Factors Associated with the Effectiveness of National Free Antiretroviral Treatment Program in HIV Infected Patients of Yi Nationality from Southwest China: Evidence from A Cohort Study to Provide Clues for Improvement

Liyu Chen
west china hospital, sichuan university
Shuang Kang
Sichuan University West China Hospital https://orcid.org/0000-0002-8390-7665
Lingyao Du
west china hospital
Fanghua Ma
People's hospital of Zhaojue county
Changmin Li
People's hospital of Zhaojue county
Lang Bai
West China hospital of Sichuan University
Hong Tang (htang6198@hotmail.com)
west china hospital, sichuan university

Research

Keywords: HIV/AIDS, antiretroviral treatment, virologic suppression, low level viremia, immune recovery

Posted Date: November 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-98257/v1

Factors associated with the effectiveness of National Free Antiretroviral Treatment Program in HIV infected patients of Yi nationality from southwest China: evidence from a cohort study to provide clues for improvement

Liyu Chen[1,2#], Shuang Kang[1,3#], Lingyao Du[1], Fanghua Ma[2], Changmin Li[2], Lang Bai[1], Hong Tang[1,3*]

Affiliations:

1. Center of Infectious Diseases, West China Hospital of Sichuan University, Chengdu, China, 610041;

2. Center of antiretroviral treatment, People's Hospital of Zhaojue County, Liangshan Yi Autonomous Prefecture, China, 616150;

3. Division of Infectious Diseases, State Key Laboratory of Biotherapy and Center of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, China, 610041.

 # The first two authors contributed equally to the manuscript.

*** Correspondence:**

Hong Tang

htang6198@hotmail.com

Abstract:

Background: Despite the current achievements of HIV management in the source-limited region of Liangshan Autonomous Prefecture, a small population remains with unsatisfactory virologic outcomes and suboptimal immune recovery. This cohort study aimed to identify potential risk factors of suboptimal clinical outcomes and to provide clues for improvement in people living with HIV (PLWH) from China's National Free Antiretroviral Treatment Program (NFATP) in Zhaojue County, Liangshan Autonomous Prefecture of Yi nationality.

Results: A total of 608 HIV infected adult patients in NFATP at the median age of 35(31, 40) were enrolled for analysis. During the 2.15(1.54, 4.00)-year follow-up, 502 (82.6%) patients achieved the viral load of <1000 copies/mL after over 6 months of antiretroviral therapy(ART). Among them, 398 (65.5%) cases achieved complete viral suppression with viral load <50 copies/mL while 104 (17.1%) cases remained with low level viremia (LLV, 50≤ viral load ≤1000 copies/mL). Patients with longer infection duration (OR =1.017 [95%CI: 1.002-1.033], p = 0.026), male gender (OR =1.632 [95%CI: 1.053-2.53], p = 0.028), positive hepatitis C virus antibody (OR =1.687 [95%CI: 1.093-2.604], p = 0.018) or infection through injecting drug use (IDU) (OR =1.584 [95%CI: 1.022-2.455], p = 0.04) were more likely to experience the undesirable outcome of LLV. Moreover, 254 (63.8%) of 398 patients with viral suppression achieved optimal immune recovery with the CD4 count ≥ 350 cells/μL. Patients with lower body mass index (BMI) (21.00±2.94 Kg/m^2, OR=0.921 [95%CI: 0.854-0.994], p = 0.034) and higher fasting blood glucose (4.99±1.01 mmol/L, OR=1.343 [95%CI: 1.087-1.658], p = 0.006) were less likely to achieve the CD4 count ≥ 350 cells/μL after viral suppression.

Conclusions: In this long-term cohort study of PLWH from Zhaojue County, Liangshan, most patients achieved virologic success on ART provided by NFATP but optimal immune recovery was yet to be expected. Approaches including strict control of illegal drug deal, patient education, and nutritional status management could be conducive to better prognosis for this population.

Keywords: HIV/AIDS; antiretroviral treatment; virologic suppression; low level viremia; immune recovery.

Background:

Human immunodeficiency virus (HIV) infection has been one of the major global challenges since 1981. Although effective ART has transformed HIV infection from a death sentence to a chronic controllable condition, certain intractable issues remain and a subset of the PLWH fail to achieve the expected recovery under current ART. It's of great urgency and importance to unravel the underlying cause to improve the treatment effectiveness in this population. At the end of 2019, there were approximately 958,000 PLWH in China. The dominant transmission route is heterosexual activities with a proportion of 71.5%, followed by homosexual of 23.3% and transmission by IDU has declined substantially to the level of 3% in 2018(1). Massive endeavor has been made for HIV/AIDS prevention and control, such as the NFATP initiated in 2002 and the rigorous implementation of "Five Expansions and Six Strengthens" since 2011. The overall treatment coverage increased to 83.4% at the end of 2018(2) and 89% of the PLWH with a viral load test in 2015 achieved viral suppression(3).

There is substantial regional variation across China in HIV epidemic and Liangshan is one of the areas with the highest HIV prevalence and very unique epidemics. It is a remote, impoverished district in southwest of China domiciled mostly with ethnic minority people of Yi nationality. Despite the relatively smaller population, people of Yi nationality accounts for 88.07% of new HIV infections from 2011-2013(4). The HIV prevalence rate in 5 counties of Liangshan was the highest across China(4) with an cumulative mortality rate of 10.02% during 2005-2015(5). The dominant transmission routes are heterosexual behaviors and IDU in Liangshan Prefecture, distinct from other regions in China. Multiple factors have given rise to the current heavy disease burden and management difficulties, including poverty, casual sexual culture, unique marriage practice and prior history of rampant drug transition. The rate of complete virologic suppression is reported as 58.2% in 2017(6), lower than that in other provinces in China. Evidence is urgently warranted to disclose the underlying problems and provide clues for further improvement. Nevertheless, there is a paucity of literature concerning the comprehensive medical characteristics of PLWH in this area recently, with most cross-sectional studies focused on the social and humanistic or epidemiological aspects. Zhaojue county is among the areas with highest HIV prevalence in Liangshan and is the

model county of NFATP with relatively complete records of patients. Thus, this study is aimed to retrospectively establish a cohort of HIV infected patients under regular ART and to assess the treatment effectiveness and identify risk factors of unsatisfactory immune recovery.

