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

Ruihua Kang,1 Liuhong Luo,2 Huanhuan Chen,2 Qiuying Zhu,2 Lingjie Liao,1 Hui Xing,1 Jinhui Zhu,2 Zhiyong Shen,2 Guanghua Lan,2 Zhenzhu Tang,2 Yiming Shao,1 Wenmin Yang,2 Yuhua Ruan1

ABSTRACT

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

Design Observational retrospective cohort study.

Setting Data from 2011 to 2013 in Guangxi, China.

Participants Patients aged ≥18 years (n=25,732) were selected.

Results A total of 25,732 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) regimens versus stavudine-based (D4T-based) regimen had an adjusted HR (AHR) for death of 0.65 (95% CI 0.58 to 0.73); the AHR of tenofovir-based (TDF-based) versus D4T-based regimens was 0.81 (95% CI 0.71 to 0.92), and of lopinavir–ritonavir-based (LPV/r-based) versus D4T-based regimens, 1.19 (95% CI 1.04 to 1.37). AZT-based versus D4T-based regimens had an AHR for dropout of 0.89 (95% CI 0.81 to 0.97); this ratio for TDF-based versus D4T-based regimens was 0.88 (95% CI 0.80 to 0.98), and for LPV/r-based versus D4T-based regimens, 1.42 (95% CI 1.27 to 1.58). AZT-based and TDF-based regimens had a lower risk compared with D4T-based regimens, while LPV/r-based regimens had a higher risk. High gastrointestinal reactions and poor adherence were observed among HIV patients whose initial ART regimen was LPV/r-based.

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

INTRODUCTION

Highly active antiretroviral therapy (ART) has been an available treatment for people living with HIV for more than three decades. In China, ART regimens are applied according to WHO guidelines. As the WHO guidelines change, ART criteria and regimens have been appropriately adjusted. The National Free Antiretroviral Treatment Program (NFATP) was initiated in China among former plasma donors as a pilot project in Henan province in 2002, and fully performed nationally in 2003.1,2 In 2005, the recommended first-line regimen in China was zidovudine (AZT) or stavudine (D4T) with lamivudine (3TC) and nevirapine (NVP).2,3 As recommended by the WHO. In the beginning of 2008, the Chinese national criteria for receiving ART treatment were revised as follows: CD4 cell count <350/μL, WHO-defined stage III/IV clinical conditions or willingness to receive ART regardless of meeting the first two criteria.4 The regimen was adjusted again and D4T was gradually replaced by AZT or tenofovir (TDF).4 To date, all individuals infected with HIV who are eligible for treatment have been treated in all 31 provinces, autonomous regions and municipalities in China.5 Current first-line ART regimens include TDF or AZT with 3TC and efavirenz (EFV) or NVP.

Strengths and limitations of this study

► Our study was conducted as an observational retrospective cohort study in Guangxi, China, using the data of 25,732 patients.
► The large sample size provides the strong evidence in support of our study results.
► The study population included only subjects who initiated antiretroviral therapy (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.
Second-line ART regimens include lopinavir-ritonavir (LPV/r) with 3TC and AZT or TDF. To achieve the Joint United Nations Programme on HIV/AIDS (UNAIDS) ‘90-90-90’ target,6 regimens that include LPV/r have been gradually and widely implemented as initial ART treatment in China. However, despite recommendations to initiate ART among all individuals infected with HIV, there exists limited understanding about the effects of different initial regimens on the mortality and attrition rates in real-world settings in China.

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

The objective of this study was to estimate the treatment effects of different initial ART regimens (including D4T-based regimen [D4T+3TC+EFV/NVP], AZT-based regimen [AZT+3TC+EFV/NVP], TDF-based regimen [TDF+3TC+EFV/NVP] and LPV/r-based regimen [LPV/r+3TC+D4T/AZT/TDF]) on death, dropout, death and dropout, 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 NFATP. The date censored was 30 April 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 of age 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. All research methods in this study were carried out in accordance with the approved guidelines.

Data collection
The baseline variables of all patients included age, sex, marital status, route of HIV infection, laboratory results of CD4 cell counts before ART, WHO clinical stage before ART, initial ART regimen, current ART regimen, date of ART initiation, date of discontinuing ART and reasons for treatment discontinuation. Follow-up status variables included: treatment continuation, loss to follow-up, survival status, transfers to another clinic and stopped ART. The follow-up visits occurred at 0.5, 1, 2 and 3 months following ART initiation, and then every 3 months thereafter.8 Loss to follow-up was defined as not having a visit for more than 90 days after the last date seen in clinic.

