Baseline Viral Load Predicts Antiretroviral Therapy Outcomes Among HIV-Infected Patients: An Observational Cohort Study

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Abstract

Background

Many factors are associated with human immunodeficiency virus (HIV) antiretroviral therapy (ART) outcomes. Viral load (VL) is a strong predictor of disease progression among HIV-infected patients. The aim of this study was to evaluate the influence of baseline VL on treatment-related mortality and virologic failure.

Methods

This retrospective study observed HIV-infected patients who were initiated on ART between 2012 and 2018 in Chongqing, China. Mortality assessment included the early mortality rate (deaths within the first 12 months) and the overall mortality rate (deaths during entire observation period). Virologic failure was defined as VL ≥ 200 copies/mL at 12 (range 9–15) months after treatment initiation. Cox proportional hazards regression and logistic regression models were used to evaluate the effects of baseline VL on mortality and virologic failure.

Results

The cohort included 9791 HIV patients; 50.1% of patients had baseline VL test at ART initiation, and only 18.4% had a baseline VL level of $< 10,000$ copies/mL. ART initiation at higher VL was significantly associated with the early mortality (10,000–99,999 copies/mL: AHR = 2.4; $\geq 100,000$ copies/mL: AHR = 3.4) and the overall mortality ($\geq 100,000$ copies/mL: AHR = 1.7). Patients with VL $\geq 100,000$ copies/mL and without baseline VL at ART initiation had higher virologic failure rate (AOR = 3.5 and AOR = 3.2, respectively).

Conclusions

ART initiation with higher VL was significantly associated with a greater risk of mortality and virologic failure, especially in the early stage of treatment. Baseline VL is essential for medical staff as it allows monitoring of treatment effect and allows for interventions to reduce HIV transmission. Continued efforts are needed to enhance the coverage of baseline VL testing.

Background

Currently, antiretroviral therapy (ART) is the most effective intervention to prevent new infections and reduce the risk of human immunodeficiency virus (HIV)/ Acquired immunodeficiency syndrome (AIDS)-associated mortality [1–3]. The World Health Organization (WHO) recommends early initiation of ART for all newly diagnosed HIV infected people, regardless of CD4 counts. In China, the National Free Antiretroviral Treatment Program (NFATP) was initiated in 2003, and in line with the national AIDS control policy of “Four Frees and One Care”, has scaled up provision of ART. By the end of 2019, an estimated 900,000 patients were receiving treatment nationwide, representing approximately 90% ART coverage among HIV-infected Chinese patients. With increased treatment coverage, the overall HIV/AIDS-associated mortality has persistently dropped in China [4]. Despite the rapid roll out of ART in China, HIV/AIDS remains the leading cause of death among infectious diseases, and HIV/AIDS-associated mortality continues to be one of the current public health concerns of national importance [5, 6].

HIV viral load (VL) is significantly associated with the degree of active HIV replication, and a high VL predicts faster disease progression to AIDS and/or death [7]. Monitoring of VL level after ART initiation to assess efficacy of treatment has gained traction in recent years [8, 9]. However, baseline VL testing has remained under-supported in clinical settings of resource-limited areas. Studies suggest that assessment of treatment outcomes should consider CD4 counts, VL, and duration of ART [10]. In most cases, baseline CD4 has been used to determine when patients should be initiated on treatment. However, following a general consensus of early and immediate ART initiation after HIV diagnosis [11, 12], baseline CD4 testing is no longer recommended as an essential component in deciding whether to initiate ART. More studies have also recommended a shift to VL monitoring before and after ART initiation where HIV VL testing is available [13, 14].

HIV-infected patients with higher VL will need a longer time to control viral replication and restore their immune system after initiation of treatment. Currently, more evidence shows that patients with high VL at the time of ART initiation were more likely to fail treatment or have low-level viremia (LLV) [15–17]. However, there is limited data on the benefits of VL testing at ART initiation in China, with need for more supportive evidence for widespread baseline VL testing.

In China, the southwest area was the region with the highest burden of the HIV epidemic [18]. Chongqing, which is just situated in southwest China, currently plays an important role in the country's HIV prevention and treatment program [19]. By the end of 2019, Chongqing reported approximately 50,000 surviving HIV patients and 14,000 HIV/AIDS-associated deaths. In order to understand the necessity of baseline VL testing, we conducted this observational cohort study to evaluate the effect of baseline VL on treatment outcomes, based on a large ART database in Chongqing.