Results:

Demographics

A total of 608 patients in Yi nationality at the median age of 35 (31, 40) years old were enrolled in the cohort. The majority of patients (84.0%) were sexually active as married or cohabiting with their partners. IDU (52.1%) and heterosexual behaviors (46.1%) are the two dominant routes of infection, which is exemplary of the unique HIV epidemiology in this area. At ART initiation, the median infection duration was about 1 year with a high HIV VL of 5.21 (5.01, 5.35) $\log_{10}$ copies/mL indicating active viral replication but most patients (486, 79.9%) showed relatively good immune state with the CD4+ counts ≥ 350 cells/μL. It was worth attention that the HBV- and HCV-coinfection were strikingly serious in this cohort. According to previous surveys in the general Chinese population, the prevalence of HBV surface antigen (HBsAg) is 7.2%(7) and that of HCV antibody 1.0–2.9%(8). PLWH are at higher risk of HBV and HCV infection with HIV-HBV co-infection rate of 9.5% and HIV-HCV 8.3% in a study including PLWH from 12 provinces across 5 regions in China(9). The prevalence of HBsAg (11.3%) and HCV antibody (46.5%) in this cohort were both much higher than the general population as well as the overall PLWH across China, which might be attributed to the IDU-dominated transmission. As for initial ART regimens, 97.2% patients started with the first-line therapy of two NRTIs combined with one NNRTI and EFV was the preferred choice of NNRTIs.

Table 1. Baseline characteristics of study subjects

N=608	
Gender (cases, ratio)	
Male	322 (53.0%)
Age(years)	35 (31, 40)
Marital status (cases, ratio)	
Married/cohabiting	511 (84.0%)
Single/divorced/widowed	74 (12.2%)
Others	13 (2.1%)
Routes of infection	
IDU	317 (52.1%)
Heterosexual contact	280 (46.1%)
Homosexual contact	2 (0.3%)
Vertical transmission	2 (0.3%)

Others	5 (0.8%)
HIV VL (copies/mL)	5.21 (5.01, 5.35)
CD4+ count (cell/μL)	364 (230, 528)
<200	20 (3.3%)
200≤CD4+<350	102 (16.8%)
350≤CD4+<500	304 (50%)
>500	182 (29.9%)
Infection duration (years)	1.00 (0.25, 2.17)
ART regimen	
AZT+3TC+EFV	182 (29.9%)
AZT+3TC+NVP	20 (3.3%)
TDF+3TC+EFV	376 (61.8%)
TDF+3TC+NVP	11 (%)
AZT/ TDF+3TC+LPV/R	17 (2.8%)
HBV coinfection	69 (11.3%)
HCV coinfection	283 (46.5%)

All statistics are shown as median (IQR) or cases (percent).

Virologic treatment efficacy and associated factors

Till the end of 2.15 (1.54, 4.00)-year follow-up, 502 (82.6%) patients achieved virologic treatment success with the VL <1000 copies/mL after 6 months of ART among whom 398 (65.5%) cases achieved complete viral suppression with VL < 50 copies/mL, indicating the relatively satisfying treatment effectiveness. At ART initiation, the patients across three subgroups were with comparable HIV viral load and CD4 cell counts. But 16.9% of the patients experienced LLV and 17.6% of the patients were observed with viral failure. The male patients were overrepresented in the subgroup with LLV (58.7%) or viral failure (67.9%) compared with the subgroup with vial suppression (47.5%, p <0.001). The duration of infection was significantly longer and the duration of ART was significantly shorter in the subgroup with suboptimal virologic outcomes (LLV or viral failure) compared with the subgroup with vial suppression as shown in Table. Besides, there were substantially more patients with positive HCV Ab in the LLV or viral failure group (51.9% vs. 66.0% vs. 39.9%, respectively, $p < 0.001$).

For patients with viral failure, drug-resistant mutation detection and change of ART regimen are recommended while the management of patients with LLV has not yet reached a consensus. It's generally recommended to monitor these patients more closely for potential clinical evolutions, and possible interventions other than regimen modification might be implemented at the same time. Thus, comparison between the subgroups with viral suppression and LLV was conducted with

univariate analysis, aiming to identify potential intervention target for better outcomes. The results unraveled several risk factors for LLV including longer infection duration (OR =1.017 [95%CI: 1.002-1.033], $p = 0.026$), male gender (OR =1.632 [95%CI: 1.053-2.53], $p = 0.028$), positive HCV Ab (OR =1.687 [95%CI: 1.093-2.604], $p = 0.018$) and infection through IDU (OR =1.584 [95%CI: 1.022-2.455], $p = 0.04$). Although multivariate analysis failed to reveal any risk factors with statistical significance, it could be implied that enhanced screening to early detect HIV infected patients, rigorous actions to control illegal drug dealing and strengthened supervision on male patients to improve treatment compliance might provide certain benefits for PLWH in this area.

