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Original Article

Effect of immunological non-response on incidence of Non-AIDS events in people living with HIV: A retrospective multicenter cohort study in Taiwan

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Abstract *Background:* People living with HIV (PLWH) are susceptible to non-AIDS-related events, particularly those with immunological nonresponses (INRs) to highly active antiretroviral therapy (HAART). This study assessed the association of INRs with incident non-AIDS-related events among PLWH.

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response

Methods: This multicenter retrospective cohort study enrolled PLWH who had newly diagnosed stage 3 HIV and received HAART between January 1, 2008, and December 31, 2019. The patients were divided into two groups according to their immunological responses on the 360th day after HAART initiation: INR and non-INR groups. Cox regression and sensitivity analyses were conducted to estimate the effects of INRs on overall and individual categories of non-AIDS-related events (malignancies, vascular diseases, metabolic disorders, renal diseases, and psychiatric disorders). Patient observation started on the 360th day after HAART initiation and continued until February 28, 2022, death, or an outcome of interest, whichever occurred first.

Results: Among the 289 included patients, 44 had INRs. Most of the included patients were aged 26—45 years (69.55%) and were men who have sex with men (89.97%). Many patients received HIV diagnoses between 2009 and 2012 (38.54%). INRs (vs. non-INRs) were associated with composite non-AIDS-related events (adjusted hazard ratio [aHR] = 1.80; 95% confidence interval [CI]: 1.19—2.73) and metabolic disorders (aHR = 1.75; 95% CI: 1.14—2.68). Sensitivity analyses revealed consistent results for each Cox regression model for both composite non-AIDS-related events and metabolic diseases.

Conclusion: Clinicians should be vigilant and implement early intervention and rigorous monitoring for non-AIDS-related events in PLWH with INRs to HAART.

Introduction

The introduction of highly active antiretroviral therapy (HAART) has engendered considerable reductions in the mortality and morbidity of people living with HIV (PLWH).[1] Although the life expectancy of PLWH is approaching that of people without HIV, the difference in comorbidity-free years between PLWH and the general population has persisted over time.[2] Non-AIDS events, including non-AIDS-related malignancies, cardiovascular events, renal and hepatic diseases, bone disorders, and neurocognitive impairment, have become the primary causes of morbidity and mortality since the introduction of potent HAART.[3—5]

Several factors are associated with the occurrence of non-AIDS-related events in PLWH. The direct effects of HIV—that is, low nadir $CD4^+$ T-cell count before antiretroviral therapy and low level of $CD4^+$ T-cell recovery after HAART, coinfections, and comorbidities—were reported to be significantly associated with the occurrence of non-AIDS-related events.[6] In the context of these factors, an immunological nonresponse (INR) is still a public health concern. Studies have revealed that approximately 25%—34% of PLWH receiving HAART failed to achieve concordant complete immunovirological responses.[7,8] The pathogenesis of suboptimal immunological responses remains unclear. The causes of immune system failure, such as thymus dysfunction and imbalanced cytokine production, may lead to T-cell activation or apoptosis.[9] Chronic inflammation and inappropriate immune responses may increase the risks of cardiovascular disease and non-AIDS-defining cancers.[10] Scholars have yet to reach a consensus regarding the definition of an optimal immunological response to HAART. For example, several studies have defined an INR as a failure to achieve an absolute increase in the $CD4^+$ T-cell count at a specific time point after HAART initiation; however, other studies have argued that an INR should be represented by a CD4+ T-cell count exceeding a specific threshold, regardless of the initial CD4+ T-cell count after HAART initiation.[11] The timing of HAART initiation has mostly been determined using T-cell count thresholds in accordance with established guidelines; for example, a couple of studies have applied a T-cell count threshold of <200 or <350 cells/μL to determine the timing of HAART initiation.[12,13] On the basis of the aforementioned INR definitions, studies have reported INR rates ranging from 10% to 30%.[8,14]

According to the literature, INRs are associated with an increased risk of non-AIDS-related events. The AIDS Therapy Evaluation in the Netherlands cohort study revealed that 3068 (27.5%) PLWH failed to reach a $CD4^+$ T-cell count of 350 cells/μL at 2 years after combination antiretroviral therapy (cART) initiation; the study indicated that this failure was associated with increased risks of fatal and nonfatal diseases and events, including non-AIDS-defining and cardiovascular diseases and even death.[13] However, a limitation of the aforementioned study is its exclusion of confounding variables (e.g., sex and use of protease inhibitors) from its multivariate model. Furthermore, a multicenter prospective cohort study conducted in Italy between January 1, 1996, and December 31, 2009, reported an association between INRs and non-AIDS-related events among 1221 PLWH.[15] However, the mentioned study examined only the association between INRs and composite outcomes—including malignancies, severe infections, cardiovascular events, renal events, hepatic events, AIDS-defining events, and death—instead of specific non-AIDS-related events, such as cardiovascular and neuropsychiatric disorders and chronic kidney disease. Determining the association between INRs and specific non-AIDS-related events is crucial because the recommended interventions and treatment strategies for individuals exhibiting INRs may vary depending on this association. HAART has been substantially improved over the past two decades with the

