup>*</sup> (95%CI)	P-value	aHR <sup>*</sup> (95%CI)	P-value
variable	Nulliber	Deatils	years	person-years (95% CI)	AHK (95%CI)	r-value	afik (93%CI)	1 -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 <sup>*</sup> (95%CI)	P-value	aHR <sup>*</sup> (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.

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Table 4. Viral load at 12 months of ART among I	HIV patients	s who initiated ART	between 2	2011 and 2013 in Guar	igxi, Chin	ha, by initial ART regin	nen
		<b>X7T</b> ( 1)*					

Variable	Ν	$VL(copies/ml)^* \ge 1000$	%	OR	Р	$aOR^*$	$P^*$
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	%	Р*	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							<b>b</b> /			
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.

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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		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)

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Page 1	5 of 15			ВМ	njopen-				
1 2 3	Supplementary table	3. Death and attrition	rates among HIV patie	nts who initiated A	RT between 2011 and 2013.	2018-025666 in Guangxi, Chi <b>9</b> a,	by year p	ost-ART initiation	
4 5 6	Variable	Number of HIV patients	Deaths and attritions	Person years	Deaths and attritions /10 person-years (95% CI)	0 on 30			
7	Overall	25789	5976	78273.01	7.63(7.44-7.83)	March	arch		
8 9 10	Year post-ART initiation					2019. [			
11 12	First year	25789	4282	23796.06	17.99(17.46-18.53)	Downloaded			
12	Second year	22056	1572	21751.83	7.23(6.87-7.58)	nloac			
14	Third year	20887	1001	18213.06	5.50(5.16-5.84)	ded t			
15 16	Fourth year	13886	495	10709.62	4.62(4.21-5.03)	from			
17	Fifth year	6512	169	3717.61	4.55(3.86-5.23)	http			
18 19 20 г	Supplementary table	4. Effects of initial Al	RT regiment on death a	nd attrition in HIV	-infected patients who starte	ed ART between	11 and 20	13 in Guangxi, Chir	na
21	Variable		Number Deaths an	d Person 🧹	Deaths and attritions /100	AHR <sup>*</sup> (95%CI)	P-value	AHR <sup>*</sup> (95%CI)	P-va

Variable	Number	Deaths and attritions	Person vears	Deaths and attritions /100 person-years (95% CI)	AHR <sup>*</sup> (95%CI)	P-value	AHR <sup>*</sup> (95%CI)	P-value
Total	25789	5976	78273.01	7.63(7.44-7.83)	.com			
Initial ART regimen					v on			
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

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 12.07(11.29-12.84)
 1.44(1.32-1.56)
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 1.84(1.71-1.98)
 <0.001</th>

 \* HR=hazard ratio; AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HTV 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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Secondary Subject Heading:	HIV/AIDS
Keywords:	HIV, ART, mortality, attrition, viral load, adherence

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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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Contributors: RKa, LLu, HCh, YRu, WYa were responsible for study design and planning. RKa, 10 25 LLu, HCh, QZh, JZu, ZSh, GLa, ZTa, YSh, YRu, WYa contributed to data collection and analysis. RKa, LLi, HXi, YSh, YRu, WYa contributed to interpretation of data. RKa, YSh, YRu, WYa contributed to writing the manuscript. All authors read and approved the final version of the manuscript. 

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# Competing interests: None declared.

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

Data sharing statement: No additional data are available. 

### 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  $\geq$  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 D4Tbased 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 68 TDF-based were better than those of D4T-based and LPV/r-based regimens. This finding could be 69 related to the higher rates of gastrointestinal reactions and poorer adherence associated with the LPV/r-70 based regimens compared to other initial ART regimens.

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

### 74 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.

- <sup>0</sup> 77 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.
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# 81 Introduction

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Highly active antiretroviral therapy (HAART) has been an available treatment for people living with HIV for ₫4 more than three decades. In China, ART regimens are applied according to World Health Organization (WHO) ۶ §5 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 **8**6 87 as a pilot project in Henan province in 2002, and fully performed nationally in 2003.<sup>1,2</sup> In 2005, the 9 88 recommended first-line regimen in China was zidovudine (AZT) or stavudine (D4T) with lamivudine (3TC) and nevirapine (NVP),<sup>2,3</sup> as recommended by the WHO. In the beginning of 2008, the Chinese national criteria 89 **9**0 for receiving ART treatment were revised as follows: CD4 cell count < 350/mm<sup>3</sup>, WHO-defined stage III/IV 13 14 clinical conditions, or willingness to receive ART regardless of meeting the first two criteria.<sup>4</sup> The regimen was adjusted again and D4T was gradually replaced by AZT or tenofovir (TDF).<sup>4</sup> To date, all individuals 93 infected with HIV who are eligible for treatment have been treated in all 31 provinces, autonomous regions, 96 94 18 95 and municipalities in China.<sup>5</sup> 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.<sup>5</sup> To achieve the UNAIDS "90-90-90" target,<sup>6</sup> regimens that include LPV/r have been gradually and widely 26 97 22 23 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. 99 100

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.<sup>7</sup> 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

118 150 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 139 ART between 2011 and 2013 through the Chinese National Free Antiretroviral Treatment Program (NFATP). 120 121 54 122 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 136 127 regimen (including D4T-based regimen, AZT-based regimen, TDF-based regimen and LPV/r-based regimen.  $1\frac{58}{59}$ 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 126 guidelines. 127

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# 129 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.<sup>8</sup> 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<sup>TM</sup> for Windows (SAS Institute Inc., Cary, NC, USA).