Statistical analysis
In this study, treatment outcomes included death and dropout from follow-up. Dropout 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 30 April 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, dropout rates and death and dropout rates with their 95% CI were analysed with incidence density rate per 100 person-years of follow-up. We used Cox proportional hazard models to estimate HR to compare the effects of initial ART regimens on death, dropout, and death and dropout.

We also collected data regarding viral load (VL) at 12 months of ART, adverse events, gastrointestinal reactions and adherence during the first 3 months. Self-reported adherence variables included missed doses in the past 7 days during the first 3 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 3 months, gastrointestinal reactions during the first 3 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 V.9.1 for Windows.

RESULTS

General characteristics of the study population
A total of 25 862 HIV/AIDS patients initiated ART between 2011 and 2013 in Guangxi, China. One hundred and thirty patients were excluded: 46 of them were less than 18 years of age, 5 were visited more than 12 months after the first visit and 79 had an initial ART regimen that was not D4T-based, AZT-based, TDF-based or LPV/r-based (online supplementary figure 1). A final total of 25 732 patients were included in this study. The baseline characteristics of these 25 732 patients are provided in table 1. Patient ages were categorised into 18–29 years, 30–49 years and ≥50 years; these age groups accounted for 13.7%, 47.4% and 39.0%, respectively, of the study population. The majority of patients (n=17 139; 66.6%) were male, and 18 074 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...
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The number of patients with CD4 counts before ART<350 cells/mm$^3$ and ≥350 cells/mm$^3$ were 22458 (87.3%) and 2756 (10.7%), respectively. An additional 518 (2.0%) patients had unknown CD4 counts before ART initiation. Patients who were WHO-defined clinical stage III/IV before ART accounted for 41.8% of the study population. Patients with initial ART regimens of D4T-based, AZT-based, TDF-based and LPV/r-based accounted for 21.3%, 47.2%, 21.0 and 11.2%, respectively. The number of patients being treated with the current first-line ART regimen was 20194 (78.5%). The proportion of patients who initiated ART in 2011, 2012 and 2013 was 30.0%, 35.7% and 34.3%, respectively.

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

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

Death and dropout rates
Among 25732 patients, 5955 deaths and dropouts 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 dropout rate was 7.62 per 100 person-years among all patients (95% CI 7.43 to 7.81) (online supplementary table 3).

Effects of initial ART regimen on death
The deaths per 100 person-years for D4T-based, AZT-based, TDF-based and LPV/r-based initial ART regimens was 3.77 (95% CI 3.48 to 4.06), 1.80 (95% CI 1.66 to 1.93), 2.71 (95% CI 2.44 to 2.98) and 4.18 (95% CI 3.72 to 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 to 0.73), the AHR for TDF-based versus D4T-based regimens was 0.81 (95% CI 0.71 to 0.92) and the AHR for LPV/r-based versus D4T-based regimens was 1.19 (95% CI 1.04 to 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 to 2.10).

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

| Variable                                      | No  | %    |
|----------------------------------------------|-----|------|
| Total                                        | 25732 | 100.0 |
| Age (years)                                  |     |      |
| 18–29                                       | 3513 | 13.7 |
| 30–49                                       | 12186 | 47.4 |
| ≥50                                          | 10033 | 39.0 |
| Sex                                          |     |      |
| Male                                         | 17139 | 66.6 |
| Female                                       | 8593 | 33.4 |
| Marital status                               |     |      |
| Married                                      | 18074 | 70.2 |
| Other                                        | 7658 | 29.8 |
| Route of HIV infection                       |     |      |
| Heterosexual intercourse                     | 22882 | 88.9 |
| Homosexual intercourse                       | 321 | 1.3 |
| Intravenous drug use                         | 1931 | 7.5 |
| Other                                        | 598 | 2.3 |
| CD4 count before ART (cells/mm$^3$)          |     |      |
| <350                                         | 22458 | 87.3 |
| ≥350                                         | 2756 | 10.7 |
| Missing                                      | 518 | 2.0 |
| WHO clinic stage before ART                  |     |      |
| I/II                                         | 14985 | 58.2 |
| III/IV                                       | 10747 | 41.8 |
| Initial ART regimen                          |     |      |
| D4T-based regimen                            | 5483 | 21.3 |
| AZT-based regimen                            | 12018 | 46.7 |
| TDF-based regimen                            | 5352 | 20.8 |
| LPV/r-based regimen                          | 2879 | 11.2 |
| Current ART regimen                          |     |      |
| The first-line ART                           | 20194 | 78.5 |
| The second-line ART                          | 5538 | 21.5 |
| Year of ART initiation                       |     |      |
| 2011                                         | 7722 | 30.0 |
| 2012                                         | 9178 | 35.7 |
| 2013                                         | 8832 | 34.3 |

ART, antiretroviral therapy; AZT, zidovudine; D4T, stavudine; LPV/r, lopinavir–ritonavir; TDF, tenofovir.

