BMC Infectious Diseases

RESEARCH

Open Access

Factors associated with immunological non-response after ART initiation: a retrospective observational cohort study

Heping Zhao[1,2†], Anping Feng[2†], Dan Luo[2†], Tanwei Yuan[2], Yi-Fan Lin[2], Xuemei Ling[1], Huolin Zhong[1], Junbin Li[1], Linghua Li[1*] and Huachun Zou[3,4,5*]

Abstract

Background Among people living with HIV (PLHIV) on antiretroviral therapy (ART), the mortality of immunological non-responders (INRs) is higher than that of immunological responders (IRs). However, factors associated with immunological non-response following ART are not well documented.

Methods We obtained data for HIV patients from the National Free Antiretroviral Treatment Program database in China. Patients were grouped into IRs (CD4 cell count ≥ 350 cells/μl after 24 months' treatment), immunological incomplete responders (ICRs) (200–350 cells/μl) and INRs (< 200 cells/μl). Multivariable logistic regression was used to assess factors associated with immunological non-response.

Results A total of 3900 PLHIV were included, among whom 2309 (59.2%) were IRs, 1206 (30.9%) ICRs and 385 (9.9%) INRs. In multivariable analysis, immunological non-response was associated with being male (2.07, 1.39–3.09), older age [40–49 years (vs. 18–29 years): 2.05, 1.29–3.25; 50–59 years: 4.04, 2.33-7.00; ≥ 60 years: 5.51, 2.84–10.67], HBV co-infection (1.63, 1.14–2.34), HCV co-infection (2.01, 1.01–4.02), lower CD4 + T cell count [50–200 cells/μl (vs. 200–350 cells/μl): 40.20, 16.83–96.01; < 50 cells/μl: 215.67, 85.62-543.26] and lower CD4/CD8 ratio (2.93, 1.98–4.34) at baseline. Compared with patients treated with non-nucleoside reverse transcriptase inhibitors (NNRTIs) based regimens, those receiving protease inhibitors (PIs) based regimens were less likely to be INRs (0.47, 0.26–0.82).

Conclusions We found a sizable immunological non-response rate among HIV-infected patients. Being male, older age, coinfection with HBV and HCV, lower CD4 + T cell count and lower CD4/CD8 ratio are risk factors of immunological non-response, whereas PIs-based regimens is a protective factor.

Keywords PLHIV, INRs, ICRs, IRs, ART

†Heping Zhao, Anping Feng and Dan Luo have contributed equally to the work.

*Correspondence:
Linghua Li
llheliza@126.com
Huachun Zou
zouhuachun@fudan.edu.cn

[1]Infectious Disease Center, Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, China
[2]School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, China
[3]School of Public Health, Fudan University, Shanghai, China
[4]School of Public Health, Southwest Medical University, Luzhou, China
[5]Kirby Institute, University of New South Wales, Sydney, Australia

Introduction

HIV/AIDS imposes considerable morbidity and mortality worldwide. According to the data of Joint United Nations Programme on HIV and AIDS (UNAIDS), approximately 1.5 million people were newly infected with HIV globally in 2020, and 680,000 people died of HIV/AIDS [1]. Among people living with HIV (PLHIV) the progressive depletion of CD4+T cells results in immunodeficiency, opportunistic infections, cancer, and death [2]. Antiretroviral therapy (ART) can effectively suppress the HIV viral load and increase the CD4+T cell count, thus greatly improving the prognosis of PLHIV and prolonging their life expectancy [3–6]. However, a considerable proportion of PLHIV fail to improve their CD4+T cell level despite of successful viral suppression [7–9], who have an increased risk of developing AIDS-related and non-AIDS-related events, and death [10–12].

The mechanisms for immunological non-response are very complicated and have not been elucidated. The impaired function of bone marrow or thymus has been clearly demonstrated to be associated with immunological non-response [13]. T cells are derived from bone marrow hematopoietic progenitor cells and populate the thymus for differentiation and maturity [14]. The bone marrow abnormalities and the consequent reduced proliferation of progenitor cells that shown in PLHIV can be improved by ART [15], but this is rarely seen in PLHIV with compromised immunological response [16]. Thymic volume is a significant independent predictor for the increase of CD4+T cells in PLHIV receiving ART [17, 18]. It has been proved that PLHIV with abundant thymic tissue show a faster improvement of naive T cell count compared with PLHIV with smaller thymic tissue [19, 20].

Understanding factors associated with immunological non-response is critical to the improvement of immunological response among PLHIV. Previous studies based on smaller samples have shown that age, sex, coinfections with hepatitis C virus (HCV) and baseline CD4+T cell count [21–25] were risk factors for immunological non-response. However, the odds ratio of above mentioned factors from different studies were inconsistent and less convincing because of smaller samples, shorter follow-up period and imprecise definition of immunological non-response. Moreover, literature on immunological non-response among PLHIV in China are scarce. In our study, we enrolled PLHIV with different immune responses from Guangzhou to assess factors associated with immunological non-response.