# Results

# General characteristics of the study population

162 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 **8**4 more than 12 months on the first visit, and seventy-nine of them whose initial ART regimen that was not D4T-165 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  $\geq$  50 years; these age groups accounted for 13.7%, 1<u>6</u>8 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 57 172 transmission (2.3%). The number of patients with CD4 counts before ART < 350 cells/mm<sup>3</sup> and  $\geq$  350 cells/mm<sup>3</sup> 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-

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based, TDF-based and LPV/r-based accounted for 21.3%, 47.2%, 21.0 and 11.2%, respectively. The number 175 of patients being treated with the current first-line ART regimen was 20194 (78.5%). The proportion of 176 137 patients who initiated ART in 2011, 2012 and 2013 was 30.0%, 35.7% and 34.3%, respectively.

#### 179 Mortality rates

Among 25732 patients who initiated ART between 2011 and 2013 in Guangxi, 2062 deaths were observed. 180 181 In the first, second, third, fourth, and fifth year of ART initiation, 1164, 427, 273, 153, and 45 patients died, 182 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 100 183 184 person-years, respectively. The average mortality rate was 2.64 deaths per 100 person-years among all patients 185 (95% CI: 2.53 – 2.75) (Supplementary Table 1).

#### **Drop-out** rates 1**8**Ø

188 18 189 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-1**20** 191 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), 1<u>9</u>2 1<u>9</u>2 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) 193 1**9**4 (Supplementary Table 2). 195

# 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/rbased 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 2**62** 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).

#### 2**1**7 Effects of initial ART regimen on drop-out

212 212 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 230 7.85 (95% CI: 7.23 – 8.48), respectively (Table 3). The AHR for drop-out of initial ART regimen that AZT-2⊉4 2<u>15</u> 2<u>15</u> 53 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 236 253 LPV/r-based versus AZT-based was 1.60 (95% CI: 1.45 – 1.76).

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#### 57 219 58 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 230 229 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).

# 5 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.<sup>9-11</sup> The total drop-out rate was higher than an international, multicenter observational study in Europe, Israel, and Argentina,<sup>12</sup> but was lower than that of a Kenyan cohort study.<sup>11</sup>

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.<sup>13</sup> 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.<sup>14</sup> In 2010, the WHO recommended heath providers to reduce or abandon D4T,<sup>15,16</sup> and in 2013 indicated that D4T should definitely be discontinued for use in first-line regimens due to its wellrecognized metabolic toxicities.<sup>17</sup>

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295 Previous studies have shown that LPV/r-based regimen had better virological efficacy or immunological 276 outcome.<sup>18-21</sup> 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 277 initial ART of adults infected with HIV.<sup>22,23</sup> However, our study showed that initial ART regimens that were 278 273 273 LPV/r-based were inferior to AZT-based and TDF-based regimens. Gastrointestinal reactions and selfreported missed dose in the past seven days were both highest among patients in our study who initiated ART 289 with LPV/r. Gastrointestinal reactions can induce discomfort and lead to missed doses or complete 2**8**6 282 18 283 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.<sup>24</sup> Another study demonstrated that at week 96, the proportion of patients 280 283 with virological failure who were in receiving a regimen of LPV/r plus two nucleoside reverse-transcriptase 285 285 inhibitors (NRTIs) was higher than those receiving EFV plus two NRTIs.<sup>25</sup> In the FHDH-ANRS CO4 cohort study, TDF/emtricitabine (FTC) plus LPV/r was less durable than TDF/FTC with a third drug; furthermore, 2**8**4 TDF/FTC plus LPV/r had a higher risk of non-AIDS morbidity.<sup>26</sup> In the ART Cohort Collaboration study 288 289 (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.<sup>27</sup> 298 299

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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Variable	Number	%
Total	25732	100.
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 <sup>3</sup> )		
<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

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Variable	Number	Deaths	Person	Deaths/100 person	AHR* (95%CI)	P-value	AHR*😇5%CI)	P-value
v allable	Number	Deatils	years	years (95% CI)	ARK (93%CI)	P-value		P-value
Total	25732	2062	78137.47	2.64(2.53-2.75)			arch	
Initial ART regimen							201	
D4T-based regimen	5483	656	17384.21	3.77(3.48-4.06)	Reference		9. D	
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 🛱 0-1.41)	< 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(120-2.10)	< 0.001

\* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 gount 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

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			Dargan	drop-out/100			bmj	
Variable	Number	Attritions	Person	person years	AHR* (95%CI)	P-value	AHR <sup>*</sup> 5%CI)	P-value
			years	(95% CI)			n/ or	
Total	25732	3893	78137.47	4.98(4.83-5.14)			n No	
Initial ART regimen						Uh	vem	
D4T-based regimen	5483	875	17384.21	5.03(4.70-5.37)	Reference		lber	
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(0.81-1.09)	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 grount before ART, WHO clinic stage before ART. 34 402