Materials And Methods

Study Design and Population

This observational cohort study of HIV patients initiated on ART was conducted in Chongqing, China. Baseline VL was used to evaluate the treatment effects on patients' outcomes, including death and virologic failure. Data for individuals who were initiated ART between 2012 and 2018 were extracted from the NFATP database. A total of 4 districts where the proportion of baseline VL testing was 20% or above were selected. The eligibility criteria for study participants included being aged ≥ 18 years, being newly initiated on treatment, and having follow-up records. The cohort observations started on the date of ART initiation, with follow-up at baseline, 1, 2, 3 months, and followed up every 3 months later, and terminated on December 31, 2019. All patients were followed up until death, dropout, or observation termination.

Data Collection

ART data was extracted from the Chinese NFATP information system, a nationwide, real-time, reporting system, which is managed by the National Center for AIDS/STD Control and Prevention (NCAIDS) of the Chinese Center for Disease Control and Prevention (China CDC) [20]. In China, all new cases and their follow-up of free ART are required to report in the information system. Baseline data collected included age, sex, marital status, transmission route, baseline CD4 counts, baseline VL, initial ART regimen, year of ART initiation and duration from HIV diagnosis to ART. Death measure was all-cause mortality. The patient's death information was corroborated

with another Chinese HIV/AIDS comprehensive response information management system database (HIV case reporting database) by treatment code. A dropout event among surviving patients was defined as cessation of treatment or loss to follow-up for 90 days after the missed scheduled appointment. Virologic failure was defined as VL $\geq$ 200 copies/mL at 12 (range 9–15) months after treatment initiation. For those who had tested VL more than once, this study selected the result closest to the 12-month test date. All records were anonymous and contain no personal privacy information. All patients signed an informed consent form at initiation of treatment. This study was approved by the Institutional Review Board of Chongqing CDC [CQCDCLS (2019)004].

Statistical Analysis

Death was treated as a time-dependent variable in data analysis. Observed time was expressed in person-years (PYs). Mortality assessment included the early mortality rate (deaths within the first 12 months) and the overall mortality rate (deaths during entire observation period). Cox proportional hazards regression model was adopted to assess the association between baseline VL and mortality. Logistic regression model was used to evaluate the effect of baseline VL on virologic failure. Based on baseline VL, all participants were categorized into 4 groups (< 10,000 copies/mL, 10,000–99,999 copies/mL, $\geq$ 100,000 copies/mL, and untested). Other potential confounders of the model included age, sex, marital status, transmission route, baseline CD4 counts, initial ART regimen, year of ART initiation, and duration from HIV diagnosis to ART. A two-sided P-value of 0.05 or less was regarded as statistically significant. All statistical analyses were performed using IBM SPSS Statistics, Version 19.0. (IBM Corp., Armonk, NY, USA).

Results

Demographic Characteristics of HIV-infected Patients

A total of 9791 HIV-infected patients were found to meet the inclusion criteria. Characteristics of these patients are shown in Table 1. Approximately 69% ($n = 6772$) of individuals were aged between 18–49 years; 80.4% were males, and 44.4% were married. The main HIV infection route was heterosexual contact (51.9%), and the most common first-line ART regimen was TDF + 3TC + EFV (87.1%, $n = 8525$). About half of the individuals started ART within 30 days of diagnosis (48.7%, $n = 4772$) and had CD4 counts $\geq$ 200 cells/mm³ before ART (56.7%, $n = 5549$). In this study, 4907 (50.1%) patients had a VL test when ARTs were initiated. The percentage of patients with baseline VL results < 10,000 copies/mL, 10,000–99,999 copies/mL, and $\geq$ 100,000 copies/mL was 18.4%, 43.3%, and 38.3%, respectively.

Table 1
Characteristics of HIV patients initiating ART between 2012 and 2018 in Chongqing, China