introduction of simplified, less toxic, and more effective regimens. In Taiwan, changes in dietary habits and lifestyles have led to increased consumption of cakes, sweets, and sugary drinks as well as the adoption of more sedentary lifestyles, resulting in increased prevalence rates of metabolic syndrome, diabetes, hypertriglyceridemia, and gout.[16] Therefore, a contemporary study determining the association between INRs and incident non-AIDS-related events is warranted.

The present study assessed the association between INRs and specific non-AIDS-related events to determine risk factors for long-term non-AIDS-related events in PLWH.

Methods

Study design and setting

We conducted this retrospective cohort study at three hospitals designated for HIV treatment: Kaohsiung Medical University Hospital (the largest referral center for treating PLWH in southern Taiwan), Kaohsiung Municipal Siaogang Hospital (a regional hospital in southern Taiwan), and Kaohsiung Municipal Ta-Tung Hospital (a regional hospital in southern Taiwan). The institutional review boards of the participating hospitals (KMUHIRB-SV[I]-20220078) approved the study protocol, and the need for written informed consent was waived.

Participants and study procedure

We screened the outpatient and inpatient department records of each participating hospital. PLWH with newly diagnosed stage 3 HIV—defined according to the US Centers for Disease Control (CDC) 2014 case definition of HIV infection[17]—who received HAART between January 1, 2008, and December 31, 2019, were enrolled. We defined the date of HAART initiation as the enrollment date. Moreover, we defined the first date of the observation period as the 360th day after HAART initiation. We excluded PLWH who had an initial $CD4^+$ T-cell count of $\geq$200 cells/μL and those who were lost to follow-up within 360 days of HAART initiation. In addition, we excluded PLWH who had non-AIDS-related events of interest at baseline and those who developed non-AIDS-related events of interest within 360 days of HAART initiation.

At the start of the observation period, we divided the included patients into two groups according to their immunological responses on the 360th ($\pm$30) day after HAART initiation: a non-INR group, comprising patients with immunological responses, and an INR group, comprising patients with INRs. We started the patient observation from the 360th day after HAART initiation to February 28, 2022, death, or the outcome of interest, whichever occurred first.

Working definitions

An INR, the variable of interest, was defined as having a $CD4^+$ T-cell count of $<$200 cells/μL at the 360th ($\pm$30) day after HAART initiation.

We examined several non-AIDS-related events: cardiovascular events, cerebrovascular events, peripheral arterial occlusive disease, dyslipidemia, dysglycemia, hypertension, chronic kidney disease, non-AIDS-related malignancies, and psychiatric diseases (Supplementary Table 1). A cardiovascular event was defined in accordance with the 2021 American Heart Association (AHA) guidelines as an acute coronary syndrome, which includes unstable angina, non—ST segment elevation myocardial infarction, and ST segment elevation myocardial infarction.[18] Cerebrovascular events were categorized as ischemic or hemorrhagic strokes confirmed through brain imaging (computed tomography [CT] or magnetic resonance imaging). Peripheral arterial occlusive disease was defined in accordance with the 2022 AHA guidelines as an ankle—brachial index of $\leq$0.9 or as an occlusion confirmed through CT or angiography.[19] Dyslipidemia was defined in accordance with the 2019 European Society of Cardiology and European Atherosclerosis Society *Guidelines for the Management of Dyslipidemias* as the occurrence of two consecutive measurements of serum low-density lipoprotein (LDL) levels of $>$130 mg/dL.[20] Dysglycemia was indicated by two consecutive measurements of fasting blood sugar levels of $>$100 mg/dL, included impaired fasting glucose and diabetes mellitus, and was defined in accordance with the 2022 American Diabetes Association Standard of Medical Care in Diabetes.[21] Hypertension was diagnosed using the *Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension*[22] and was categorized according to the time of diagnosis and initiation of antihypertensive agent treatment. Chronic kidney disease was defined as an estimated glomerular filtration rate of $<$60 mL/min/1.73 m^2 for three or more months in accordance with the Kidney Disease Improving Global Outcomes *2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease*.[23] Non-AIDS-related malignancy was defined as any malignancy other than AIDS-related malignancies. AIDS-related malignancies were defined using the US CDC 2014 guidelines.[17] The malignancies considered were cervical cancer, Kaposi's sarcoma, primary central nervous system lymphoma, Burkitt lymphoma, and immunoblastic lymphoma (or equivalent term). Psychiatric diseases were defined using diagnostic codes for depression, mania, psychosis, and anxiety but not diagnostic codes for psychiatric diseases related to substance use disorder. All psychiatric diseases were diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders* guidelines.