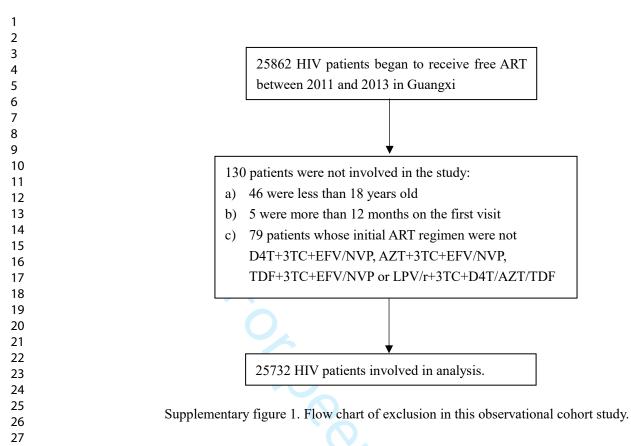
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Table 4. Viral load at 12 mo	nths of ART amo	ong HIV patie	ents who		J Open between 2011 and	2013 in	Guangxi, Chir	njopen-2018-025666 on na3by initia	l ART regi	men	
Variable	N	VL (copie			OR	Р			P*		
Total	21463	16	139	75.0				rch			
Initial ART regimen								2019			
LPV/r-based regimen	2220	16	533	73.7	Reference		Refe	erepice			
D4T-based regimen	4393	31	80	72.5	0.94(0.84-1.06)	0.2	9 0.94(0.	.8월1.06)	0.32		
AZT-based regimen	10293	77	741	75.3	1.09(0.98-1.21)	0.1	3 1.05(0.	.9\$ 1.18)	0.33		
TDF-based regimen	4601	35	553	77.6	1.23(1.10-1.39)	< 0.0	01 1.25(1.	.10-1.41)	< 0.001		
T 11. C 4 1	ogistic regression	-					T	nttp://bmjo		2011	10010
Table 5. Adverse event, gast Guangxi, China, by initial A Variable	trointestinal react	-		ring the first 3	months of ART am Gastrointestinal reaction	ong HIV %	<sup>7</sup> patients who P*	en.b	RT betwee	n 2011 ar	
Guangxi, China, by initial A	trointestinal react RT regimen	tion and adher	rence dur		Gastrointestinal			Adh			nd 2013 P
Guangxi, China, by initial A Variable	Trointestinal react RT regimen Number	tion and adher Adverse event	rence dur		Gastrointestinal reaction	%		Adh	erence	%	
Guangxi, China, by initial A Variable Total Initial ART regimen LPV/r-based regimen	Trointestinal react RT regimen Number	tion and adher Adverse event	rence dur % 28.4 27.6	P*	Gastrointestinal reaction 4203 613	% 17.1 22.9	P* Reference	Adh	erence 673 59	% 10.9 13.4	P
Guangxi, China, by initial A Variable Total Initial ART regimen LPV/r-based regimen D4T-based regimen	trointestinal react RT regimen Number 24517 2672 5133	tion and adher Adverse event 6966	rence dur % 28.4 27.6 27.3	P* Reference 0.26	Gastrointestinal reaction 4203 613 774	% 17.1 22.9 15.1	P* Reference <0.001	Adh On 20 Movember 20 Movemb	erence 673 59 74	%           10.9           13.4           11.2	P Refer
Guangxi, China, by initial A Variable Total Initial ART regimen LPV/r-based regimen D4T-based regimen AZT-based regimen	Trointestinal react RT regimen Number 24517 2672 5133 11587	tion and adher Adverse event 6966 737 1400 3666	rence dur % 28.4 27.6 27.3 31.6	P* Reference 0.26 <0.001	Gastrointestinal reaction 4203 613 774 2231	%       17.1       22.9       15.1       19.3	P* Reference <0.001 0.004	ni.com/ Adh ni.com/ on 20 November 22 5	erence 673 59 74 324	%           10.9           13.4           11.2           11.4	P Refer 0.0
Table 5. Adverse event, gast Guangxi, China, by initial AVariableTotalInitial ART regimenLPV/r-based regimenD4T-based regimenAZT-based regimenTDF-based regimen	rointestinal react RT regimen Number 24517 2672 5133 11587 5125	tion and adher Adverse event 6966 737 1400 3666 1163	rence dur % 28.4 27.6 27.3 31.6 22.7	P* Reference 0.26 <0.001 <0.001	Gastrointestinal reaction 4203 613 774 2231 585	%       17.1       22.9       15.1       19.3       11.4	P* Reference <0.001 0.004 <0.001	n.bm com Adh n 20 Novem 3 22 22 12 22 4 IQCelinic sta	erence 673 59 74 324 16	%           10.9           13.4           11.2           11.4           8.1	Refe           0.
Guangxi, China, by initial A Variable Total Initial ART regimen LPV/r-based regimen D4T-based regimen AZT-based regimen TDF-based regimen	rointestinal react RT regimen Number 24517 2672 5133 11587 5125	tion and adher Adverse event 6966 737 1400 3666 1163	rence dur % 28.4 27.6 27.3 31.6 22.7	P* Reference 0.26 <0.001 <0.001	Gastrointestinal reaction 4203 613 774 2231 585	%       17.1       22.9       15.1       19.3       11.4	P* Reference <0.001 0.004 <0.001	n.bm com/ on 20 Novem 3 Pr 22, 2024 b	erence 673 59 74 324 16	%           10.9           13.4           11.2           11.4           8.1	



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	Deaths	Person years	Deaths/100 person
	patients			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)

The neutrary table 3. Death + attrition rates among HIV patients who initiated ART between 2011 and 2013 in C Number of HIV patients Deaths + attritions Person years Deaths + attritions /100 person years (95% CI)
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ll 25732 5955 78137.47 7.62(7.43-7.81)
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ion la
st year 25732 4269 23746.03 17.98(17.44-18.52)
ond year         22012         1563         21711.84         7.20(6.84-7.56)
rd year 20852 1000 18183.13 5.50(5.16-5.84)
rth year 13867 495 10697.61 4.63(4.22-5.03)
h year 6505 169 3714.04 4.55(3.86-5.24)
ion25732426923746.0317.98(17.44-18.52)ond year22012156321711.847.20(6.84-7.56)rd year20852100018183.135.50(5.16-5.84)urth year1386749510697.614.63(4.22-5.03)

China					<u> </u>			
Variable	Number	Deaths+	Person	Deaths + drop-out /100	HR* \$5%CI)	P-value	HR* (95%CI)	P-value
Variable	Nullidei	drop-out	years	person years (95% CI)		r-value	IIK (9576CI)	r-value
Total	25732	5955	78137.47	7.62(7.43-7.81)	No I			
Initial ART regimen				Uh	vem			
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(\$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(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.