Variables	Entire study cohort N (%)	Baseline viral load testing		P value
		Yes N (%)	No N (%)	
Total	9791(100)	4907(100)	4884(100)	
Age(years)				0.087
18–49	6772(69.2)	3433(70.0)	3339(68.4)	
≥50	3019(30.8)	1474(30.0)	1545(31.6)	
Sex				0.247
Male	7870(80.4)	3967(80.8)	3903(79.9)	
Female	1921(19.6)	940(19.2)	981(20.1)	
Marital status				< 0.001
Single	3905(39.9)	1901(38.7)	2004(41.0)	
Married	4343 (44.3)	2277(46.4)	2066(42.3)	
Divorced and others	1543(15.8)	729(14.9)	814(16.7)	
Transmission route				< 0.001
Heterosexual contact	5085(51.9)	2505(51.0)	2580(52.8)	
Homosexual contact	3856(39.4)	1919(39.1)	1937(39.7)	
Injection drug use	81(0.8)	28(0.6)	53(1.1)	
Unknown	769(7.9)	455(9.3)	314(6.4)	
Baseline CD4 counts (cells/mm3)				< 0.001
< 200	4006(40.9)	2345(47.8)	1661(34.0)	
≥ 200	5549(56.7)	2508(51.1)	3041(62.3)	
Unknown	236(2.4)	54(1.1)	182(3.7)	
Initial ART regimen				< 0.001
TDF + 3TC + EFV	8525(87.1)	4569(93.1)	3956(81.0)	
Others	1266(12.9)	338(6.9)	928(19.0)	
Year of ART initiation				< 0.001
2012–2015	4524(46.2)	2019(41.1)	2505(51.3)	
2016–2018	5267(53.8)	2888(58.9)	2379(48.7)	

Note. TDF, Tenofovir; 3TC, Lamivudine; EFV, Efavirenz.

Variables	Entire study cohort N (%)	Baseline viral load testing		P value
		Yes	No	
		N (%)	N (%)	
Duration from HIV diagnosis to ART (days)				< 0.001
≤ 30	4772(48.7)	2779(56.6)	1993(40.8)	
31–365	3655(37.3)	1589(32.4)	2066(42.3)	
> 365	1364(14.0)	539(11.0)	825(16.9)	
Baseline viral load (copies/ml)				-
< 10,000	903(9.2)	903(18.4)	-	
10,000–99,999	2126(21.7)	2126(43.3)	-	
≥ 100,000	1878(19.2)	1878(38.3)	-	
Untested	4884(49.9)	-	4884(100)	
<i>Note.</i> TDF, Tenofovir; 3TC, Lamivudine; EFV, Efavirenz.				

Effects of baseline VL on Death

The early mortality rate (deaths within the first 12 months) and the overall mortality rate (deaths during entire observation period) were 4.0 per 100 PY(370 deaths) and 2.1 per 100 PY (707 deaths) (Table 2). ART initiation at higher VL and absence of baseline VL testing were significantly associated with early deaths (10,000–99,999 copies/mL: AHR = 2.4; ≥100,000 copies/mL: AHR = 3.4; and untested: AHR = 2.6), and patients with VL ≥ 100,000 copies/mL exhibited a higher risk of overall mortality (AHR = 1.7). However, there was no association between baseline VL and mortality from 12 months to termination.

Table 2
Effects of baseline viral load on death among HIV patients initiating ART in Chongqing, China, 2012–2018

Baseline viral load (copies/ml)	Number	Deaths	Observed time (PY)	Mortality rate per 100 PY	HR (95% CI)	P value	AHR (95% CI)	P value
Study cohort observed from initiation to 12 months								
Overall	9791	370	9337.4	4.0(3.6,4.4)				
< 10,000	903	8	877.6	0.9(0.3,1.5)	1.0		1.0	
10,000–99,999	2126	60	2045.4	2.9(2.2,3.7)	3.2(1.5,6.6)	0.002	2.4(1.1,5.0)	0.021
≥ 100,000	1878	131	1754.6	7.5(6.2,8.7)	8.1(4.0,16.6)	< 0.001	3.4(1.7,7.0)	0.001
Untested	4884	171	4659.8	3.7(3.1,4.2)	4.0(2.0,8.1)	< 0.001	2.6(1.3,5.3)	0.009
Study cohort observed from 12 months to termination								
Overall	9058	337	24379.0	1.4(1.2,1.5)				
< 10,000	860	24	2309.3	1.0(0.6,1.5)	1.0		1.0	
10,000–99,999	1993	49	4781.1	1.0(0.7,1.3)	1.0 (0.6,1.6)	0.935	0.9(0.6,1.5)	0.781
≥ 100,000	1682	76	4095.3	1.9(1.4,2.3)	1.8(1.1,2.8)	0.016	1.1(0.7,1.7)	0.835
Untested	4523	188	13193.3	1.4(1.2,1.6)	1.4(0.9,2.1)	0.148	1.0(0.6,1.5)	0.983
Entire study cohort								
Overall	9791	707	33716.4	2.1(1.9,2.2)				
< 10,000	903	32	3186.9	1.0(0.7,1.4)	1.0		1.0	
10,000–99,999	2126	109	6826.5	1.6(1.3,1.9)	1.5(1.0,2.3)	0.036	1.3(0.9,1.9)	0.196
≥ 100,000	1878	207	5849.9	3.5(3.1,4.0)	3.4(2.3,4.9)	< 0.001	1.7(1.2,2.5)	0.006
Untested	4884	359	17853.1	2.0(1.8,2.2)	2.0(1.4,2.9)	< 0.001	1.4(1.0,2.0)	0.076
*PY = person years; HR = hazard ratio; AHR = adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, transmission route, baseline CD4 counts, initial ART regimen, year of ART initiation, duration from HIV diagnosis to ART.								