The non-AIDS-related events of interest were further divided into five categories: vascular diseases (cardiovascular disease, cerebrovascular disease, and peripheral arterial occlusive disease), metabolic diseases (dyslipidemia, dysglycemia, and hypertension), malignancies (non-AIDS-related malignancies), renal disease (chronic renal disease), and psychiatric diseases (Supplementary Table 2).

Primary and secondary outcomes

The primary outcome of the study was the survival analysis of the influence of INR on the composite non-AIDS-related events, including: cardiovascular events, cerebrovascular

events, peripheral arterial occlusive disease, dyslipidemia, dysglycemia, hypertension, chronic kidney disease, non-AIDS-related malignancies, and psychiatric diseases. We considered individuals who had any of these non-AIDS-related events as experiencing the primary outcome. Moreover, the secondary outcome was the cause-specific survival analysis of the influence of INR on the non-AIDS-related events in the following categories: vascular diseases, metabolic diseases, renal diseases, malignancies, and psychiatric diseases. We considered individuals who had events in any of these categories as experiencing the secondary outcome.

Statistical analysis

Categorical variables are presented using frequency tables. We analyzed between-group differences in several characteristics by using Fisher's exact test or the χ^2 test for categorical variables.

We estimated the unadjusted cumulative probabilities of the incidence of composite non-AIDS-related events over time by using the Kaplan–Meier method and log-rank test. We also performed univariable and Cox regression analyses with backward selection to examine variables associated with time to the occurrence of composite non-AIDS-related events. The covariables in the Cox regression included sociodemographic variables (gender, age group at HIV presentation, period of starting HAART, HIV transmission route, occupation, and marital status), composite AIDS-defining opportunistic illness, laboratory examination (CD4 count at start of HAART, plasma viral load at start of HAART and hepatitis virus markers), and type of first-line HAART at initiation. In our cause-specific survival analyses, we estimated the cumulative probabilities of the incidence of each categorized non-AIDS-related events of interest and analyzed the association between INRs and each group outcome by using univariable and Cox regression analyses with backward selection. A two-sided P value of <0.05 indicated significance.

Finally, we conducted a sensitivity analysis to determine the robustness of the significant associations of INRs with the incident composite non-AIDS-related events and categorized events, as determined in the aforementioned cause-specific survival analyses. The covariables in the sensitivity analysis were the same with those in the original model. This sensitivity analysis included patients with different durations of observation after HAART initiation and different thresholds of $CD4^+$ T-cell recovery after HAART initiation. We used two models for our analysis (Supplementary Table 3). All statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC, USA).

Results

Patient selection process

This study enrolled a total of 522 patients who had newly diagnosed stage 3 HIV and received HAART between January 1, 2008, and December 31, 2019. Of these patients, 233 were excluded; specifically, we excluded patients with initial $CD4^+$ T-cell counts of $\geq$200 cells/μL (n = 16), those with no follow-up $CD4^+$ T-cell count (n = 39), those lost to follow-up or dying within 360 days after cART initiation (n = 38), those with non-AIDS-related events of interest at baseline (n = 30), and those experiencing any episodes of the outcomes of interest within 360 days of cART initiation (n = 110). We divided the remaining 289 patients into a non-INR group (n = 245) and an INR group (n = 44) according to their immunological responses on the 360th day after HAART initiation (i.e., the first day of the observation period; Fig. 1).

Characteristics of patients in the two groups

The patients' baseline sociodemographic characteristics, composite AIDS-defining opportunistic infections, laboratory profiles, and first-line cART types at initiation are listed in Table 1.

The majority of the patients were men (98.27%), were aged 26–45 years (69.55%), were men who have sex with men (89.97%), had a $CD4^+$ T-cell count of 51–199 cells/μL at cART initiation (59.17%), had a plasma viral load of $>$100,000 copies/mL at cART initiation (68.17%), and started cART with a nonnucleoside reverse transcriptase inhibitor (nNRTI)-based regimen (59.52%). Moreover, 38.54% of the patients received a diagnosis of HIV between 2009 and 2012, and 38.75% of the patients had composite AIDS-defining opportunistic infections.

The two groups differed significantly in terms of the time of cART initiation, incidence of composite AIDS-defining opportunistic infections, $CD4^+$ T-cell count at cART initiation, and type of first-line cART used at initiation.

Factors associated with the occurrence of incident composite non-AIDS-related events during the observation period.