Methods

Study design and participants

We performed a retrospective observational cohort study using data retrieved from the National Free Antiretroviral Treatment Program database. This database, which is maintained by the National Center for AIDS/STD Control and China Center for Disease Control and Prevention (China CDC), includes PLHIV who meet China free ART criteria and received free ART. All of the provinces, municipalities and autonomous regions have access to the database within their jurisdiction.

We included all PLHIV who were treated in Guangzhou Eighth People's Hospital between January 2010 and December 2017, aged 18 years and older, baseline CD4+T cell count < 350cells/ul, and had not previously received ART. We excluded PLHIV who: (1) did not have CD4+or CD8+T cell count records at baseline or follow-up; (2) route of HIV infection is unknow; (3) were pregnant; (4) had follow-up < 24 months.

This study was approved by the institutional review board of the Guangzhou Eighth People's Hospital (202033166).

Procedures

We analyzed the baseline and follow-up information from the National Free Antiretroviral Treatment Program database [26]. Baseline information measured at ART initiation included demographics [sex, age, body-mass index (BMI) and marital status], self-reported route of HIV infection, clinical and laboratory characteristics, date of HIV diagnosis, date of ART start and initial ART regimens.

The immunological non-responders (INRs) were defined as a CD4+T cell count < 200 cells/ul and HIV viral load < 50 copies/ml after 24 months of ART [27]. Immunological incomplete responders (ICRs) were defined as a CD4+T cell count within 200~350 cells/ul and HIV viral load < 50 copies/ml after 24 months of ART. Immunological responders (IRs) were defined as a CD4+T cell count ≥ 350 cells/ul and HIV viral load < 50 copies/ml after 24 months of ART. Comorbidities include one of the following symptoms at baseline: skin lesion, thrush, hairy leukoplakia, persistent diarrhoea, and persistent or intermittent fever. Coinfections include one of the following viruses or bacteria at baseline: tuberculosis, esophageal candidiasis, non-pulmonary cryptococcal, pneumocystis jiroveci pneumonia, disseminated mycosis, cytomegalovirus, extrapulmonary tuberculosis, recurrent severe bacterial pneumonia, zoster and other infections or tumor.

Statistical analysis

Baseline characteristics were compared using Chi-squared test or Fisher exact test for categorical variables. Multivariable logistic regression analysis was conducted to explore factors associated with immunological non-response. IRs was the reference group. All variables with *P*value less than 0.1 ($P \leq 0.1$) in the Chi-squared

test or proved to be associated with immunological non-response in previous studies were included in the multivariable analysis. Statistical significance was set as a $P \leq 0.05$ for all analyses. Statistical analyses were performed using R version 4.0.3.

Results

Participants selection

We identified 14629 PLHIV whose CD4+T cell or CD8+T cell records were complete at baseline, of whom 4209 were treated with ART less than 24 months, 5324 had a baseline CD4+T cell count≥350 cells/ul or HIV viral load≥50 copies/ml after 24 months. Of 5096 PLHIV, 1166 missing values for key variables, 4 treated with rare regimens, 26 routes of infection were rare, leaving 3900 PLHIV eligible for analyses, including 2309 (59.2%) IRs, 1206 (30.9%) ICRs and 385 (9.9%) INRs (Fig. 1).

Patient characteristics at baseline

Patient baseline characteristics are summarized in Table 1. Among all included participants, 3239 (83.1%) were men and 661 (16.9%) were women. 481 PLHIV (12.3%) were older than 50 years old. 720 PLHIV (18.5%) had BMI<18.5, and 628 PLHIV (16.1%) had BMI≥24.0. 1881 PLHIV (48.2%) were married. 3770 (96.6%) reported acquiring HIV through sexual exposure (1807 heterosexual transmission [46.3%] and 1963 homosexual transmission [50.3%]), and 130 (3.3%) through intravenous drug use.

Compared with IRs, more older people were ICRs and INRs ($P<0.001$). The percentage of overweight PLHIV (BMI≥24.0) in the IRs group (18.7%) is the highest among the three groups. A total of 1315 PLHIV (57.0%) in the IRs group reported acquiring HIV through homosexual transmission, significantly higher than that in the ICRs and INRs group. The co-infection rates of hepatitis B virus (HBV) (18.7%) and HCV (7.5%) in the INRs group were significantly higher than that in the IRs group. Similarly, the percentage of previous using sulfamethoxazole and trimethoprim (SMZ-TMP) (81.0%) in the INRs group was significantly higher than that in the IRs (21.6%) group. The baseline CD4+T cell count and baseline CD4/CD8 ratio in the INRs group were significantly lower than those in the IRs group. The percentage of HIV load more than 100,000 in the INRs group (60.5%) was significantly higher than that in the IRs group (29.6%). Meanwhile, the rates of comorbidities (30.4%) and coinfections (20.8%) in INRs were significantly higher than that in the IRs group (7.5% and 5.8%). As a result, sex, age, BMI, marital status, infection route, HBV, HCV, CD4, CD4/CD8, time before ART, ART regimens, SMZ-TMP, comorbidities and coinfections were included in the multivariable analysis.