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	Item No	Recommendation	Reported on page #
Title and abstract	1	( <i>a</i> ) Indicate the study's design with a commonly used term in the	P.3
		title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of	P.3
		what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the	P.4
		investigation being reported	
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	P.4
		periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of	P.4-P.5
1		selection of participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of	No
		exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential	P.5
vanabies	,	confounders, and effect modifiers. Give diagnostic criteria, if	1.0
		applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of	P.5
measurement	U	methods of assessment (measurement). Describe comparability of	1.0
measurement		assessment methods if there is more than one group	
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	11	Explain how due study size was dirived at Explain how quantitative variables were handled in the analyses. If	P.5
variables		applicable, describe which groupings were chosen and why	1.5
Statistical methods	12	( <i>a</i> ) Describe all statistical methods, including those used to control	P.5
Statistical methods	12	for confounding	1.5
		(b) Describe any methods used to examine subgroups and	P.5
		interactions	1.5
		(c) Explain how missing data were addressed	P.5
			P.5
		(d) If applicable, explain how loss to follow-up was addressed	
D		$(\underline{e})$ Describe any sensitivity analyses	No
Results	1.2.4		D 5 D 6
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	P.5-P.6
		numbers potentially eligible, examined for eligibility, confirmed	
		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Table 1
		(c) Consider use of a flow diagram	Supplementar
			figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	Table 1
		clinical, social) and information on exposures and potential	
		confounders	
		(b) Indicate number of participants with missing data for each	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-	Table 2-table 5
		adjusted estimates and their precision (eg, 95% confidence	
		interval). Make clear which confounders were adjusted for and why	
		they were included	
		(b) Report category boundaries when continuous variables were	Table 2-table 5
		categorized	
		(c) If relevant, consider translating estimates of relative risk into	No
		absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done-eg analyses of subgroups and	No
		interactions, and sensitivity analyses	
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	P.8-P.9
		potential bias or imprecision. Discuss both direction and magnitude	
		of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering	P.8-P.9
		objectives, limitations, multiplicity of analyses, results from similar	
		studies, and other relevant evidence	
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	P.2
		present study and, if applicable, for the original study on which the	
		present article is based	

\*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 <a href="http://www.strobe-statement.org">http://www.strobe-statement.org</a>.

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

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<b>Primary Subject Heading</b> :	Infectious diseases
Secondary Subject Heading:	HIV/AIDS
Keywords:	HIV, ART, mortality, attrition, viral load, adherence

$     \begin{array}{r}       1 \\       2 \\       3 \\       4 \\       5 \\       6 \\       7 \\       8 \\       9 \\       10 \\       11 \\       12 \\       13 \\       14 \\       15 \\       16 \\       17 \\       18 \\       19 \\       20 \\       21 \\       22 \\       23 \\       24 \\       25 \\       26 \\       27 \\       28 \\       29 \\       30 \\       31 \\       32 \\       \end{array} $	<section-header></section-header>
38         39         40         41         42         43         44         45         46         47         48         49         50         51         52         53         54         55         56         57         58         59         60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

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Contributors: RKa, LLu, HCh, YRu, WYa were responsible for study design and planning. RKa, 10 25 LLu, HCh, QZh, JZu, ZSh, GLa, ZTa, YSh, YRu, WYa contributed to data collection and analysis. RKa, LLi, HXi, YSh, YRu, WYa contributed to interpretation of data. RKa, YSh, YRu, WYa contributed to writing the manuscript. All authors read and approved the final version of the manuscript. 

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# Competing interests: None declared.

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  $\geq 18$  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 AZTbased 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.

# 81 Introduction

### 1 82

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.<sup>1,2</sup> In 2005, the recommended first-line regimen in China was zidovudine (AZT) or stavudine (D4T) with lamivudine (3TC) and nevirapine (NVP),<sup>2,3</sup> 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<sup>3</sup>, WHO-defined stage III/IV clinical conditions, or willingness to receive ART regardless of meeting the first two criteria.<sup>4</sup> The regimen was adjusted again and D4T was gradually replaced by AZT or tenofovir (TDF).<sup>4</sup> 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.<sup>5</sup> 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.<sup>5</sup> To achieve the UNAIDS "90-90-90" target,<sup>6</sup> 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.<sup>7</sup> 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

8 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.<sup>8</sup> 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<sup>TM</sup> 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, AZTbased, 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  $\geq$  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<sup>3</sup> and  $\geq$  350 cells/mm<sup>3</sup> 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 175

LPV/r-based accounted for 21.3%, 47.2%, 21.0, and 11.2%, respectively. The number of patients being treated 17,6 137 with the current first-line ART regimen was 20194 (78.5%). The proportion of patients who initiated ART in

1<u>7</u>8 2011, 2012, and 2013 was 30.0%, 35.7%, and 34.3%, respectively.