(1.3%), and other routes of transmission (2.3%).
The effects of initial ART regimen on dropout

The dropout per 100 person-years for D4T-based, TDF-based and LPV/r-based initial ART regimen was 5.03 (95% CI: 4.70 to 5.37), 4.37 (95% CI: 4.16 to 4.57) and 7.85 (95% CI: 7.23 to 8.48), respectively (table 3). The AHR for dropout of initial ART regimen that was LPV/r-based versus D4T-based was 1.60 (95% CI: 1.45 to 1.76).

Adverse events and adherence

Information for adverse events during the first 3 months was available for 24,517 patients (table 5). A total of 6966 (28.4%) patients had adverse events, and the proportion of patients that had adverse events among those whose initial ART regimen was LPV/r-based, D4T-based, AZT-based and TDF-based was 27.6%, 27.3%, 31.6% and 22.7%, respectively. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART and WHO clinical stage before ART, differences in adverse events were not statistically significant between LPV/r-based and D4T-based regimens (p=0.26), but were statistically significant between LPV/r-based and AZT-based regimens (p<0.001) and between LPV/r-based and TDF-based regimens (p<0.001).

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 21,463 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, 10,293 and 4601, respectively, and the respective proportion of VL <50 copies/mL in these groups was 73.7%, 72.5%, 75.3% and 77.6%. After adjusting for factors of age, sex, marital status, route of HIV infection, CD4 count before ART and WHO clinical stage before ART, differences in VL <50 copies/mL were not statistically significant between LPV/r-based and D4T-based regimens (p=0.32) or between LPV/r-based and AZT-based regimens (p=0.33), but were statistically significant between LPV/r-based and TDF-based regimens (p<0.001).

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                  | No   | Deaths | Person-years | Deaths/100 person-years (95% CI) | AHR* (95% CI) | P values | AHR* (95% CI) | P values |
|---------------------------|------|--------|--------------|----------------------------------|---------------|----------|---------------|----------|
| Total                     | 25,732 | 2062   | 78,137.47    | 2.64 (2.53 to 2.75)              |               |          |               |          |
| Initial ART regimen       |      |        |              |                                  |               |          |               |          |
| D4T-based regimen         | 5483  | 656    | 17,384.21    | 3.77 (3.48 to 4.06)              | Reference     |          |               |          |
| AZT-based regimen         | 12,018 | 695    | 38,705.61    | 1.80 (1.66 to 1.93)              | 0.65 (0.58 to 0.73) | <0.001   | Reference     |          |
| TDF-based regimen         | 5352  | 388    | 14,315.82    | 2.71 (2.44 to 2.98)              | 0.81 (0.71 to 0.92) | 0.001    | 1.24 (1.10 to 1.41) | <0.001   |
| LPV/r-based regimen       | 2879  | 323    | 77,311.82    | 4.18 (3.72 to 4.63)              | 1.19 (1.04 to 1.37) | 0.01     | 1.83 (1.60 to 2.10) | <0.001   |

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

AHR, adjusted HR; ART, antiretroviral therapy; AZT, zidovudine; D4T, stavudine; LPV/r, lopinavir–ritonavir; TDF, tenofovir.
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 3 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 3-year observational cohort study among HIV patients in Guangxi, China, the total mortality rate was 2.62 per 100 person-years and the total dropout rate was 4.98 per 100 person-years. The mortality rate was higher than that in developed countries and lower than previously reported rates in resource-limited settings.9–11 The total dropout rate was higher than an international, multicentre observational study in Europe, Israel and Argentina,12 but was lower than that of a Kenyan cohort study.11