Factors associated with immunological non-response

Table 2 shows the factors associated with immunological incomplete response and immunological non-response at baseline. In the multivariable logistic regression analysis, immunological non-response was associated with being male (adjusted odds ratio [aOR], 2.07; 95% confidence interval [CI], 1.39–3.09), older age (40–49 years vs. 18–29 years: 2.05, 1.29–3.25; 50–59 years vs. 18–29 years: 4.04, 2.33-7.00; ≥ 60 years vs. 18–29 years: 5.51, 2.84–10.67), HBV co-infection (1.63, 1.14–2.34), HCV co-infection (2.01, 1.01–4.02), lower baseline CD4+T cell count (50–200 cells/μl vs. 200–350 cells/μl: 40.20, 16.83–96.01; < 50 cells/μl vs. 200–350 cells/μl: 215.67, 85.62-543.26) and lower baseline CD4/CD8 ratio (<0.2 vs.≥0.2: 2.93, 1.98–4.34). Compared with patients treated with non-nucleoside reverse transcriptase inhibitors (NNRTIs) based regimens, those receiving protease inhibitors (PIs) based regimens were less likely to be INRs (nucleoside reverse transcriptase inhibitors [NRTIs]+PIs vs. NRTIs+NNRTIs: 0.47, 0.26–0.82).

Discussion

In this analysis from a large observational cohort, we found that being male, older age, HBV co-infection, HCV co-infection, lower CD4+T cell and lower CD4/CD8 ratio at baseline were associated with immunological non-response. Compared with patients treated with NNRTIs-based regimens, those receiving PIs-based regimens were less likely to be INRs.

Compared to younger PLHIV, older PLHIV have poorer immune recovery. After the introduction of ART, several studies reported that immunological response was less marked in older PLHIV [28, 29]. Similarly, a study performed in the EuroSIDA cohort in which older age was associated with a lower increase in the CD4+T cell count after 12 months of ART [30]. This could be explained because older PLHIV who initiate ART with an advanced degree of clinical progression and their CD4+T cell levels reach an earlier plateau than that in younger PLHIV after ART. Besides, the effect of age on immune recovery may be related to the poorer thymic function and lower ART adherence in older PLHIV [31]. However, a prospective case-control study of immunological recovery in 596 PLHIV demonstrated that although older PLHIV (≥50) present a more severe HIV infection, they can achieve the same immunological success as their younger counterparts (20–35) [32]. These differences may come from sample size, age stratification and observation duration, for the PLHIV in the prospective case-control study mentioned above were followed up for 6 years, which was significantly longer than our 2-year follow-up period. Of note, we found that time before ART was not proven to be a risk factor for CD4 restoration, which probably because that all the included patients were late