Table 2. Subject characteristics by virologic outcomes

	Viral suppression	LLV	Viral failure	*p*
N	398 (65.5%)	104 (17.1%)	106 (17.4%)	
Gender (cases, ratio)				
Male	189 (47.5)	61 (58.7%)	72 (67.9%)	<0.001
Age(years)	35 (31-41)	35 (30-40)	36 (31-40)	
Marital status (cases, ratio)				
Married/cohabiting	339 (85.2%)	89 (85.6%)	93 (85.6%)	
Single/divorced/widowed	48 (12.1%)	15 (14.4%)	11 (12.5%)	
Others	11 (2.8%)	0	2 (1.9%)	
Routes of infection				
IDU	192 (48.2%)	62 (59.6%)	63 (59.4%)	
Heterosexual contact	200 (50.3%)	37 (35.6%)	43 (40.6%)	
Homosexual contact	2 (0.5%)	0	0	
Vertical transmission	1 (0.3%)	0	0	
Others	3 (0.8%)	5 (2.0)	0	
Baseline HIV VL (copies/ML)	5.21 (5.03-5.36)	5.24 (4.99-5.36)	5.16 (4.92-5.34)	
Baseline CD4+ count (cell/μL)	369 (234-531)	336 (204-536)	364 (219-505)	
<200	75 (18.8%)	23 (22.1%)	24 (22.6%)	
200≤CD4+<350	115 (28.9%)	32 (30. 8%)	27 (25. 5%)	
350≤CD4+<500	87 (21.9%)	18 (17.3%)	25 (23.6%)	
>500	121 (30.4)	31 (29.8%)	30 (28.3%)	
Endpoint CD4+ count (cell/μL)	402 (278, 598)	365 (235, 472)	251 (166, 401)	< 0.001
Infection duration (years)	4.13 (3.25-4.75)	4.25 (3.31-4.92)	4.29 (3.08-5.08)	< 0.001
ART duration (years)	2.43 (1.66-4.00)	2.01(1.40-4.02)	2.02 (1.38-3.41)	0.008
Initial ART Regimen				
AZT+3TC+EFV	109 (27.4%)	34 (32.7%)	39 (36.8%)	
AZT+3TC+NVP	252 (63.3%)	62 (59.6%)	62 (58.5%)	
TDF+3TC+EFV	15 (3.8%)	2 (1.9%)	3 (2.8%)	
TDF+3TC+NVP	8 (2%)	2 (1.9%)	1 (0.9%)	
AZT/ TDF+3TC+LPV/r	14 (3.5%)	4 (1.6%)	1 (0.9%)	
HBV coinfection	40 (10.1%)	16 (15.3%)	13 (12.3%)	
HCV coinfection	159 (39.9%)	54 (51.9%)	70 (66.0%)	<0.001

Immunological treatment efficacy and associated factors

Despite the relatively satisfying virologic outcomes, only 254 (63.8%) of the 398 patients with viral suppression achieved optimal immune recovery with the CD4 counts ≥ 350 cells/μL. The approximate 2-year follow-up may be inadequate to determine immune non-responder since the increase of CD4 count could span more than 5 years. But early identification of relevant risk factors and timely intervention could potentially bring additional benefits. Therefore, logistic regression analysis was conducted. Since more and more studies have been looking into the metabolic diseases in PLWH and have found certain evidence indicating the association of metabolic profiles and ART outcomes, baseline metabolic profiles including BMI, fasting blood glucose, and blood lipids were also included in the analysis. All the patients in this subgroup analysis displayed a metabolic profile within normal ranges (data not shown). The risk factors significantly related to suboptimal immune recovery identified by multivariate analysis include baseline CD4 count (OR=1.000, [95%CI: 1.000-1.000], p = 0.004), BMI (21.00±1.94 Kg/m^2, OR=0.921 [95%CI: 0.854-0.994], p = 0.034) and fasting blood glucose (4.99±1.01 mmol/L, OR=1.343 [95%CI: 1.087-1.658], p = 0.006). After achieving viral suppression, patients with higher BMI, higher CD4+ T cell count, or lower baseline fasting blood glucose were more likely to experience optimal immune recovery with CD4 count ≥ 350 cells/μL.

Table 3. Subject characteristics by immunological outcomes

	Suboptimal immune recovery group (CD4+ count < 350 cells/μL)	**Immune recovery group (CD4+ count ≥ 350 cells/μL)**	***p***
N	144 (36.2%)	254 (63.8%)	
Gender(cases, ratio)			
Male	69 (17.34%)	120 (30.15)	
Age(years)	35 (32-42)	35 (30-40)	
Marital status (cases, ratio)			
Married/cohabiting	122 (84.7%)	217 (85.4%)	
Single/divorced/widowed	19 (13.2%)	29 (11.4%)	
Others	3 (2.2%)	8 (3.1%)	
Routes of infection			
IDU	74 (29.1%)	118 (46.5%)	
Heterosexual contact	67 (26.4%)	133 (52. 4%)	
Homosexual contact	1 (0.4%)	1 (0.4%)	
Vertical transmission	1 (0.4%)	0	
Others	1 (0.4%)	1 (0.4%)	
Baseline HIV VL (copies/mL)	5.16 (4.94-5.37)	5.2 (5.07-5.35)	

Baseline CD4+ count (cell/μL)	325 (230-521)	395 (241-542)	
<200	30 (11.8%)	45 (17.7%)	
200≤CD4+<350	49 (19.3%)	66 (26.0%)	
350≤CD4+<500	25 (9.8%)	62 (24.4%)	
>500	40 (15.7%)	81 (31.9%)	
Endpoint CD4+ count (cell/μL)	231 (172-290)	536 (413-707)	
Infection duration (years)	4.25 (3.13-4.83)	4.04 (3.25-4.75)	
ART duration	2.30 (1.58-3.88)	2.46 (1.71-4.04)	
ART regimen			
AZT+3TC+EFV	41 (16.1%)	68 (26.8%)	
AZT+3TC+NVP	93 (36.6%)	159 (62.6%)	
TDF+3TC+EFV	5 (2.0%)	10 (3.9%)	
TDF+3TC+NVP	1 (0.4%)	7 (2.8%)	
AZT/ TDF+3TC+LPV/r	4 (1.6%)	10 (3.9%)	
HBV coinfection	12 (8.3%)	28 (11.0%)	
HCV coinfection	62 (43.1%)	97 (38.2%)	0.021

Table 4. Factors related to suboptimal immune recovery as indicated by CD4+ T cell count

Factors	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	*p*	OR (95%CI)	*p*
Gender[a]	1.027(0.682-1.547)	0.897		
Age	1.013(0.986-1.040)	0.362		
Marital status[b]	0.946(0.533-1.676)	0.848		
Route of infection	0.926(0.760-1.129)	0.449		
Baseline HIV viral load (log_{10})	0.541(0.216-1.358)	0.191		
Baseline CD4+ T-cell count[*]	0.999(0.998-1.000)	0.123	1.000(1.000-1.000)	0.004
Baseline CD4/CD8 ratio	0.845(0.424-1.684)	0.632		
HBV coinfection	0.734(0.361-1.492)	0.392		
HCV coinfection	1.224(0.807-1.855)	0.341		
Treatment Duration	0.884(0.744-1.051)	0.162		
Adjustment of treatment	1.068(0.596-1.916)	0.825		
BMI[*]	0.915(0.847-0.988)	0.023	0.921(0.854-0.994)	0.034
Baseline total cholesterol	1.002(0.815-1.233)	0.984		
Baseline triglyceride	1.003(0.995-1.012)	0.417		
Baseline glucose[*]	1.341(1.091-1.647)	0.005	1.343(1.087-1.658)	0.006

Abbreviation: OR = Odds ratio; CI = confidence interval.