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### 1**8**0 Mortality rates

181 Among 25732 patients who initiated ART between 2011 and 2013 in Guangxi, 2062 deaths were observed. 182 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: 183 184 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 100 185 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). 186

# **Drop-out** rates

18 189 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 1**20** 191 fifth year of ART initiation was 3105, 1136, 727, 342, and 124, respectively. In these years, the drop-out rates 1<u>9</u>2 1<u>9</u>2 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 193 194 in the study period was 4.98 per 100 person-years among all patients (95% CI: was 4.83 - 5.15) 195 (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 204 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 2**ØZ** AHR for TDF-based versus D4T-based regimens was 0.81 (95% CI: 0.71 – 0.92), and the AHR for LPV/rbased 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

212 212 The drop-out per 100 person-years for D4T-based, AZT-based, TDF-based, and LPV/r-based initial ART 230 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 2⊉4 2<u>15</u> 2<u>15</u> 53 (95% CI: 7.23 – 8.48), respectively (Table 3). The AHR for drop-out of initial ART regimen that was AZTbased, TDF-based, and LPV/r-based versus D4T-based was 0.89 (95% CI: 0.81 - 0.97), 0.88 (95% CI: 0.80 -236 0.98), and 1.42 (95% CI: 1.27 – 1.58), respectively. After adjustment, the AHR for drop-out of initial ART 253 2<u>18</u> regimen that was LPV/r-based versus AZT-based was 1.60 (95% CI: 1.45 – 1.76). 57 219 58

### Effects of initial ART regimen on death and drop-out 239

229 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).

# 6 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 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 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.<sup>9-11</sup> The total drop-out rate was higher than an international, multicenter observational study in Europe, Israel, and Argentina,<sup>12</sup> but was lower than that of a Kenyan cohort study.<sup>11</sup>

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

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that were D4T-based. Beginning in 2008, D4T was gradually replaced by AZT or TDF in China. A prospective 269 cohort study in South Africa found that initial ART including TDF performed better than D4T overall.<sup>13</sup> A 27,0 231 three-year randomized trial in South Africa, Europe, and the United States showed that a regimen of TDF, 272 273 3TC, and EFV was highly effective and had less toxicity than a regimen that included D4T, 3TC, and EFV over 144 weeks.<sup>14</sup> In 2010, the WHO recommended heatlh providers to reduce or abandon D4T,<sup>15,16</sup> and in 2013 indicated that D4T should definitely be discontinued for use in first-line regimens due to its well-2**7**4 295 recognized metabolic toxicities.<sup>17</sup>

276 Previous studies have shown that LPV/r-based regimens had better virological efficacy or immunological 277 278 outcome.<sup>18-21</sup> Additionally, some studies comparing protease inhibitors (PIs) demonstrated that a combination 273 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 289 LPV/r-based were inferior to AZT-based and TDF-based regimens. Gastrointestinal reactions and self-2**8**6 282 18 283 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 280 283 study found that, due to toxicity or patient choice, patients on LPV/r had a significantly higher discontinuation 285 rate compared with patients on NVP.<sup>24</sup> 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 2**8**4 inhibitors (NRTIs) was higher than those receiving EFV plus two NRTIs.<sup>25</sup> In the FHDH-ANRS CO4 cohort 288 289 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.<sup>26</sup> In the ART Cohort Collaboration study 290 (ART-CC), the odds of virological failure (HIV-1 RNA level > 200 copies/ml) at 48 weeks were higher for 299 292 31 LPV/r compared with EFV in ART-CC.<sup>27</sup> -31 293

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.

3**∂**₹ In summary, among the patients included in Guangxi, initial ART regimens that included AZT or TDF were 44 303 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 306 383 in the past seven days. Thus, it is important to improve the current training for HIV care among treatment staff 30g and enhance patient education regarding ART adherence. Future research is needed to assess the treatment effects after such improvements have been implemented. 3**9**7

# **Supplementary materials**

3ðð This study also showed the number of patients lost to death, drop-out and death and drop-out at the first year, 332 second year, third year, fourth year and fifth year of ART initiation (Supplementary Table 1 - 3). The effect 355 3<u>1</u>2 of different initial ART regimens on death and drop-out is shown in Supplementary Table 4. Additionally, the 57 313 58 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 3**59** 3**9**9 5 - 7.

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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 <sup>3</sup> )		
<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

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Table 2. Effects of initial AR			Person	Deaths/100 person			<u> </u>	
Variable	Number	Deaths	years	years (95% CI)	AHR* (95%CI)	P-value	$AHR^* \overset{(0)}{\cong} 5\%CI)$	P-value
Total	25732	2062	78137.47	2.64(2.53-2.75)			arch	
Initial ART regimen							201	
D4T-based regimen	5483	656	17384.21	3.77(3.48-4.06)	Reference		<u> 19</u> . Г	
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 20-1.41)	< 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(120-2.10)	< 0.001
* AHR=adjusted hazard ratio	; covariates of	the adjust	ed model inc	luded: age, sex, marit	al status, route of	HIV infection	on, CD4 sount bef	ore ART, V

\* AHR=adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, route of HIV infection, CD4 Sound 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

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			Person	drop-out/100			bmj	
Variable	Number	Drop-out		person years	AHR* (95%CI)	P-value	AHR <sup>*</sup> 5%CI)	P-value
			years	(95% CI)			n/ or	
Total	25732	3893	78137.47	4.98(4.83-5.14)			No	
Initial ART regimen							vem	
D4T-based regimen	5483	875	17384.21	5.03(4.70-5.37)	Reference		ber	
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(0.21-1.09)	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\$5-1.76)	< 0.001

 EP VI-based regiment
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 7/31.62
 7.63(7.23-6.48)
 1.42(1.27-1.38)
 <0.001</td>
 1.60(19)-1.76)
 <0.001</td>

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

 ART.
 \* Offer the adjusted model included: age, sex, marital status, route of HIV infection, CD4 grount before ART, WHO clinic stage before ART.