The median observational duration (interquantile range) were 712 (514–2097) days. The cumulative probability of composite non-AIDS-related events at 360 days after cART initiation differed significantly between the two groups (log-rank test, P = 0.012; Fig. 2). Factors associated with the occurrence of incident composite non-AIDS-related events during the observation period are listed in Table 2. Older age (26–45 vs. $\leq$25 years; adjusted hazard ratio [aHR]: 1.92; 95% confidence interval [CI]: 1.23–3.01; $\geq$46 vs. $\leq$25 years; aHR: 2.30; 95% CI: 1.03–5.13) and INRs (vs. non-INRs: aHR: 1.81; 95% CI: 1.19–2.73) were associated with the occurrence of incident composite non-AIDS-related events.

Factors associated with the occurrence of incident categorized non-AIDS-related events during the observation period in cause-specific survival analysis.

In our cause-specific survival analysis, the cumulative probability of metabolic outcomes at 360 days after cART initiation differed significantly between the two groups (log-rank test, P = 0.016; Fig. 3). The Cox regression results revealed that INRs were significantly associated with metabolic outcomes (aHR: 1.75; 95% CI: 1.14–2.68). However, the Kaplan–Meier analysis and Cox regression results indicated that INRs were not significantly associated with other non-AIDS-related events in the four categories

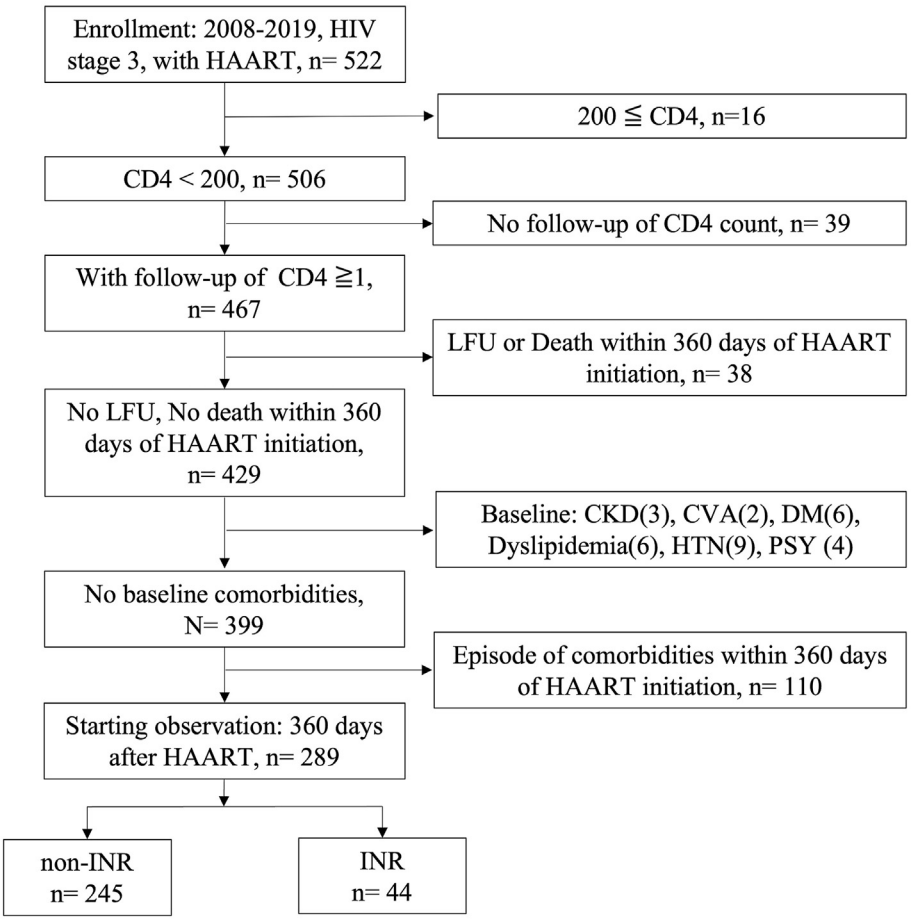

Figure 1. Flowchart of enrollment of patients with newly diagnosed stage—3 HIV (2008—2019). Abbreviations: CKD, chronic kidney disease; CVA, cardiovascular accident; DM, diabetes mellitus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HTN, hypertension; INR, immunological nonresponse; LFU, loss of follow-up; non-INR, non—immunological nonresponse; PSY, psychiatric disorder.

(vascular diseases, malignancies, renal disease, and psychiatric diseases).

Sensitivity analysis

The sensitivity analysis results revealed that the results of each Cox regression model were consistent in terms of composite events and metabolic diseases (Supplementary Tables 3 and 4).

Discussion

Despite improvements in the potency of HAART, our study revealed associations between composite events and INRs. This finding is consistent with those of previous studies.[13,15]Notably, we observed that INRs were associated with metabolic diseases (e.g., dyslipidemia, dysglycemia, and hypertension). These findings indicate that PLWH with poor immunological responses require more rigorous metabolic risk factor management strategies than do PLWH with adequate immunological responses. Additional studies are warranted to identify the optimal frequencies for the follow-up of metabolic parameters used to identify individuals vulnerable to metabolic events.