[a] referred to males.

[b] referred to those postulated to be without fixed sexual partners, i.e. those who were single/divorced/widowed and others.

[*] Variables reaching significance in multivariate analysis.

Discussion:

This study regularly followed up an HIV/AIDS cohort with all patients of Yi nationality from NFATP in source limited region for over two years. The patients were mostly mid-aged with balanced gender distribution and mostly infected through IDU or heterosexual behaviors. At

baseline, the patients were with relatively high HIV VL of around 5 $\log_{10}$ copies/mL and relatively high CD4 counts of cells/μL. After about 2-year ART, the majority patients achieved virologic treatment success (82.6%) or complete viral suppression (65.5%) but quite a proportion (36.2%) of patients showed suboptimal immune recovery. Longer infection duration, male gender, positive HCV Ab and infection through IDU were associated with LLV while lower BMI and higher fasting blood glucose were associated with suboptimal CD4 count recovery after viral suppression. To our knowledge, this study is one of the few cohort studies with long-term follow-up in this unique population, with interventions and surveillances in strict compliance with the national policy and with only government financed resources as far as possible. Thus, this study delineates detailed medical profiles of PLWH in Liangshan under management in NFATP and provides clues to maximize patients' clinical benefit without aggravating personal or national burden.

Viral suppression is the hallmark of HIV treatment success as well as optimal long-term prognosis. While definite viral failure, generally resulting from drug-resistant mutation, requires regimen modification, the grey zone of the persistent LLV remains a controversial issue concerning its clinical consequences and management. There were slightly more patients observed with LLV in this cohort than in other studies (16.9% vs 15.7%)(10). The speculation that LLV foreshadows subsequent viral failure is quite reasonable. Evidence from several studies has corroborated that LLV is strongly associated with viral failure with the HR of around 3.14-3.97 (11-14). But findings concerning the impact of LLV on clinical outcomes such as AIDS events and mortality failed to reach a consensus even in these studies. There are also studies reporting no association between transient LLV and adverse virologic and immunological outcomes(15-17). In this study, patients with LLV on ART displayed significantly lower CD4 count compared with patients with viral suppression at endpoint (402 [278, 598] vs 365 [235, 472], $p = 0.024$). There is the possibility that longer follow-up are required to explicitly disclose the influence of LLV on clinical outcomes. Besides, for such observations, more frequent monitoring such as every 3 or 6 months should be necessary to more aptly delineate the VL dynamics during ART.

Concerning the mechanism of LLV, a recent study has reported that most viral non-suppression episodes [173/1935 (8.9%)] were attributable to nonadherence in 30% and to pre-treatment drug

resistance (PDR) to NRTIs in 10% (18). Notably, at contemporary PDR prevalence of 10–25%, PDR would explain 13–30% of viral non-suppression(18). PDR has been one of the epidemic characteristics in Liangshan area. A survey in 2017 unraveled a PDR rate of 12.2% in this area, reported as the highest in China, and the subgroup of injecting drug users showed significantly higher PDR(19). In our analysis, infection through IDU (OR =1.584 [95%CI: 1.022-2.455], $p = 0.04$) is associated with higher risk of LLV. It's reasonable to speculate that transmission of PDR viral subtypes through IDU have contributed to relatively high prevalence of LLV. It's even more worrying that previous study reported 2.03-fold higher prevalence of PDR among patients diagnosed from 2017-2018 than that among patients diagnosed from 2009-2016, suggesting a rapidly growing PDR prevalence over time(95% CI: 1.18-5.76; P=0.018)(20). Rigorous actions to control illegal drug deal and education on the pernicious influence of IDU are in urgent need to improve the HIV epidemics in this area. Male gender (OR =1.632 [95%CI: 1.053-2.53], $p = 0.028$) is another risk factor of unsatisfactory CD4 count recovery identified in this study. It's widely accepted that ≥ 95% adherence to antiretroviral medications is required for optimal treatment effect. The viral suppression rate was reported to be 81% in patients with a >95% treatment compliance and dramatically decreased to 64% in those with 90~95% compliance(21). One study looking into self-management of PLWH in Liangshan area has found lower overall self-management scores and an even lower score in male patients, indicating poor adherence to ART medications(22). Moreover, a global survey revealed more IDU in men than in women in south Asia(23), which could also be the case in Liangshan area. Patient education and supervision should be strengthened to promote better self-management for improved long-term prognosis. Therefore, the unique characteristic of injecting drug users contributes a lot to the less satisfying treatment outcomes in Liangshan area. Closer monitoring of drug resistance, more rigorous treatment, pre-treatment drug resistance tests are potential approaches for better therapeutic effectiveness in this area.