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

Previous studies have shown that LPV/r-based regimens had better virological efficacy or immunological outcome.18–21 Additionally, some studies comparing protease inhibitors (PIs) demonstrated that a combination regimen including LPV/r was well tolerated and superior to regimens containing nelfinavir for the initial ART of adults infected with HIV.22 23 However, our study showed that initial ART regimens that were LPV/r-based were inferior to AZT-based and TDF-based regimens. Gastrointestinal reactions and self-reported missed dose in the past 7 days were both highest among patients in our study who initiated ART with LPV/r. Gastrointestinal reactions can induce discomfort and lead to missed doses or complete discontinuation of ART. Other studies have shown similar results to our findings. For example, the EuroSIDA study...
found that, due to toxicity or patient choice, patients on LPV/r had a significantly higher discontinuation rate compared with patients on NVP.24 Another study demonstrated that at week 96, the proportion of patients with virological failure who were in receiving a regimen of LPV/r plus two nucleoside reverse-transcriptase inhibitors (NRTIs) was higher than those receiving EFV plus two NRTIs.25 In the French Hospital Database on HIV, Agence Nationale de Recherches sur le Sida, cohort 4 (FHDH-ANRS CO4) cohort study, TDF/emtricitabine (FTC) plus LPV/r was less durable than TDF/FTC with a third drug; furthermore, TDF/FTC plus LPV/r had a higher risk of non-AIDS morbidity.26 In the ART Cohort Collaboration study (ART-CC), the odds of virological failure (HIV-1 RNA level >200 copies/mL) at 48 weeks were higher for LPV/r compared with EFV in ART-CC.27

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

In summary, among the patients included in Guangxi, initial ART regimens that included AZT or TDF were found to have better treatment effects than initial ART that included D4T or LPV/r. Patients that initiated an ART regiment that included LPV/r had higher rates of gastrointestinal reaction and self-reported missed doses in the past 7 days. Thus, it is important to improve the current training for HIV care among treatment staff and enhance patient education regarding ART adherence. Future research is needed to assess the treatment effects after such improvements have been implemented.

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

| Variable | No | VL (copies/mL)* | % | OR  | P values | AOR* | P values* |
|----------|----|-----------------|----|-----|----------|------|-----------|
| Total    | 21463 | 16139          | 75.0 |     | Reference | Reference |
| Initial ART regimen |          |                |     |     |          |      |           |
| LPV/r-based regimen | 2220 | 1633            | 73.7 | 0.94 (0.84 to 1.06) | 0.29 | 0.94 (0.83 to 1.06) | 0.32 |
| D4T-based regimen | 4393 | 3180            | 72.5 | 1.00 (0.98 to 1.21) | 0.13 | 1.05 (0.95 to 1.18) | 0.33 |
| AZT-based regimen | 10293 | 7741           | 75.3 | 1.23 (1.10 to 1.39) | <0.001 | 1.25 (1.10 to 1.41) | <0.001 |
| TDF-based regimen | 4601 | 3553            | 77.6 |       |          |      |           |

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

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

| Variable | No | Adverse event % | P values* | Gastrointestinal reaction % | P values* | Adherence % | P values* |
|----------|----|-----------------|-----------|-----------------------------|-----------|-------------|-----------|
| Total    | 24517 | 6966           | 28.4      | 4203                        | 17.1      | 2673        | 10.9      |
| Initial ART regimen |          |                |           |                             |           |             |           |
| LPV/r-based regimen | 2672 | 737            | 27.6      | 613                         | 22.9      | 359         | 13.4      |
| D4T-based regimen | 5133 | 1400           | 27.3      | 774                         | 15.1      | 574         | 11.2      |
| AZT-based regimen | 11587 | 3666         | 31.6      | 2231                        | 19.3      | 1324        | 11.4      |
| TDF-based regimen | 5125 | 1163           | 22.7      | 585                         | 11.4      | 416         | 8.1       |

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

ART, antiretroviral therapy; AZT, zidovudine; D4T, stavudine; LPV/r, lopinavir–ritonavir; TDF, tenofovir.
Supplementary materials

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

Author affiliations

1 State Key Laboratory of Infectious Disease Prevention and Control, National Center for AIDS/STD Control and Prevention (NCAIDS), Chinese Center for Disease Control and Prevention (China CDC), Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Beijing, China

2 Guangxi Center for Disease Control and Prevention, Nanning, China

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Contributors

RK, LL, HC, YR, WY were responsible for study design and planning. RK, LL, HC, OZ, JZ, LS, 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.

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Competing interests

None declared.

Patient consent for publication

Obtained.

Ethics approval

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

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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