Our study revealed that INRs were associated with an increased risk of metabolic diseases. The reason for this association may be multifactorial. Previous studies have reported that bone marrow dysfunction increased T-cell apoptosis and that decreased thymic activity may be involved in delayed $CD4^+$ T-cell recovery.[8,24—26] An Italian cohort study observed lower levels of interleukin (IL)-2 and IL-7 and a higher level of tumor necrosis factor α in its INR group; this imbalance in cytokine production may prevent the mediation of T-cell differentiation and activation, leading to T-cell apoptosis,[25] which contributes to chronic inflammation and may engender comorbidities. In addition to these immune system abnormalities, microbial translocation and dysbiosis in PLWH were revealed to play a major role in immune activation.[27] This association could be due to gastrointestinal tract mucosal dysfunction, including immunological alterations in the gut, disruption of the epithelial barrier, translocation of microbial products into circulation, and dysbiosis of the gut microbiome. Circulating microbial products interfere with the immune system by persistently inducing immune activation, as evidenced by

Table 1 Comparisons of sociodemographic characteristics of the non-INR group (n = 245) and INR group (n = 44).

	All n = 289	non-INR group n = 245	INR group n = 44	*P*-value
Sociodemographic variables				
Male, n (%)	284 (98.27)	240 (97.96)	44 (100.0)	0.339
Subgroup of age at HIV presentation, (years) n (%)				0.751
≦25	74 (25.61)	62 (25.31)	12 (27.27)	
26-45	201 (69.55)	172 (70.20)	29 (65.91)	
46≦	14 (4.84)	11 (4.49)	3 (6.84)	
Period of starting HAART, n (%)				0.018
2009—2012	111 (38.54)	86 (35.25)	25 (56.82)	
2013—2016	103 (35.76)	90 (36.89)	13 (29.55)	
2017—2019	74 (25.69)	68 (27.87)	6 (13.64)	
HIV transmission route, n (%)				0.832
MSM	260 (89.97)	220 (89.80)	40 (90.91)	
Heterosexual contact	27 (9.34)	23 (9.39)	4 (9.09)	
IDU	2 (0.69)	2 (0.89)	0 (0.00)	
Occupation, n (%)				0.101
Unemployed	44 (15.22)	33 (13.47)	11 (25.00)	
Employed	219 (75.78)	188 (76.73)	31 (70.45)	
Student	26 (9.00)	24 (9.80)	2 (4.55)	
Marital status				0.420
Unmarried	274 (94.81)	234 (95.51)	40 (90.91)	
Married	12 (4.15)	9 (3.67)	3 (6.82)	
Divorced	3 (1.04)	2 (0.82)	1 (2.27)	
Composite AIDS-defining Opportunistic illness, n (%)	112 (38.75)	89 (36.33)	23 (52.27)	0.046
Pneumocystis jiroveci pneumonia	99 (34.26)	82 (33.47)	17 (38.64)	0.506
Disseminated *Mycobacterium avium-intracellulare* complex	11 (3.81)	8 (3.27)	3 (6.82)	0.257
Mycobacterium tuberculosis infection	8 (2.77)	5 (2.04)	3 (6.82)	0.075
Cryptococcosis	6 (2.08)	2 (0.82)	4 (9.09)	<0.001
Kaposi's sarcoma	1 (0.35)	1 (0.41)	0 (0.00)	0.671
Lymphoma	1 (0.35)	1 (0.41)	0 (0.00)	0.671
Laboratory examination				
CD4 count at start of HAART, cells/μL				<0.001
≦50	118 (40.83)	86 (35.10)	32 (72.73)	
51—199	171 (59.17)	159 (64.90)	12 (27.27)	
PVL at start of HAART, copies/mL				0.293
<100,000	92 (31.83)	75 (30.61)	17 (38.64)	
100,000≦	197 (68.17)	170 (69.39)	27 (61.36)	
HAV Ab seropositivity, n (%)	48 (17.14)	39 (16.39)	9 (21.43)	0.424
HBsAg seropositivity, n (%)	31 (10.08)	26 (10.70)	5 (11.36)	0.896
HCV Ab seropositivity, n (%)	10 (3.52)	9 (3.73)	1 (2.33)	0.644
VDRL≧1:8	67 (23.18)	60 (24.49)	7 (15.91)	0.214
Type of first-line HAART at initiation, n (%)rowhead				
Backbone regimen, n (%)				
Zidovudine-based	107 (37.02)	90 (36.73)	17 (38.64)	0.810
Abacavir-based	111 (38.41)	92 (37.55)	19 (43.18)	0.480
TDF/TAF-based	71 (24.57)	63 (25.71)	8 (18.18)	0.285
Third regimen, n (%)				
nNRTI-based	172 (59.52)	141 (57.55)	31 (70.45)	0.108
PI-based	29 (10.03)	23 (9.39)	6 (13.64)	0.388
II-based	88 (30.45)	81 (33.06)	7 (15.91)	0.023

Abbreviations: Ab, antibody; AIDS, acquired immunodeficiency syndrome; HAART, highly active combination antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; II, integrase inhibitors; INR, immunological nonresponse; MSM, men who have sex with men; nNRTI, non-nucleoside reverse transcriptase inhibitor; non-INR, non—immunological nonresponse; PI, protease inhibitor; PVL, plasma viral load; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VDRL, venereal disease research laboratory.