Immune recovery as indicated by CD4 count increase or absolute CD4 count is another aim of HIV healthcare. After around 2-year ART, 63.8% of the patients with viral suppression achieved optimal immune recovery of ≥350 cells/μL in our cohort with the remaining displaying unsatisfactory immunological outcomes. However, the ART duration in some patients have not

reached 2 years at the endpoint, which is one of the criteria for immunological non-response proposed by one study after comprehensive comparison of different definitions across studies(24). Thus, these patients might retain the chance of experiencing optimal immune after prolonged ART. At the endpoint of our study, per the criteria of an absolute CD4+ T-cell count <350 cells/μL after ≥24 months of ART with viral suppression, there were 48 (18.1%) patients determined as immune non-responders, which is comparable to that reported in other studies (10-40%, depending on the definitions and cohorts)(25). Suboptimal immune recovery has long been proved to be associated with increased mortality and morbidity (26-29). Risk factors for this suboptimal response to treatment include older age, lower nadir CD4 count, coinfection with HBV/HCV/CMV(30, 31). The analysis of this cohort revealed factors related to suboptimal immune recovery less frequently reported in other studies, including BMI and fasting blood glucose. Although both indicators of the study cohort were within normal range, most HIV infected patients in Liangshan are known to be weakened by malnutrition, which would exacerbate metabolic disorders and accelerate hyper-catabolism(32-34). A randomized controlled trial reported that nutritional deficiency hampers CD4+ T cell recovery even during antiretroviral therapy(34) and higher BMI has been found to be significantly associated with long-term advantages in immune recovery on ART(35). Nutritional status assessment might be included in routine management of PLWH in this area for a better immunological response. Meanwhile, it seems paradoxical that higher fasting blood glucose within normal range is related to suboptimal immune recovery in our analysis. PLWH experience a 2- to 4-fold greater incidence of elevated fasting glucose or hyperinsulinemia than the general population(36). Glucose metabolic disorders together with other non-AIDS comorbidities is associated with chronic systemic inflammation and residual immune cell activation, which are known as status related to suboptimal immune recovery(37). A study of HIV+ patients with impaired glucose tolerance defined impaired fasting glucose as 5.56-6.94 mmol/L(38), which is comparable to that (4.99±1.01 mmol/L) of patients in our cohort. It's reasonable to interpret our patients as with impaired fasting glucose, especially when the patients' lower BMI is taken into consideration. Under this speculation, higher fasting blood glucose indicates poor glucose tolerance with pro-inflammatory effect, further contributing to poor immune recovery.

Although the detailed profiles of HIV patients from NFATP delineated in this study could provide important clues to better deployment of HIV management for achieving the 90-90-90 targets, there are certain limitations. The follow-up period was not long enough to observe long-term outcomes of these patients and the information obtained merely from observation was inadequate to delve into the underlying mechanisms in issues such as LLV and suboptimal immune recovery. Based on evidence from this study, elaborately-designed trial with more frequent monitoring and drug resistant mutation detection is expected to provide more evidence to guide better HIV management in Zhaojue county, Liangshan Prefecture.

Conclusions

PLWH in Zhaojue County, Liangshan is a unique population with high prevalence of IDU and HIV-HBV/HCV coinfection, which is associated with suboptimal immune recovery despite satisfactory virologic outcomes after ART. The majority achieved virologic treatment success but improvement is in urgent need for patients with LLV and those with suboptimal immune recovery. Close monitoring, integrated management including nutrition status management and treatment compliance education and stringent control of illegal drug deal by relevant local authorities should be conducive.

Methods

Study aim and design

This is a retrospective cohort study aimed to assess the clinical outcomes of PLWH from NFATP and explore risk factors associated with suboptimal outcomes, so as to provide clues for better better HIV management in Zhaojue county, Liangshan Prefecture.

Subject enrollment

NFATP provides free ART as well as free routine follow-up tests, including hematology, urinalysis and blood liver function every 6 months; renal function for patients taking tenofovir disoproxil fumarate (TDF) and serum lipid for patients taking lopinavir/ritonavir (LPV/r) every 6 months; CD4+ count and HIV viral load (VL) every year. A national data system has been established for NFATP, designed to record comprehensive patient profiles including sociodemographics, baseline medical condition and follow-up data. Considering the local

implementation of relevant policies and that the changed clinical practice after the release of guidelines for HIV prevention and control, the 3rd version, patients from NFATP who initiated ART between January 1, 2015 and December 31, 2017 were screened. Patients were included who i) were ≥18 years old at ART initiation; ii) had confirmed HIV diagnosis by Western Blot; iii) had routine lab tests performed; iv) had follow-up records of test results available. The baseline was the date of recorded ART initiation and the endpoint was defined as December 31, 2019, death, regimen switched to charged options because of personal choice or medical needs, whichever came first. The details of patient screening are shown in Figure 1.