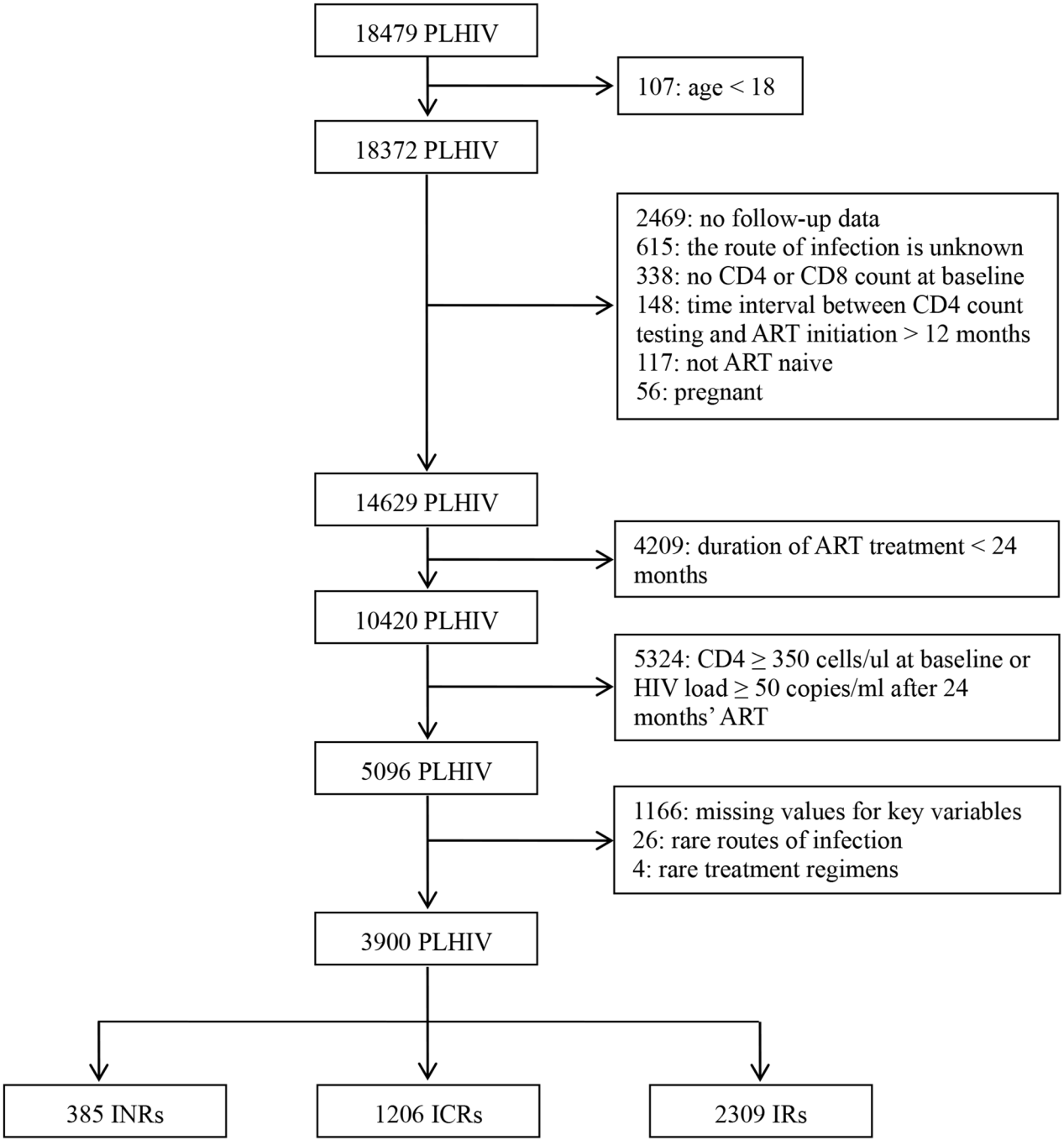

Fig. 1 Study flow chart

PLHIV, people living with HIV; ART, antiretroviral therapy

INRs (Immunological non-responders) were defined as a CD4 + T cell count < 200cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

ICRs (immunological incomplete responders) were defined as a CD4 + T cell count within 200~350 cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

IRs (immunological responders) were defined as a CD4 + T cell count ≥ 350 cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

Table 1 Baseline characteristics of PLHIV stratified by CD4 + T cell count after 24 months' ART ($N = 3900$)

Variable	Overall (%)	INRs (%)	ICRs (%)	IRs (%)	*P* value
	3900(100)	**385(9.9)**	**1206(30.9)**	**2309(59.2)**	
Sex					
Male	3239 (83.1)	332 (86.2)	996 (82.6)	1911 (82.8)	0.213
Female	661 (16.9)	53 (13.8)	210 (17.4)	398 (17.2)	
Age (years)					
Median (IQR)	34 [27–43]	42 [32–50]	35 [28–44]	32 [26–40]	**< 0.001**
18–29	1329 (34.1)	68 (17.7)	365 (30.3)	896 (38.8)	**< 0.001**
30–39	1273 (32.6)	101 (26.2)	382 (31.7)	790 (34.2)	
40–49	817 (20.9)	115 (29.9)	293 (24.3)	409 (17.7)	
50–59	324 (8.3)	64 (16.6)	111 (9.2)	149 (6.5)	
≥ 60	157 (4.0)	37 (9.6)	55 (4.6)	65 (2.8)	
BMI					
Median (IQR)	20.8 [19.0-22.9]	19.9 [18.3–22.1]	20.4 [18.7–22.4]	21.1 [19.4–23.2]	**< 0.001**
< 18.5	720 (18.5)	105 (27.3)	266 (22.1)	349 (15.1)	**< 0.001**
18.5–24.0	2552 (65.4)	243 (63.1)	781 (64.8)	1528 (66.2)	
≥ 24.0	628 (16.1)	37 (9.6)	159 (13.2)	432 (18.7)	
Marital status					
Married	1881 (48.2)	258 (67.0)	637 (52.8)	986 (42.7)	**< 0.001**
Unmarried	1828 (46.9)	107 (27.8)	500 (41.5)	1221 (52.9)	
Divorced	191 (4.9)	20 (5.2)	69 (5.7)	102 (4.4)	
Infection route					
Heterosexual	1807 (46.3)	234 (60.8)	639 (53.0)	934 (40.5)	**< 0.001**
Homosexual	1963 (50.3)	132 (34.3)	516 (42.8)	1315 (57.0)	
Intravenous drug use	130 (3.3)	19 (4.9)	51 (4.2)	60 (2.6)	
HBV					
Positive	495 (12.7)	72 (18.7)	172 (14.3)	251 (10.9)	**< 0.001**
Negative	3405 (87.3)	313 (81.3)	1034 (85.7)	2058 (89.1)	
HCV					
Positive	184 (4.7)	29 (7.5)	69 (5.7)	86 (3.7)	**0.001**
Negative	3716 (95.3)	356 (92.5)	1137 (94.3)	2223 (96.3)	
Baseline CD4 + cell count (cells/μl)					
Median (IQR)	203 [88–271]	28 [10–73]	122 [38–198]	250 [194–297]	**< 0.001**
< 50	718 (18.4)	245 (63.6)	346 (28.7)	127 (5.5)	**< 0.001**
50–200	1184 (30.4)	134 (34.8)	562 (46.6)	488 (21.1)	
200–350	1998 (51.2)	6 (1.6)	298 (24.7)	1694 (73.4)	
Baseline CD4+/CD8 ratio					
Median (IQR)	0.22 [0.12–0.32]	0.06 [0.03–0.13]	0.15 [0.07–0.25]	0.27 [0.18–0.36]	**< 0.001**
< 0.2	1721 (44.1)	341 (88.6)	744 (61.7)	636 (27.5)	**< 0.001**
≥ 0.2	2179 (55.9)	44 (11.4)	462 (38.3)	1673 (72.5)	
HIV load (copies/ml)					
< 10,000	88 (13.5)	6 (7.9)	23 (10.8)	59 (16.3)	**< 0.001**
10,000–30,000	124 (19.1)	8 (10.5)	33 (15.6)	83 (22.9)	
30,000–100,000	192 (29.5)	16 (21.1)	63 (29.7)	113 (31.2)	
> 100,000	246 (37.8)	46 (60.5)	93 (43.9)	107 (29.6)	
Time before ART (months)					
Median (IQR)	1.0 [0.5–6.4]	0.9 [0.5–2.2]	1.0 [0.5–3.9]	1.1 [0.5–8.8]	**< 0.001**
< 1	1858 (47.6)	203 (52.7)	587 (48.7)	1068 (46.3)	**< 0.001**
1–6	1038 (26.6)	116 (30.1)	358 (29.7)	564 (24.4)	
6–12	250 (6.4)	19 (4.9)	59 (4.9)	172 (7.4)	