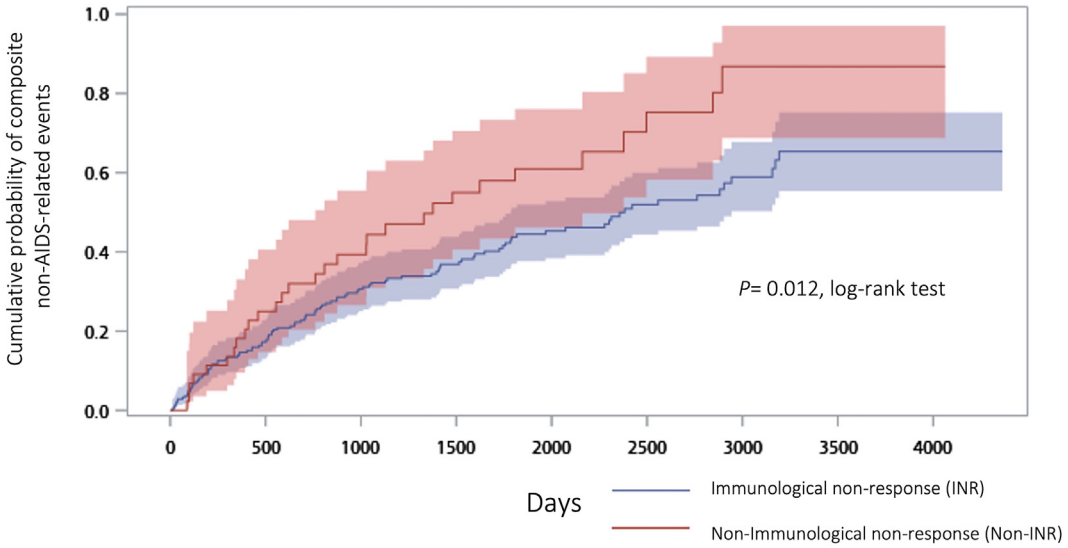

Figure 2. Cumulative probability of composite non-AIDS-related events from the 360th day after highly active antiretroviral therapy initiation to the end of follow-up. The Kaplan—Meier curve indicates the difference between the non-INR and INR groups in terms of the cumulative probability of composite non-AIDS-related events (P = 0.012, log-rank test). Abbreviations: INR, immunological nonresponse; non-INR, non—immunological nonresponse.

high plasma lipopolysaccharide levels in PLWH.[27] This form of microbial translocation starts during an acute infection and continues in the chronic disease stage; it is associated with several morbidities, including insulin resistance, hypertension, cardiovascular disease, neurocognitive disorders, depression, liver disease, non-Hodgkin lymphoma,[28—30] and metabolic diseases. Therefore, to reduce the morbidity of PLWH with poor immunological responses, novel therapies have been developed for restoring the microbiome and repairing damaged gastrointestinal epithelial barriers. Probiotics have also emerged as a therapeutic option for treating PLWH with poor immunological responses,[31,32] but additional studies are warranted to determine the optimal content and dosage of probiotics for reducing the burden of comorbidities in such PLWH.

In addition to the aforementioned factors, older age, the male sex,[33] a low nadir $CD4^+$ T-cell count,[34] a low CD4/CD8 ratio, and a low naïve/memory $CD4^+$ T-cell count ratio[35] are associated with unfavorable $CD4^+$ T-cell recovery. Host genetic factors, metabolic characteristics, and specific antiretroviral therapy (ART) regimens may also contribute to a suboptimal immunological response. Additionally, evidence in the literature indicates a relationship between ART and metabolic diseases, including increased insulin resistance, hyperlipidemia, and lipodystrophy. Different classes of ART have different effects on lipid profiles and insulin resistance.[36] Protease inhibitors used in ART were reported to contribute the most to increased lipid levels and to engender chronic inflammation and cardiovascular events or other morbidities.[37] However, the present study did not observe an increase in the incidence of non-AIDS-related events related to ART use. The absence of this association is attributable to our small sample size. In addition, we examined only ART regimens implemented at treatment initiation. We could not determine whether regimen switches between different classes of ART affected incident non-AIDS-related events. To address this limitation, future studies should determine when ART regimens should be switched and examine the association between ART switching and non-AIDS-related events. A time-dependent Cox regression model can also be applied to address this limitation.