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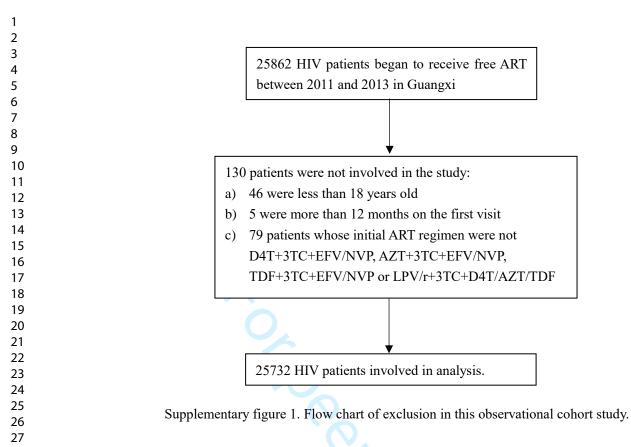
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D4T-based regimen         5133         1400         27.3         0.26         774         15.1         <0.001						BM.	J Open			njopen-2018-025666 o			
Total       21463       16139       75.0       Imitial ART regimen       Imitial ART regimen         LPV/r-based regimen       2220       1633       73.7       Reference       Reference       Reference         D4T-based regimen       4393       3180       72.5       0.94(0.84-1.06)       0.29       0.94(0.86,1.06)       0.32         AZT-based regimen       10293       7741       75.3       1.09(0.98-1.21)       0.13       1.05(0.96,1.18)       0.33         TDF-based regimen       4601       3553       77.6       1.23(1.10-1.39)       <0.001       1.25(1.10,1.41)       <0.001         *Adjusted for multivariate logistic regression: age, sex, marital status, route of HIV infection, CD4 count before ART, WHOP linic stage before ART.         Guangxi, China, by initial ART regimen       Adverse       %       P*       Gastrointestinal       %       P*       Adherence       %         Variable       Number       Adverse       %       P*       Gastrointestinal       %       P       Initial ART regimen       10.9         Initial ART regimen       1       2672       737       27.6       Reference       613       22.9       Reference       %       74       15.1       <0.001       2673       10.9         Ini	7									<u> </u>		men	
Initial ART regimen       Imitial ART regimen		Total	21463	· ·						rch			
LPV/r-based regimen         2220         1633         73.7         Reference         Reference         Reference           D4T-based regimen         4393         3180         72.5         0.94(0.84-1.06)         0.29         0.94(0.8§1.06)         0.32           AZT-based regimen         10293         7741         75.3         1.09(0.98-1.21)         0.13         1.05(0.9§1.18)         0.33           TDF-based regimen         4601         3553         77.6         1.23(1.10-1.39)         <0.001						,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				2019			
D4T-based regimen       4393       3180       72.5       0.94(0.84-1.06)       0.29       0.94(0.85,1.06)       0.32         AZT-based regimen       10293       7741       75.3       1.09(0.98-1.21)       0.13       1.05(0.96,1.18)       0.33         TDF-based regimen       4601       3553       77.6       1.23(1.10-1.39)       <0.001       1.25(1.16,1.41)       <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 2 Guangxi, China, by initial ART regimen       Adverse event $\%$ P*       Gastrointestinal reaction $\%$ P* $\phi$ Adherence $\%$ Initial ART regimen       Number       Adverse event $\%$ P*       Gastrointestinal reaction $\%$ P* $\phi$ <td></td> <td>-</td> <td>2220</td> <td>16</td> <td>533</td> <td>73.7</td> <td>Reference</td> <td></td> <td>Refe</td> <td></td> <td></td> <td></td> <td></td>		-	2220	16	533	73.7	Reference		Refe				
TDF-based regimen4601355377.6 $1.23(1.10-1.39)$ $<0.001$ $1.25(1.10-1.41)$ $<0.001$ *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 initial ART between 2011 and 2 Guangxi, China, by initial ART regimenVariableNumberAdverse event $%$ P*Gastrointestinal reaction $%$ P* $Gastrointestinalreaction%PTotal24517696628.4420317.19267310.9Initial ART regimen$		D4T-based regimen	4393	31	80	72.5	0.94(0.84-1.06)	0.2	9 0.94(0.5	8.3.1.06)	0.32		
*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 2 Guangxi, China, by initial ART regimen         Variable       Number       Adverse event, event       %       P*       Gastrointestinal reaction       %       P*       Adherence       %         Total       24517       6966       28.4       4203       17.1       9       2673       10.9         Initial ART regimen		AZT-based regimen	10293	77	/41	75.3	1.09(0.98-1.21)	0.1	3 1.05(0.9	9æ1.18)	0.33	1	
Table 5. Adverse event, gastrointestinal reaction and adherence during the first 3 months of ART among HIV patients who inditated ART between 2011 and 2 Guangxi, China, by initial ART regimen         Variable       Number       Adverse event       %       P*       Gastrointestinal reaction       %       P*       Mathematical ART between 2011 and 2         Variable       Number       Adverse event       %       P*       Gastrointestinal reaction       %       P*       Mathematical ART between 2011 and 2         Total       24517       6966       28.4       4203       17.1       9       2673       10.9         Initial ART regimen       Initial ART regim		TDF-based regimen	4601	35	53	77.6	1.23(1.10-1.39)	< 0.0	01 1.25(1.)	16-1.41)	< 0.001		
Total       24517       6966       28.4       4203       17.1       9       2673       10.9         Initial ART regimen		Table 5 Adverse event gast	rointestinal react	ion and adher	ence du	ring the first 3	months of ART am	ong HR	natients who	initiated A	RT hetwee	n 2011 ar	nd 2013 ir
Initial ART regimen         Z		Guangxi, China, by initial Al	RT regimen	Adverse			Gastrointestinal	-		en.b			nd 2013 in P*
D4T-based regimen         5133         1400         27.3         0.26         774         15.1         <0.001 $\frac{10}{12}$ 574         11.2           AZT-based regimen         11587         3666         31.6         <0.001		Guangxi, China, by initial Al Variable	RT regimen Number	Adverse event	%		Gastrointestinal reaction	%		en.b mj. com/ Adho	erence	%	
D4T-based regimen         5133         1400         27.3         0.26         774         15.1         <0.001 $\frac{10}{12}$ 574         11.2           AZT-based regimen         11587         3666         31.6         <0.001		Guangxi, China, by initial Al Variable Total	RT regimen Number	Adverse event	%		Gastrointestinal reaction	%		ni. Adhe	erence	%	
AZ1-based regimen       11587       3666       31.6       <0.001       2231       19.3       0.004       N       1324       11.4         TDF-based regimen       5125       1163       22.7       <0.001		Guangxi, China, by initial Al Variable Total Initial ART regimen	RT regimen Number 24517	Adverse event 6966	% 28.4	P*	Gastrointestinal reaction 4203	%	P*	Adho Adho Adho Adho Adho Adho Adho Adho	erence 573	% 10.9	
		Guangxi, China, by initial Al Variable Total Initial ART regimen LPV/r-based regimen	RT regimen Number 24517 2672	Adverse event 6966 737	% 28.4 27.6	P*	Gastrointestinal reaction 4203 613	% 17.1 22.9	P* Reference	Adho Adho Adho Adho Adho Adho Adho Adho	erence 573 59	% 10.9 13.4	P*
*Adjusted for multivariate logistic regression: age say marital status route of UIV infection CD4 count before ADT WUCS linia stage before ADT		Guangxi, China, by initial Al Variable Total Initial ART regimen LPV/r-based regimen D4T-based regimen	RT regimen           Number           24517           2672           5133	Adverse event 6966 737 1400	% 28.4 27.6 27.3	P* Reference 0.26	Gastrointestinal reaction 4203 613 774	% 17.1 22.9 15.1	P* Reference <0.001	Adho Adho Adho Adho Adho November 20 Sovember 22 Sovember 22 Sovember 22	erence 573 59 74	% 10.9 13.4 11.2	P*
		Guangxi, China, by initial Al Variable Total Initial ART regimen LPV/r-based regimen D4T-based regimen AZT-based regimen TDF-based regimen	RT regimen           Number           24517           2672           5133           11587           5125	Adverse event 6966 737 1400 3666 1163	%           28.4           27.6           27.3           31.6           22.7	P* Reference 0.26 <0.001 <0.001	Gastrointestinal reaction 4203 613 774 2231 585	%       17.1       22.9       15.1       19.3       11.4	P* Reference <0.001 0.004 <0.001	B.bmi. Com Adho On 20 Vovem 3 Pr 27, 2024 4	erence 673 59 74 324 16	%           10.9           13.4           11.2           11.4           8.1	Ref