Table 1 (continued)

Variable	Overall (%)	INRs (%)	ICRs (%)	IRs (%)	*P* value
	3900(100)	**385(9.9)**	**1206(30.9)**	**2309(59.2)**	
≥ 12	754 (19.3)	47 (12.2)	202 (16.7)	505 (21.9)	
ART regimens					
NRTIs + NNRTIs	3465 (88.8)	313 (81.3)	1073 (89.0)	2079 (90.0)	**< 0.001**
NRTIs + PIs	260 (6.7)	22 (5.7)	74 (6.1)	164 (7.1)	
NRTIs + INSTIs	78 (2.0)	18 (4.7)	29 (2.4)	31 (1.3)	
NRTIs	97 (2.5)	32 (8.3)	30 (2.5)	35 (1.5)	
SMZ-TMP					
Yes	1515 (38.8)	312 (81.0)	705 (58.5)	498 (21.6)	**< 0.001**
No	2385 (61.2)	73 (19.0)	501 (41.5)	1811 (78.4)	
Comorbidities					
Yes	495 (12.7)	117 (30.4)	205 (17.0)	173 (7.5)	**< 0.001**
No	3405 (87.3)	268 (69.6)	1001 (83.0)	2136 (92.5)	
Coinfections					
Yes	380 (9.7)	80 (20.8)	165 (13.7)	135 (5.8)	**< 0.001**
No	3520 (90.3)	305 (79.2)	1041 (86.3)	2174 (94.2)	

PLHIV, people living with HIV; ART, antiretroviral therapy; BMI, body mass index

HBV, hepatitis B virus. HCV, hepatitis C virus

INRs (Immunological non-responders) were defined as a CD4 + T cell count < 200 cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

ICRs (immunological incomplete responders) were defined as a CD4 + T cell count within 200~350 cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

IRs (immunological responders) were defined as a CD4 + T cell count ≥ 350 cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

Time before ART, time interval between HIV diagnosis and ART initiation

NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors; SMZ-TMP, sulfamethoxazole and trimethoprim

Comorbidities include one of the following symptoms at baseline: skin lesion, thrush, hairy leukoplakia, persistent diarrhoea, and persistent or intermittent fever

Coinfections include one of the following viruses or bacteria at baseline: tuberculosis, esophageal candidiasis, non-pulmonary cryptococcal, pneumocystis jiroveci pneumonia, disseminated mycosis, cytomegalovirus, extrapulmonary tuberculosis, recurrent severe bacterial pneumonia, zoster and other infections or tumor

IQR = interquartile range

presenters, so it is not so relevant when treatment was started because they have probably acquired HIV more than 6–8 years before HIV was diagnosed.

We found that HBV and HCV co-infection significantly increase the risk of immunological non-response. HIV shares similar routes of transmission with HBV and HCV, co-infection with HBV and HCV are very common in PLHIV. HCV or HBV co-infection could affect the timing of ART initiation and broaden the indication for anti-HBV or anti-HCV treatment. The issue has been investigated in several previous studies with conflicting results. A swiss HIV cohort study found that HCV seropositivity was associated with a smaller CD4 + T cell recovery [24], which is consistent with findings from our study. However, Peters et al. found that HCV co-infection had no significant effect on CD4 + T cell number recovery as long as viral load was suppressed to the maximum extent [33]. It is probably because that Peters et al. assessed the influence of HCV genotype on the CD4 + T cell recovery, and differences in adherence between HCV-infected and HCV-uninfected PLHIV may contribute to the disparate findings. In our study, we did not identify HCV genotype and assess the role of ART adherence on immunological response. Of note, we found HBV co-infection was the risk factor that rarely reported in previous studies, which serves as a reminder for physicians to pay more attention to PLHIV coinfected with HBV.