The strength of this study is its contemporariness relative to previous studies; specifically, our study covered the period from January 1, 2008, to December 31, 2019. Thus, our findings may be more applicable to the current era of potent HAART compared with those of earlier studies. Our study also demonstrated that INRs were associated with an increased risk of composite outcomes—a finding that is consistent with previous findings—particularly for metabolic diseases. We performed two sensitivity analyses regarding the definition of INR, and the analysis results indicate that our results were consistent for both composite events and metabolic diseases, further demonstrating the robustness of our findings.

The present study has several limitations. First, the retrospective cohort study design may have been affected by incomplete or missing documentation, which would have affected the accuracy and reliability of our statistical analyses. Second, the definition of the metabolic disease category in this study is not fully consistent with those used in practice. Although our working definition of metabolic diseases included dysglycemia, elevated LDL levels, and hypertension, the current definition of metabolic syndrome also includes dyslipidemia (low high-density lipoprotein levels and elevated triglyceride levels) and central obesity (waist circumference).[38] Finally, some variables were not included in this study, including body weight, body mass index, and visceral fat, which may have contributed to an increased risk of

Table 2 Univariable and multivariable analysis results for factors associated with occurrence of composite non-AIDS-related events during the observation period.

	Univariable analysis		Multivariable analysis	
	Crude HR (95%CI)	*P*-value	Adjusted HR (95%CI)	*P*-value
Sociodemographic variables				
Males (vs. Females)	0.68 (0.22−2.14)	0.507		
Subgroup of age at HIV presentation (years)				
≦25	Reference		Reference	
26-45	1.90 (1.21−3.00)	0.005	1.92 (1.23−3.01)	0.004
46≦	2.32 (1.03−5.18)	0.041	2.30 (1.03−5.13)	0.043
Period of starting HAART				
2009−2012	Reference			
2013−2016	0.86 (0.58−1.28)	0.471		
2017−2019	1.09 (0.65−1.82)	0.758		
HIV transmission route				
MSM	Reference			
Heterosexual contact	1.26 (0.70−2.29)	0.443		
IDU	3.96 (0.55−28.78)	0.173		
Occupation				
Unemployed	Reference			
Employed	1.00 (0.62−1.62)	1.000		
Student	0.44 (0.19−1.04)	0.061		
Marital status				
Unmarried	Reference			
Married	2.40 (1.17−5.00)	0.018		
Divorced	2.80 (1.03−7.57)	0.044		
Composite AIDS-defining Opportunistic illness (vs. No)	1.23 (0.87−1.74)	0.236		
Laboratory examination				
CD4 count at start of HAART, cells/μL				
50<	Reference			
≦50	1.37 (0.97−1.93)	0.071		
PVL at start of HAART, copies/mL				
<100,000	Reference			
100,000≦	0.79 (0.56−1.13)	0.196		
HAV Ab seropositivity (vs. No)	1.70 (1.09−2.66)	0.019		
HBsAg seropositivity (vs. No)	1.18 (0.72−1.95)	0.509		
HCV Ab seropositivity (vs. No)	2.14 (0.94−4.89)	0.069		
VDRL≧1:8 (vs. No)	0.92 (0.61−1.38)	0.672		
INR (vs. No)	1.81 (1.10−2.98)	0.020	1.81 (1.19−2.73)	0.005
Type of first-line HAART at initiation				
Backbone regimen				
Zidovudine-based (vs. No)	1.08 (0.76−1.53)	0.679		
Abcavir-based (vs. No)	0.92 (0.65−1.32)	0.663		
TDF/TAF-based (vs. No)	1.00 (0.66−1.54)	0.982		
Third regimen				
nNRTI-based (vs. No)	0.85 (0.59−1.22)	0.363		
PI-based (vs. No)	1.09 (0.65−1.80)	0.752		
I-based (vs. No)	1.20 (0.78−1.86)	0.406		

Abbreviations: Ab, antibody; AIDS, acquired immunodeficiency syndrome; HAART, highly active combination antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injection drug use; II, integrase inhibitors; INR, immunological nonresponse; MSM, men who have sex with men; nNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PVL, plasma viral load; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VDRL, venereal disease research laboratory.

metabolic diseases.[39] However, our finding of the association between INRs and metabolic diseases may not have been confounded by body weight or waist circumference because no evidence suggests an association between INRs and either of these factors.[40] This study did not include variables regarding patient lifestyles and nutritional status, which may have confounded the results and limited the causal inference of the association of INRs with increased risks of composite non-AIDS-related events and metabolic diseases among PLWH.