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

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Variable	Number of HIV	Deaths	Person years	Deaths/100 person
variable	patients	Deaths	r erson years	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)

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oplementary table 3 tiation	5. Death + drop-out rate	es among HIV patients	who initiated ART	between 2011 and 2013 in Gu
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 week	20852	1000	18183.13	5.50(5.16-5.84)
Third year	13867	495	10697.61	4.63(4.22-5.03)
Fourth year	13807			

						<u> </u>		
Variable	Number	Deaths+	Person	Deaths + drop-out /100	AHR* (95%CI)	e-value	AHR* (95%CI)	P-value
Variable	Number	drop-out	years	person years (95% CI)	AIIK (9576CI)	e-value e	AIIK (9570CI)	I -value
Total	25732	5955	78137.47	7.62(7.43-7.81)		No		
Initial ART regimen					$O_{\Delta}$	vem		
D4T-based regimen	5483	1531	17384.21	8.81(8.37-9.25)	Reference	ber		
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)	S0.001	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)	ई0.001	1.67(1.54-1.81)	< 0.001

 LP V/I-based regiment
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 12.05(11.20-12.80)
 1.32(1.22-1.44)
 \$0.001
 1.07(1.34-1.81)
 <0.001</td>

 \* 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.

 \* For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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Variable	Number	Deatha	Person	Deaths /100 person		∃ P-vælue	ALLD* (050/ CI)	Draha
Variable	Number	Deaths	years	years (95% CI)	AHR* (95%CI)	P-volue	AHR* (95%CI)	P-value
Total	25732	2062	78137.47	2.64(2.53-2.75)		arch		
Initial ART regimen						201		
NNRTI-based regimen	22853	1739	70405.65	2.47(2.35-2.59)	Reference	9. D		
PI-based regimen	2879	323	7731.82	4.18(3.72-4.63)	1.51(1.33-1.71)	<0.201		
NNRTI-based regimen						lload		
D4T-based regimen	5483	656	17384.21	3.77(3.48-4.06)	Reference	ided		
AZT-based regimen	12018	695	38705.61	1.80(1.66-1.93)	0.64(0.57-0.71)	<0.901	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			~ (V_			o://b		
LPV/r+3TC+D4T	280	45	717.04	6.28(4.44-8.11)	Reference	mjop		
LPV/r+3TC+AZT	863	39	2471.79	1.58(1.08-2.07)	0.62(0.40-0.97)	0.93	Reference	
LPV/r+3TC+TDF	1736	239	4542.99	5.26(4.59-5.93)	0.96(0.70-1.32)	0.31	1.54(1.09-2.48)	0.01