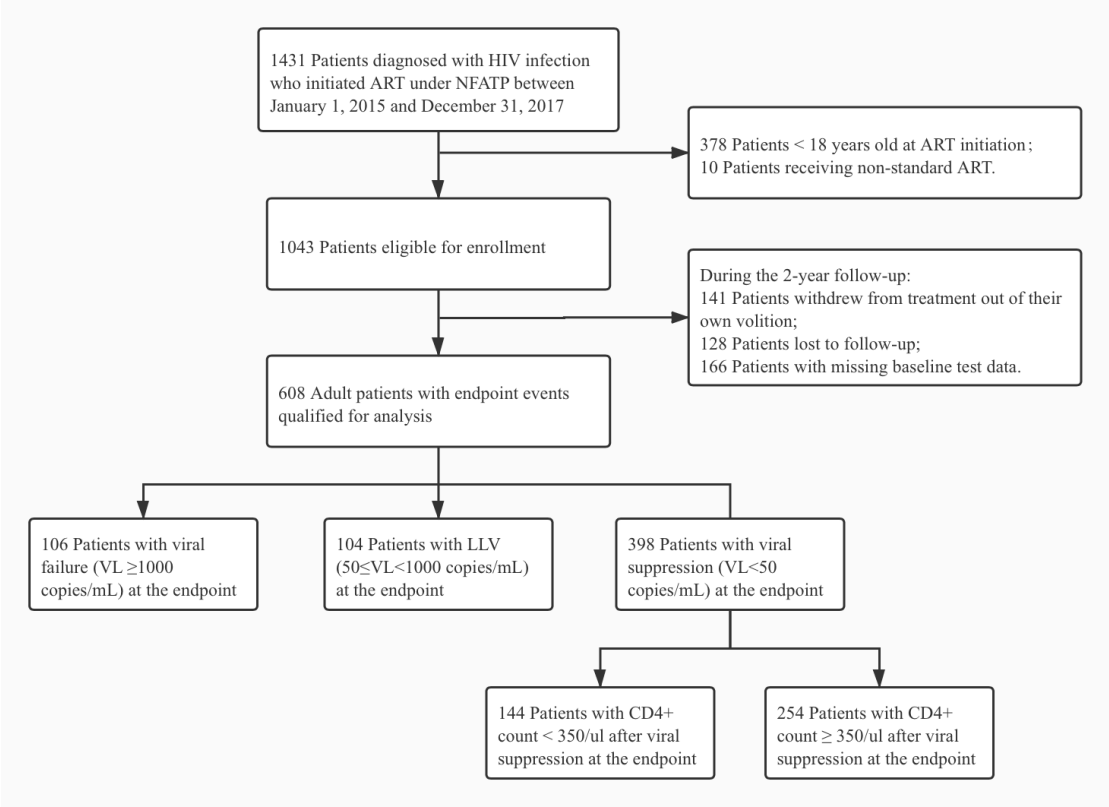

Figure 1 Flowchart of subject enrollment.

Variables, definitions and outcomes

The definitions of some terminology varies across various studies due to different detection techniques and study population. The definitions to be clarified in this study include:

- Viral suppression was defined as the viral load < 50 copies/mL, viral failure was defined as the viral load ≥ 1000 copies/mL and low-level viremia (LLV) was defined as the viral load of 50-999 copies/mL after 6 months of ART;

  Note: the definition of viral failure in Chinese guidelines for diagnosis and treatment of HIV/AIDS (2018) is a viral load persistently > 200 copies/mL after 1 year of ART. But

considering the local circumstances, the lower limit of 1000 copies/mL in WHO guidelines, 2016 is adopted.

- Immune recovery is the most controversial terms differing greatly across studies. Generally, immune recovery is measured as absolute CD4+ count or the absolute or percentage increase of CD4+ count with suppressed viral replication after certain period of ART(39). The cutoff values of CD4+ count for optimal and suboptimal immune recovery are 200, 250, 350, 400 and 500 cells/μL and the duration of ART varies from 1 to 12 years across studies. In this study, the relatively well-recognized criteria was adopted as suboptimal immune recovery, that is, CD4+ count <350 cells/μL at endpoint with VL < 50 copies.
- Regimen switch. Six out of all the free antiretroviral regimens were applied in this area, namely TDF + lamivudine (3TC) + efavirenz (EFV), zidovudine (AZT) + 3TC + EFV, AZT + 3TC + nevirapine (NVP), AZT+3TC+LPV/r, TDF+3TC+NVP and TDF+3TC+LPV/r. Regimen switch between these regimens after ART initiation were recorded regardless of the rationale for switch.
- The main outcomes of the analysis were the rate of viral suppression and optimal immune recovery at endpoint and the secondary outcomes were the risks factors associated with suboptimal immune recovery at endpoint.

Statistics

Data were extracted from the NFATP Data System and exported to SPSS 24.0 (IBM, Armonk, New York, US). The category variables were described as number and percent and analyzed with chi-square test. The continuous variables were described as median and interquartile range (IQR) or mean and standard deviation (SD) and analyzed by *U* test or *t* test as appropriate. Univariate and multivariate log-binomial regression models were used to assess determinants of suboptimal immune recovery, producing odds ratios (ORs) and confidence intervals (CIs). All *p*-values were 2-sided, and $p < 0.05$ was considered statistically significant.

List of abbreviations

3TC	Lamivudine
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
AZT	Zidovudine
BMI	Body mass index
CI	Confidence interval
EFV	Efavirenz

HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDU	Injecting drug use
LLV	Low level viremia
LPV/r	Lopinavir/ ritonavir
NFATP	National Free Antiretroviral Treatment Program
NNRTI	Non-nucleotide reverse transcriptase inhibitor
NRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
OR	Odds ratio
PDR	Pre-treatment drug resistance
PLWH	People living with HIV
SD	Standard deviation
TDF	Tenofovir disoproxil fumarate
VL	Viral load

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of West China Hospital of Sichuan University and written informed consents were acquired from all participants (Annual Audit No. 450, Version 2020.5).

Consent for publication

Not applicable.

Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This study was supported by the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (No. ZYGD20009).

Authors' contributions

HT and LB proposed the conception and designed the study. LC, LD, SK, FM and CL implemented the study and collected the data. LC and SK analyzed the data. SK drafted the manuscript. LB and HT revised the manuscript. HT provided fund support and approved the submitted version

Acknowledgments

Not applicable.

References:

1. Ding Y, Ma Z, He J, Xu X, Qiao S, Xu L, et al. Evolving HIV Epidemiology in Mainland China: 2009-2018. Curr HIV/AIDS Rep. 2019;16(6):423-30.
2. Prevention NCfASCa, Prevention CfDCa. Annals of information on comprehensive prevention and treatment for AIDS, STD and hepatitis C. 2018.
3. Ma Y, Dou Z, Guo W, Mao Y, Zhang F, McGoogan JM, et al. The Human Immunodeficiency Virus Care Continuum in China: 1985-2015. Clin Infect Dis. 2018;66(6):833-9.
4. Zhao QG, Gong YH, Liao Q, Yu G, Wang K, Wang J, et al. [Estimation on the HIV-1 incidence in Liangshan Yi Autonomous Prefecture, under BED-capture enzyme immunoassay, from 2011 to 2013]. Zhonghua Liu Xing Bing Xue Za Zhi. 2016;37(8):1105-7.
5. Jiang X, Xu JL, Jike KCN, Yu G, Yu HL, Wang J, et al. [Epidemiological analysis of the deaths with antiretroviral treatment among adult HIV/AIDS patients in Liangshan Yi Autonomous Prefecture from 2005 to 2015]. Zhonghua Liu Xing Bing Xue Za Zhi. 2019;40(9):1116-9.
6. Yuan D, Liu M, Jia P, Li Y, Huang Y, Ye L, et al. Prevalence and determinants of virological failure, genetic diversity and drug resistance among people living with HIV in a minority area in China: a population-based study. BMC Infect Dis. 2020;20(1):443.
7. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. Vaccine. 2009;27(47):6550-7.