Effects of baseline VL on Virologic Failure

Of the 5043 patients who had VL tested at 12 months after treatment initiation, 230 patients (4.6%) exhibited virologic failure (Table 3). The virologic failure rate of patients with pre-ART VL < 10,000 copies/mL, 10,000–99,999 copies/mL, ≥ 100,000 copies/mL and untested were 1.3%, 2.8%, 7.0%, and 5.3%, respectively. The adjusted model showed that both VL ≥ 100,000 copies/mL and being untested for VL increased the risk of virologic failure, compared with VL < 10,000 copies/mL (≥ 100,000 copies/mL: AOR = 3.5; untested: AOR = 3.2).

Table 3
Effects of baseline viral load on virologic failure at 12 months among HIV patients initiating ART in Chongqing, China, 2012–2018

Variables	Number	Virologic failure	Virologic failure rate (95% CI)	OR (95% CI)	<i>P</i> value	AOR (95% CI)	<i>P</i> value
Overall	5043	230	4.6(4.0,5.1)				
Baseline viral load (copies/ml)							
< 10,000	522	7	1.3(0.4,2.3)	1.0		1.0	
10,000–99,999	1272	35	2.8(1.9,3.7)	2.1(0.9,4.7)	0.079	1.7(0.8,4.0)	0.185
≥ 100,000	961	67	7.0(5.4,8.6)	5.5(2.5,12.1)	< 0.001	3.5(1.6,7.8)	0.002
Untested	2288	121	5.3(4.4,6.2)	4.1(1.9,8.9)	< 0.001	3.2(1.5,6.9)	0.003
*OR = odds ratio; AOR = adjusted odds ratio; virologic failure: VL ≥ 200 copies/ml; covariates of the adjusted model included: age, sex, marital status, transmission route, baseline CD4 counts, initial ART regimen, year of ART initiation, duration from HIV diagnosis to ART.							

Effects of baseline VL on death stratified by baseline CD4 counts

Given the interaction between VL and CD4 counts, a further analysis by stratification is presented in Table 4. In the different groups of baseline CD4, ART initiation at higher VL was significantly associated with early death (<200 cells/mm³: AHR = 3.3; ≥200 cells/mm³: AHR = 5.0), but there was no significant difference in the entire cohort.

Table 4
Effects of baseline viral load on death stratified by baseline CD4 counts among HIV patients initiating ART in Chongqing, China, 2012–2018

Baseline viral load (copies/ml)	CD4 < 200 cells/mm ³				CD4 ≥ 200 cells/mm ³			
	Deaths	Mortality rate per 100 PY	AHR (95% CI)	<i>P</i> value	Deaths	Mortality rate per 100 PY	AHR (95% CI)	<i>P</i> value
Study cohort observed from initiation to 12 months								
Overall	285	7.6			73	1.4		
< 10,000	5	2.4	1.0		2	0.3	1.0	
10,000–99,999	43	5.9	2.3(0.9,5.8)	0.081	17	1.3	3.5(0.8,15.5)	0.092
≥ 100,000	119	9.6	3.3(1.4,8.2)	0.009	12	2.4	5.0(1.1,22.7)	0.036
Untested	118	7.6	2.5(1.0,6.2)	0.043	42	1.4	3.2(0.8,13.5)	0.106
Entire study cohort								
Overall	476	3.7			205	1.0		
< 10,000	16	2.1	1.0		15	0.6	1.0	
10,000–99,999	70	3.1	1.3(0.7,2.2)	0.366	37	0.8	1.3(0.7,2.3)	0.457
≥ 100,000	178	4.4	1.6(1.0,2.7)	0.068	28	1.6	1.9(1.0,3.5)	0.050
Untested	212	3.6	1.3(0.8,2.2)	0.263	125	1.1	1.4(0.8,2.3)	0.269
*PY = person years; AHR = adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, transmission route, initial ART regimen, year of ART initiation, duration from HIV diagnosis to ART.								