# BMJ Open Supplementary table 5. Effects of initial ART regimen on death in HIV-infected patients who started ART between 201 leand 2013 in Guangxi, China

\* 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 2811 and 2013 in Guangxi, China
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		-	_					
Variable	Number	Drop-out	Person	Drop-out /100 person	AHR* (95%CI)	Revalue	AHR* (95%CI)	P-value
			years	years (95% CI)				
Total	25732	3893	78137.47	4.98(4.83-5.14)		2024		
Initial ART regimen						ł by		
NNRTI-based regimen	22853	3286	70405.65	4.67(4.51-4.83)	Reference	gue		
PI-based regimen	2879	607	7731.82	7.85(7.23-8.48)	1.55(1.42-1.70)	≤0.001		
NNRTI-based regimen						rote		
D4T-based regimen	5483	875	17384.21	5.03(4.70-5.37)	Reference	ctec		
AZT-based regimen	12018	1690	38705.61	4.37(4.16-4.57)	0.88(0.80-0.95)	<b>E</b> 0.001	Reference	
	•			•		сор		
						yright		3
	Fo	or neer review	only - http://bn	nionen hmi com/site/abou	ıt/auidelines yhtml	it.		

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TDF-based regimen	5352	721	14315.82	5.04(4.67-5.40)	0.88(0.79-0.97)	<b>4</b> 0.001	1.00(1.05-1.24)	0.002
PI-based regimen						n 30		
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)	<b>≥</b> 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 etween 2011 and 2013 in Guangxi,

from China

Variable	Number	Deaths + drop-out	Person years	Deaths + drop-out /100 person years (95% CI)	AHR* (95%CI)	-value	AHR* (95%CI)	P-value
Total	25732	5955	78137.47	7.62(7.43-7.81)		mjo		
Initial ART regimen				$\langle \mathbf{Q} \rangle$		pen.		
NNRTI-based regimen	22853	5025	70405.65	7.14(6.94-7.33)	Reference	bmj		
PI-based regimen	2879	930	7731.82	12.03(11.26-12.80)	1.54(1.44-1.66)	§0.001		
NNRTI-based regimen						n on		
D4T-based regimen	5483	1531	17384.21	8.81(8.37-9.25)	Reference	No		
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)	<b>\$</b> 0.001	1.07(1.00-1.15)	0.06
PI-based regimen						22, 2		
LPV/r+3TC+D4T	280	116	717.04	16.18(13.23-19.12)	Reference	2024		
LPV/r+3TC+AZT	863	202	2471.79	8.17(7.05-9.30)	0.89(0.70-1.13)	ई0.32	Reference	
LPV/r+3TC+TDF	1736	612	4542.99	13.47(12.40-14.54)	0.89(0.73-1.09)	Ge 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.

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STROBE Statement—Checklist of items that shoul	ld be included in reports of <i>cohort studies</i>

	Item No	Recommendation	Reported on page #
Title and abstract	1	( <i>a</i> ) Indicate the study's design with a commonly used term in the	P.3
		title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of	P.3
		what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the	P.4
C		investigation being reported	
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	P.4
8		periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of	P.4-P.5
I	-	selection of participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of	No
		exposed and unexposed	110
Variables	7	Clearly define all outcomes, exposures, predictors, potential	P.5
v unuoios	,	confounders, and effect modifiers. Give diagnostic criteria, if	1.0
		applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of	P.5
measurement	0	methods of assessment (measurement). Describe comparability of	1.5
measurement		assessment methods if there is more than one group	
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	10	Explain how the study size was arrived at Explain how quantitative variables were handled in the analyses. If	P.5
variables	11	applicable, describe which groupings were chosen and why	г.3
	10		P.5
Statistical methods	12	( <i>a</i> ) Describe all statistical methods, including those used to control	P.3
		for confounding	D 5
		(b) Describe any methods used to examine subgroups and	P.5
		interactions	
		(c) Explain how missing data were addressed	P.5
		(d) If applicable, explain how loss to follow-up was addressed	P.5
		( <i>e</i> ) Describe any sensitivity analyses	No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	P.5-P.6
		numbers potentially eligible, examined for eligibility, confirmed	
		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Table 1
		(c) Consider use of a flow diagram	Supplementar
			figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	Table 1
		clinical, social) and information on exposures and potential	
		confounders	
		(b) Indicate number of participants with missing data for each	Table 1
		variable of interest	

		(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-	Table 2-table 5
		adjusted estimates and their precision (eg, 95% confidence	
		interval). Make clear which confounders were adjusted for and why	
		they were included	
		(b) Report category boundaries when continuous variables were	Table 2-table 5
		categorized	
		(c) If relevant, consider translating estimates of relative risk into	No
		absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done-eg analyses of subgroups and	No
		interactions, and sensitivity analyses	
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	P.8-P.9
		potential bias or imprecision. Discuss both direction and magnitude	
		of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering	P.8-P.9
		objectives, limitations, multiplicity of analyses, results from similar	
		studies, and other relevant evidence	
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	P.2
		present study and, if applicable, for the original study on which the	
		present article is based	

\*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 <a href="http://www.strobe-statement.org">http://www.strobe-statement.org</a>.