In our cohort, we found that baseline CD4 + T cell count < 50 cells/μl greatly increase the risk of immunological non-response, indicating that recommend PLHIV initiate ART earlier could lead to an increase in the number who achieve immunological response, since a low CD4 count at baseline is mainly the result of late diagnosis and treatment. Likewise, a study of immunological recovery in 861 PLHIV demonstrated that most PLHIV with CD4 + T cell count < 200 cells/μl before ART failed to achieve a CD4 + T cell count of > 500/ul [34]. PLHIV with low CD4 + T cell count at diagnosis were supposed to be late presenters, previous study showed that late presenters had a higher level of T cell activation than those with higher baseline CD4 + T cell count [35], which may contribute to the failure restoration of CD4 + T cell. we found the lower baseline CD4/CD8 ratio was associated with a higher risk of INRs, which is in accordance with a previous report [36]. This finding suggests that imbalance between CD4 and CD8 + T cell populations at baseline may be an important predictor to identify PLHIV

Table 2 Factors associated with immunological incomplete response and immunological non-response among PLHIV

Variable	ICRs			INRs		
	aOR	95% CI	*P* value	aOR	95% CI	*P* value
Sex						
Female	1.00			1.00		
Male	1.50	1.17–1.92	**0.001**	2.07	1.39–3.09	**< 0.001**
Age (years)						
18–29	1.00			1.00		
30–39	0.91	0.74–1.13	0.406	1.06	0.71–1.58	0.789
40–49	1.16	0.88–1.52	0.290	2.05	1.29–3.25	**0.002**
50–59	1.29	0.90–1.85	0.162	4.04	2.33-7.00	**< 0.001**
≥ 60	1.41	0.88–2.26	0.152	5.51	2.84–10.67	**< 0.001**
BMI						
< 18.5	1.15	0.93–1.43	0.209	1.26	0.91–1.75	0.163
18.5–24.0	1.00			1.00		
≥ 24.0	0.78	0.62–0.98	**0.035**	0.68	0.44–1.04	0.074
Marital status						
Married	1.00			1.00		
Unmarried	0.97	0.77–1.22	0.797	0.82	0.55–1.21	0.310
Divorced	1.15	0.79–1.68	0.461	0.84	0.46–1.55	0.584
Infection route						
Heterosexual	1.00			1.00		
Homosexual	0.84	0.68–1.05	0.131	1.34	0.93–1.91	0.113
Intravenous drug use	0.78	0.44–1.39	0.407	0.51	0.23–1.17	0.115
HBV						
Positive	1.24	0.98–1.58	0.079	1.63	1.14–2.34	**0.008**
Negative	1.00			1.00		
HCV						
Positive	1.27	0.79–2.06	0.328	2.01	1.01–4.02	**0.047**
Negative	1.00			1.00		
Baseline CD4 + cell count (cells/μl)						
200–350	1.00			1.00		
50–200	5.14	4.05–6.52	**< 0.001**	40.20	16.83–96.01	**< 0.001**
< 50	10.38	7.32–14.70	**< 0.001**	215.67	85.62-543.26	**< 0.001**
Baseline CD4+/CD8 ratio						
≥ 0.2	1.00			1.00		
< 0.2	1.57	1.29–1.89	**< 0.001**	2.93	1.98–4.34	**< 0.001**
Time before ART (months)						
< 1	1.00			1.00		
1–6	1.15	0.95–1.40	0.158	1.05	0.77–1.43	0.771
6–12	0.89	0.62–1.26	0.504	1.27	0.69–2.34	0.447
≥ 12	0.82	0.66–1.02	0.076	0.75	0.50–1.11	0.151
ART regimens						
NRTIs + NNRTIs	1.00			1.00		
NRTIs + PIs	0.70	0.49–0.98	**0.037**	0.47	0.26–0.82	**0.008**
NRTIs + INSTIs	0.71	0.40–1.29	0.265	0.84	0.41–1.73	0.632
NRTIs	0.62	0.35–1.09	0.098	1.13	0.61–2.10	0.698
SMZ-TMP						
Yes	1.00			1.00		
No	0.91	0.72–1.14	0.407	0.79	0.56–1.11	0.176
Comorbidities						
Yes	1.00			1.00		
No	1.24	0.93–1.65	0.145	1.19	0.83–1.72	0.348
Coinfections						

Table 2 (continued)

Variable	ICRs			INRs		
	aOR	95% CI	*P* value	aOR	95% CI	*P* value
Yes	1.00			1.00		
No	0.97	0.72–1.31	0.851	1.14	0.77–1.69	0.528