8. Cui Y, Jia J. Update on epidemiology of hepatitis B and C in China. J Gastroenterol Hepatol. 2013;28 Suppl 1:7-10.
9. Xie J, Han Y, Qiu Z, Li Y, Li Y, Song X, et al. Prevalence of hepatitis B and C viruses in HIV-positive patients in China: a cross-sectional study. J Int AIDS Soc. 2016;19(1):20659.
10. Elvstam O, Medstrand P, Yilmaz A, Isberg PE, Gisslen M, Bjorkman P. Virological failure and all-cause mortality in HIV-positive adults with low-level viremia during antiretroviral treatment. PLoS One. 2017;12(7):e0180761.
11. Bernal E, Gomez JM, Jarrin I, Cano A, Munoz A, Alcaraz A, et al. Low-Level Viremia Is Associated With Clinical Progression in HIV-Infected Patients Receiving Antiretroviral Treatment. J Acquir Immune Defic Syndr. 2018;78(3):329-37.
12. Joya C, Won SH, Schofield C, Lalani T, Maves RC, Kronmann K, et al. Persistent Low-level Viremia While on Antiretroviral Therapy Is an Independent Risk Factor for Virologic Failure. Clin Infect Dis. 2019;69(12):2145-52.
13. Vandenhende MA, Perrier A, Bonnet F, Lazaro E, Cazanave C, Reigadas S, et al. Risk of virological failure in HIV-1-infected patients experiencing low-level viraemia under active antiretroviral therapy (ANRS C03 cohort study). Antivir Ther. 2015;20(6):655-60.
14. Havlir DV, Bassett R, Levitan D, Gilbert P, Tebas P, Collier AC, et al. Prevalence and predictive value of intermittent viremia with combination hiv therapy. JAMA. 2001;286(2):171-9.
15. Eastburn A, Scherzer R, Zolopa AR, Benson C, Tracy R, Do T, et al. Association of low level viremia with inflammation and mortality in HIV-infected adults. PLoS One. 2011;6(11):e26320.
16. Quiros-Roldan E, Raffetti E, Castelli F, Foca E, Castelnuovo F, Di Pietro M, et al. Low-level viraemia, measured as viraemia copy-years, as a prognostic factor for medium-long-term all-cause mortality: a MASTER cohort study. J Antimicrob Chemother. 2016;71(12):3519-27.
17. Garcia-Gasco P, Maida I, Blanco F, Barreiro P, Martin-Carbonero L, Vispo E, et al. Episodes of low-level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome. J Antimicrob Chemother. 2008;61(3):699-704.
18. Inzaule SC, Bertagnolio S, Kityo CM, Siwale M, Akanmu S, Wellington M, et al. The relative contributions of HIV drug resistance, nonadherence and low-level viremia to viremic episodes on antiretroviral therapy in sub-Saharan Africa. AIDS. 2020;34(10):1559-66.
19. Kang RH, Liang SJ, Ma YL, Liang S, Xiao L, Zhang XH, et al. Pretreatment HIV drug resistance in adults initiating antiretroviral therapy in China, 2017. Infect Dis Poverty. 2020;9(1):54.
20. Liu L, Dong A, Liao L, Feng Y, Shao Y, Liang S, et al. Survey of Pretreatment HIV Drug Resistance and Genetic Transmission Network Analysis Among HIV Patients in a High Drug-Use Area of Southwest China. Curr HIV Res. 2019;17(6):441-51.
21. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al.

399 Adherence to protease inhibitor therapy and outcomes in patients with HIV infection.
400 Ann Intern Med. 2000;133(1):21-30.
401 22. Wang H, Chen AC, Wan S, Chen H. Status and associated factors of self-
402 management in people living with HIV/AIDS in Liangshan area, China: a cross-
403 sectional study. Patient Prefer Adherence. 2019;13:863-70.
404 23. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al.
405 Global prevalence of injecting drug use and sociodemographic characteristics and
406 prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic
407 review. Lancet Glob Health. 2017;5(12):e1192-e207.
408 24. Rb-Silva R, Goios A, Kelly C, Teixeira P, Joao C, Horta A, et al. Definition of
409 Immunological Nonresponse to Antiretroviral Therapy: A Systematic Review. J Acquir
410 Immune Defic Syndr. 2019;82(5):452-61.
411 25. Nakanjako D, Kiragga AN, Musick BS, Yiannoutsos CT, Wools-Kaloustian K,
412 Diero L, et al. Frequency and impact of suboptimal immune recovery on first-line
413 antiretroviral therapy within the International Epidemiologic Databases to Evaluate
414 AIDS in East Africa. AIDS. 2016;30(12):1913-22.
415 26. Massanella M, Negredo E, Clotet B, Blanco J. Immunodiscordant responses to
416 HAART--mechanisms and consequences. Expert Rev Clin Immunol. 2013;9(11):1135-
417 49.
418 27. Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, et al. HIV-
419 infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term
420 combination antiretroviral therapy reach same mortality rates as the general population.
421 J Acquir Immune Defic Syndr. 2007;46(1):72-7.
422 28. Antiretroviral Therapy Cohort C. Life expectancy of individuals on combination
423 antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort
424 studies. Lancet. 2008;372(9635):293-9.
425 29. Engsig FN, Gerstoft J, Kronborg G, Larsen CS, Pedersen G, Roge B, et al. Long-
426 term mortality in HIV patients virally suppressed for more than three years with
427 incomplete CD4 recovery: a cohort study. BMC Infect Dis. 2010;10:318.
428 30. Collazos J, Valle-Garay E, Carton JA, Montes AH, Suarez-Zarracina T, De la
429 Fuente B, et al. Factors associated with long-term CD4 cell recovery in HIV-infected
430 patients on successful antiretroviral therapy. HIV Med. 2016;17(7):532-41.
431 31. Kroeze S, Ondoa P, Kityo CM, Siwale M, Akanmu S, Wellington M, et al.
432 Suboptimal immune recovery during antiretroviral therapy with sustained HIV
433 suppression in sub-Saharan Africa. AIDS. 2018;32(8):1043-51.
434 32. Fajardo-Rodriguez A, Lara del Rivero-Vera CM. [Nutritional intervention in
435 HIV/AIDS: practical guide for its implementation and follow-up]. Gac Med Mex.
436 2001;137(5):489-500.
437 33. Roubenoff R. The pathophysiology of wasting in the elderly. J Nutr. 1999;129(1S
438 Suppl):256S-9S.
439 34. Sun PT, Yu W, Li TS, Lin Q, Guo FP, Zhou XH, et al. Association of Body
440 Composition and Other Clinical Factors with Incomplete Immune Response after