Discussion

Our study showed that among patients with VL results, >80% started ART with VL level ≥ 10,000 copies/mL and one third had a baseline VL level of ≥ 100,000 copies/mL. These results are similar to those reported in an international cohort across Europe and Australia [21]. The overall mortality rate in the current study was lower than that in the previous study in Chongqing, China (2.1 vs. 3.0 per 100 PY) [22]. The mortality rate was also lower than that of the study reported in 2017 in southwest China's Guangxi Zhuang Autonomous Region (2.1 vs. 2.63 per 100 PY) [23]. The reasons may be that the individuals in current study came from areas where the economic condition was better.

In our study, ART initiation with a higher level of VL was significantly associated with a greater risk of mortality, especially in early stages of treatment. A VL ≥ 100,000 copies/mL increased the risk of mortality by 2.4 times within the first 12 months and 0.7 times in the entire follow-up duration. We did not find the association between baseline VL and mortality from 12 months to termination. In most instances, it takes several months after initiation of treatment to achieve VL suppression [24]. However, patients with a high baseline VL would need a longer time to achieve viral suppression and immune reconstitution [25], in which case, the virus would continue

to damage the patients' immune system and increase the possibility of opportunistic infection and HIV-related mortality [26, 27]. Moreover, many studies have shown that patients with higher baseline VL were more likely to have lower CD4 counts and worse disease progression. Although some studies have shown no significant association between baseline VL and mortality [28], our study showed that higher baseline VL was an indication of patients mortality. The stratification analysis showed that ART initiation at higher VL was not significantly associated with the overall mortality in the entire cohort. The reasons may be the interaction between VL and CD4 counts and/or the sample size reduction of each group.

We also found that patients with a high baseline VL had a greater risk of virologic failure at 12 months on ART. A VL $\geq 100,000$ copies/mL significantly increased the risk of virologic failure (AOR = 3.5). Similar to our study, a study in China demonstrated that patients with baseline VL $> 100,000$ copies/mL were 3.2 times more likely to fail [29]. Additionally, a study on HIV-infected youth found that a low baseline VL was a predictor of viral suppression (AHR = 1.56) [30]. Another study on TB-HIV patients indicated that patients with higher baseline VL ($\log_{10}$) were more likely to fail (AOR = 1.5) [28]. Patients with a higher VL might have a larger HIV reservoir which might require a longer time to achieve VL suppression compared to individuals with low VL [25]. Therefore, there is an increased risk of HIV transmission to partners when patients carried higher VL for a longer time after ART initiation.

In this study, we also found that patients who did not have a baseline VL at ART initiation had a higher risk of early death and virologic failure. The Joint United Nations Program on HIV/AIDS (UNAIDS) suggests that routine VL monitoring is a powerful motivator for patients to keep taking their medicines after starting treatment. Additionally, VL testing might influence medical staff to employ VL-triggered adherence interventions which could benefit the patients [31]. Therefore, baseline VL testing may play the role of adherence support intervention.

Our study had some limitations. First, approximately half of the individuals without baseline VL were included in this study, which may influence assessment results. To observe the effect of influence, we included patients without baseline VL (as an independent group) in the analysis. Second, records of virologic failure only included individuals tested for VL during the 9 to 15 months following ART initiation; therefore, some patients' follow-up information was missing in our data.

In conclusion, our study indicated that a large proportion of patients had high baseline VL, and that ART initiation with high VL was significantly associated with a greater risk of mortality and virologic failure. These findings highlight the importance of strengthening baseline VL monitoring. To improve the treatment effects and reduce the risk of HIV transmission, continued efforts are needed to enhance the coverage of baseline VL testing.

Abbreviations

AIDS: Acquired immunodeficiency syndrome; ART: antiretroviral therapy; China CDC: Chinese Center for Disease Control and Prevention; HIV: human immunodeficiency virus; LLV: low-level viremia; NCAIDS: National Center for AIDS/STD Control and Prevention; NFATP: National Free Antiretroviral Treatment Program; PY: person-years; UNAIDS: United Nations Program on HIV/AIDS; VL: viral load; WHO: World Health Organization

Declarations

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Authors' contributions

CZ, GH-W, YH-R, HX and YM-S designed the study. CZ, WZ, RR-L and LO collected and analysed data. CZ drafted the article, and GH-W and YH-R revised the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All patients signed an informed consent form at initiation of treatment. This study was approved by the Institutional Review Board of Chongqing CDC [CQCDCLS (2019)004].

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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