PLHIV, people living with HIV; ART, antiretroviral therapy; BMI, body mass index

HBV, hepatitis B virus. HCV, hepatitis C virus

ICRs (immunological incomplete responders) were defined as a CD4+T cell count within 200~350 cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

INRs (Immunological non-responders) were defined as a CD4+T cell count < 200cells/ul and HIV viral load < 50 copies/ml after 24 months' ART

Time before ART, time interval between HIV diagnosis and ART initiation

NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors; SMZ-TMP, sulfamethoxazole and trimethoprim

Comorbidities include one of the following symptoms at baseline: skin lesion, thrush, hairy leukoplakia, persistent diarrhoea, and persistent or intermittent fever

Coinfections include one of the following viruses or bacteria at baseline: tuberculosis, esophageal candidiasis, non-pulmonary cryptococcal, pneumocystis jiroveci pneumonia, disseminated mycosis, cytomegalovirus, extrapulmonary tuberculosis, recurrent severe bacterial pneumonia, zoster and other infections or tumor

with the worse prognosis. Of note, our data found that PIs-containing regimens reduce the risk of immunological non-response, which might suggest that PIs-containing regimens is a clinical benefit factor, probably because of a less toxic effect of PIs. However, previous study showed no differences in terms of immunological response between PIs and NNRTIs [30], which probably because the baseline CD4+T cell count were significantly different between different ART regimen groups in previous study, while our participants were naïve to ART and had < 350 CD4+T cell count at ART initiation. We did not see better immune recovery in PLHIV with INSTIs when compared to other ART regimens, which was probably due to the low proportion of PLHIV who started with INSTIs in this cohort.

Our analysis had some limitations. Firstly, we restricted INRs to be within 2 years, which may lead to missed INRs if longer follow-up period were given. However, most PLHIV whose CD4+T cell count should have already reached their maximum potential within 2 years [27]. For example, Richard conducted a longitudinal observational study for six years to characterize the increase of CD4+T cell count in PLHIV in clinical practice who maintained sustained viral suppression, and he found that CD4+T cell increased most rapidly in the first two years, after which the rate of increase was slow and gradually reached a plateau [28]. Secondly, we found that the number of CD4+T cell at baseline had an effect on INRs, but we were unable to differentiate CD4+T cell subsets. Different CD4+T cell subgroups have different roles. For example, Th17 cells are T cells with proinflammatory properties, and they may play an important role in immunological non-response [37].

In conclusion, our results based on a large cohort show that being male, older age, HBV/HCV co-infection, lower baseline CD4+T cell count and lower CD4/CD8 ratio increase the risk of immunological non-response. Receiving PIs-containing regimens tend to be protective factor.

Acknowledgements
We thank Linghua Li from Guangzhou Eighth People's Hospital for her helpful suggestions in the manuscript preparation.

Author contributions
This study was conceived and designed by Huachun Zou and Linghua Li in consultation with the other authors. Heping Zhao and Anping Feng were responsible for data compilation and data analysis. All authors have contributed to interpretation of data and study findings. Heping Zhao, Anping Feng and Dan Luo drafted the manuscript with all authors critically reviewing the paper. We thank all the participants involved in this study.

Funding
This study was supported by the Special Support Plan for High-Level Talents of Guangdong Province [2019TQ05Y230], the Natural Science Foundation of China Excellent Young Scientists Fund [82022064], Natural Science Foundation of China International/Regional Research Collaboration Project [72061137001], the Sanming Project of Medicine in Shenzhen [SZSM201811071], the High Level Project of Medicine in Longhua, Shenzhen [HLPM201907020105], the Shenzhen Science and Technology Innovation Commission Basic Research Program [JCYJ20190807155409373]. All funding parties did not have any role in the design of the study or in the explanation of the data.

Data availability
The datasets generated and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of the Guangzhou Eighth People's Hospital (202033166). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 18 July 2023 / Accepted: 14 January 2024
Published online: 29 January 2024

References

1. Global regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the global burden of disease study 2013. Lancet. 2015;385:117–71.