Highly Active Antiretroviral Therapy. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2017;39(4):459-64.
35. Koethe JR, Jenkins CA, Lau B, Shepherd BE, Wester W, Rebeiro PF, et al. Higher Time-Updated Body Mass Index: Association With Improved CD4+ Cell Recovery on HIV Treatment. J Acquir Immune Defic Syndr. 2016;73(2):197-204.
36. Brown TT, Li X, Cole SR, Kingsley LA, Palella FJ, Riddler SA, et al. Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the Multicenter AIDS Cohort Study. AIDS. 2005;19(13):1375-83.
37. Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS. 2015;29(4):463-71.
38. Best C, Struthers H, Laciny E, Royal M, Reeds DN, Yarasheski KE. Sitagliptin Reduces Inflammation and Chronic Immune Cell Activation in HIV+ Adults With Impaired Glucose Tolerance. J Clin Endocrinol Metab. 2015;100(7):2621-9.
39. Yang X, Su B, Zhang X, Liu Y, Wu H, Zhang T. Incomplete immune reconstitution in HIV/AIDS patients on antiretroviral therapy: Challenges of immunological non-responders. J Leukoc Biol. 2020;107(4):597-612.

Figures

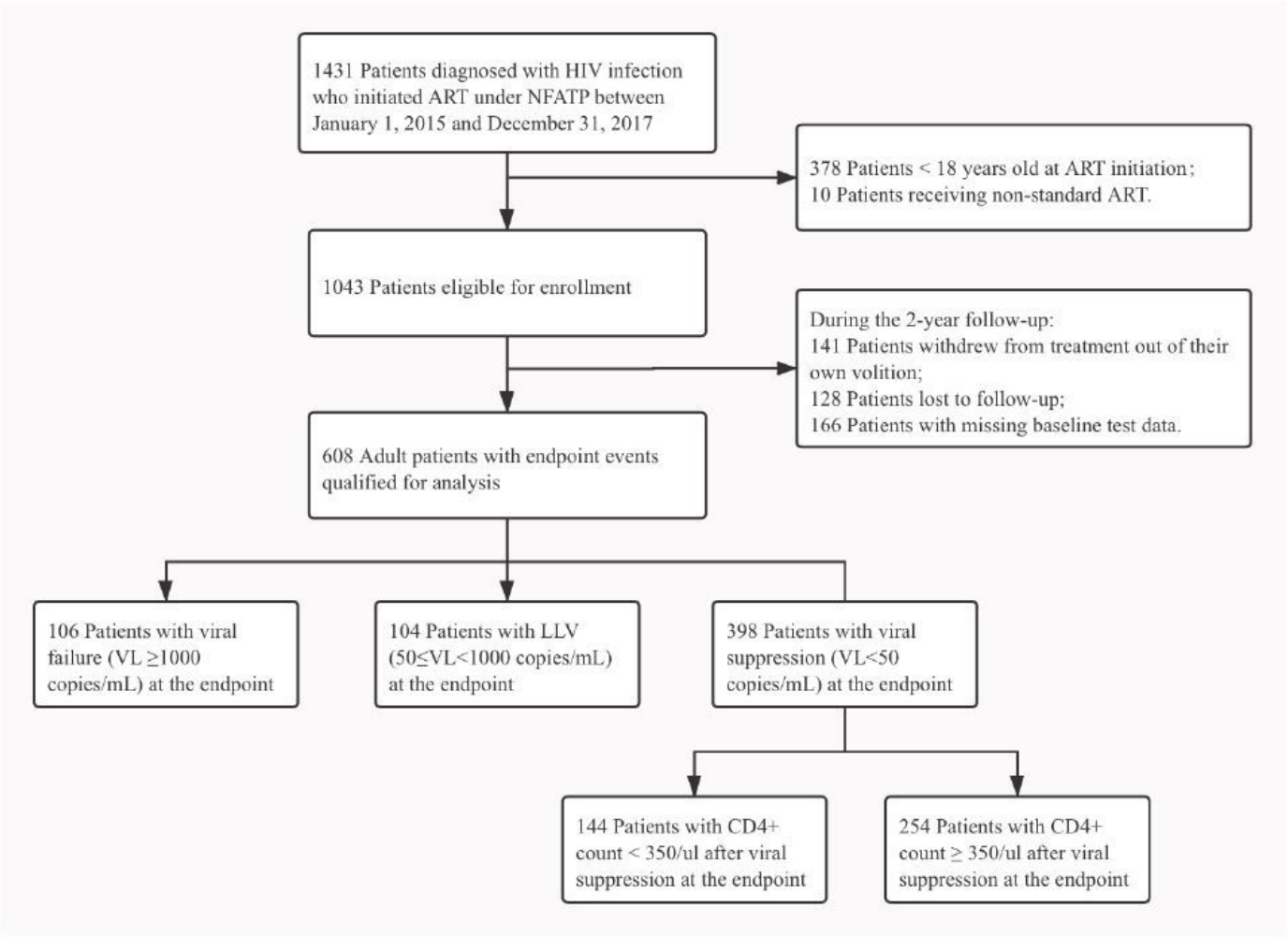

Figure 1

Flowchart of subject enrollment.