2. Lucas S, Nelson AM. HIV and the spectrum of human disease. J Pathol. 2015;235:229–41.
3. Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV cohort study. BMJ. 1997;315:1194–9.
4. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. N Engl J Med. 1998;338:853–60.
5. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA study group. Lancet. 1998;352:1725–30.
6. May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4 + cell count and viral load response to antiretroviral therapy. Aids. 2014;28:1193–202.
7. Pacheco YM, Jarrín I, Del AJ, et al. Risk factors, CD4 long-term evolution and mortality of HIV-infected patients who persistently maintain low CD4 counts, despite virological response to HAART. Curr Hiv Res. 2009;7:612–9.
8. Battegay M, Nüesch R, Hirschel B, Kaufmann GR. Immunological recovery and antiretroviral therapy in HIV-1 infection. Lancet Infect Dis. 2006;6:280–7.
9. Maggiolo F, Leone S. CD4 + T lymphocyte recovery in individuals with type 1 human immunodeficiency virus infection. Clin Infect Dis. 2010;51:465–7.
10. Young J, Psichogiou M, Meyer L, et al. CD4 cell count and the risk of AIDS or death in HIV-infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. Plos Med. 2012;9:e1001194.
11. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to < 500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis. 2005;41:361–72.
12. Baker JV, Peng G, Rapkin J, et al. CD4 + count and risk of non-AIDS diseases following initial treatment for HIV infection. Aids. 2008;22:841–8.
13. Aiuti F, Mezzaroma I. Failure to reconstitute CD4 + T-cells despite suppression of HIV replication under HAART. Aids Rev. 2006;8:88–97.
14. Spits H, Blom B, Jaleco AC, et al. Early stages in the development of human T, natural killer and thymic dendritic cells. Immunol Rev. 1998;165:75–86.
15. Isgrò A, Aiuti A, Leti W, et al. Immunodysregulation of HIV disease at bone marrow level. Autoimmun Rev. 2005;4:486–90.
16. Isgrò A, Leti W, De Santis W, et al. Altered clonogenic capability and stromal cell function characterize bone marrow of HIV-infected subjects with low CD4 + T cell counts despite viral suppression during HAART. Clin Infect Dis. 2008;46:1902–10.
17. de la Rosa R, Leal M, Rubio A, et al. Baseline thymic volume is a predictor for CD4 T cell repopulation in adult HIV-infected patients under highly active antiretroviral therapy. Antivir Ther. 2002;7:159–63.
18. Ruiz-Mateos E, Rubio A, Vallejo A, et al. Thymic volume is associated independently with the magnitude of short- and long-term repopulation of CD4 + T cells in HIV-infected adults after highly active antiretroviral therapy (HAART). Clin Exp Immunol. 2004;136:501–6.
19. Smith KY, Valdez H, Landay A, et al. Thymic size and lymphocyte restoration in patients with human immunodeficiency virus infection after 48 weeks of zidovudine, lamivudine, and ritonavir therapy. J Infect Dis. 2000;181:141–7.
20. Franco JM, Rubio A, Martínez-Moya M, et al. T-cell repopulation and thymic volume in HIV-1-infected adult patients after highly active antiretroviral therapy. Blood. 2002;99:3702–6.
21. Hunt PW, Deeks SG, Rodriguez B, et al. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. Aids. 2003;17:1907–15.
22. Greenblatt R, Bacchetti P, Boylan R, et al. Genetic and clinical predictors of CD4 lymphocyte recovery during suppressive antiretroviral therapy: whole exome sequencing and antiretroviral therapy response phenotypes. PLoS ONE. 2019;14:e219201.
23. Tanuma J, Matsumoto S, Haneuse S et al. Long-term viral suppression and immune recovery during first-line antiretroviral therapy: a study of an HIV-infected adult cohort in Hanoi, Vietnam. J Int Aids Soc. 2017; 20.
24. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV cohort study. Lancet. 2000;356:1800–5.
25. Miller MF, Haley C, Koziel MJ, Rowley CF. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. Clin Infect Dis. 2005;41:713–20.
26. Ma Y, Zhang F, Zhao Y, et al. Cohort profile: the Chinese national free antiretroviral treatment cohort. Int J Epidemiol. 2010;39:973–9.
27. Rb-Silva R, Goios A, Kelly C, et al. Definition of immunological nonresponse to antiretroviral therapy: a systematic review. J Acquir Immune Defic Syndr. 2019;82:452–61.
28. Moore RD, Keruly JC. CD4 + cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. Clin Infect Dis. 2007;44:441–6.
29. Micheloud D, Berenguer J, Bellón JM, et al. Negative influence of age on CD4 + cell recovery after highly active antiretroviral therapy in naive HIV-1-infected patients with severe immunodeficiency. J Infect. 2008;56:130–6.
30. Florence E, Lundgren J, Dreezen C, et al. Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. Hiv Med. 2003;4:255–62.
31. Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. J Infect Dis. 2001;183:1290–4.
32. Tumbarello M, Rabagliati R, de Gaetano DK, et al. Older age does not influence CD4 cell recovery in HIV-1 infected patients receiving highly active antiretroviral therapy. BMC Infect Dis. 2004;4:46.
33. Peters L, Mocroft A, Soriano V, et al. Hepatitis C virus coinfection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. J Acquir Immune Defic Syndr. 2009;50:457–63.
34. García F, de Lazzari E, Plana M, et al. Long-term CD4 + T-cell response to highly active antiretroviral therapy according to baseline CD4 + T-cell count. J Acquir Immune Defic Syndr. 2004;36:702–13.
35. Nakanjako D, Ssewanyana I, Mayanja-Kizza H, et al. High T-cell immune activation and immune exhaustion among individuals with suboptimal CD4 recovery after 4 years of antiretroviral therapy in an African cohort. BMC Infect Dis. 2011;11:43.
36. Mussini C, Lorenzini P, Cozzi-Lepri A, et al. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. Lancet HIV. 2015;2:e98–106.
37. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006;441:235–8.

Publisher's Note