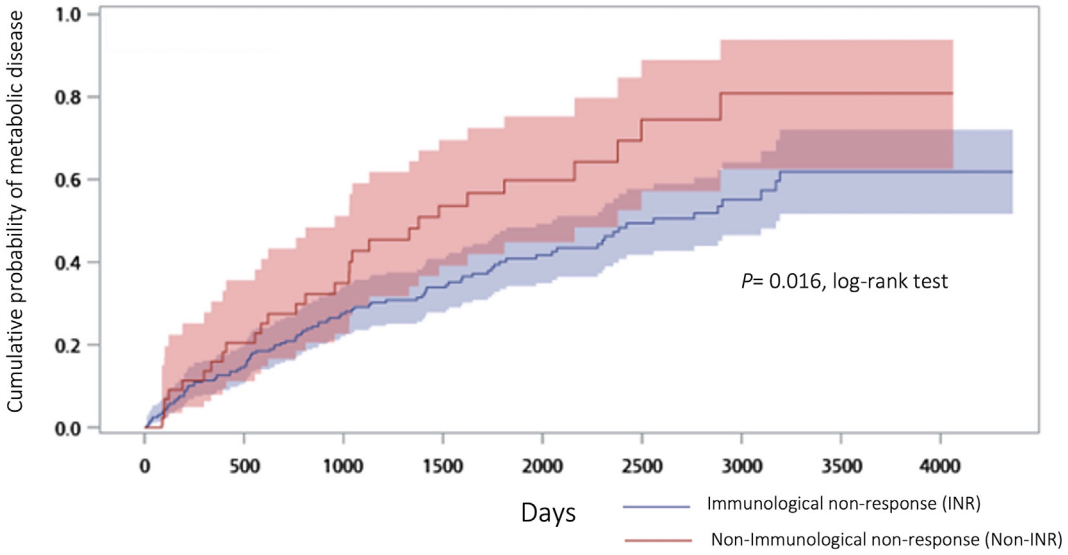

Figure 3. Cumulative probability of metabolic diseases from the 360th day after highly active antiretroviral therapy initiation to the end of follow-up. In the cause-specific survival analysis, the Kaplan—Meier curve indicates the difference between the non-INR and INR groups in terms of the cumulative probability of metabolic diseases (P = 0.016, log-rank test). Abbreviations: INR, immunological nonresponse; non-INR, non—immunological nonresponse.

Conclusion

Our results indicate that PLWH with poor immunological responses after HAART initiation may be more likely to develop composite non-AIDS-related events, particularly metabolic diseases such as dyslipidemia, dysglycemia, and hypertension, compared with those with superior immunological responses. Accordingly, clinicians should be vigilant and provide early intervention and more rigorous monitoring for non-AIDS-related events in PLWH with INRs. With the advancement of medical care, improved and personalized health care can be provided to patients. Additional studies are warranted to identify the metabolic diseases that are more likely to occur in PLWH with INRs.

Authorship contributions

Conception and design of study: Chia-Hui Wen, Chun-Yuan Lee, Po-Liang Lu, Yen-Hsu Chen. Acquisition of data: Chung-Hao Huang, Shih-Hao Lo, Shang-Yi Lin, Ya-Ting Chang. Analysis and interpretation of data: Chia-Hui Wen, Chun-Yuan Lee, Yi-Pei Lin. Drafting of manuscript and critical revision: Po-Liang Lu, Chun-Yu Lin, Tun-Chieh Chen, Shin-Huei Kuo. Approval of final version of manuscript: all authors.

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Authorship

All named authors meet the International Committee of Medical Journal Editors criteria for authorship of this article, assume responsibility for the integrity of the work as a whole, and have given their approval for the publication of this version.

Declaration of competing interest

The authors declare that they have no conflicts of interest to this study.

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References

1. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998;**352**:1725—30.
2. Marcus JL, Leyden WA, Alexeeff SE, Anderson AN, Hechter RC, Hu H, et al. Comparison of overall and comorbidity-free life expectancy between insured adults with and without HIV infection, 2000-2016. *JAMA Netw Open* 2020;**3**:e207954.
3. Croxford S, Kitching A, Desai S, Kall M, Edelstein M, Skingsley A, et al. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. *Lancet Public Health* 2017;**2**:e35—46.

4. Wu P-Y, Chen M-Y, Sheng W-H, Hsieh S-M, Chuang Y-C, Cheng A, et al. Estimated risk of cardiovascular disease among the HIV-positive patients aged 40 years or older in Taiwan. *J Microbiol Immunol Infect* 2019;**52**:549—55.
5. Yang C-J, Chen M-Y, Hsieh S-M, Sheng W-H, Sun H-Y, Hung C-C, et al. Non-Hodgkin's lymphoma in patients with human immunodeficiency virus infection in Taiwan. *J Microbiol Immunol Infect* 2010;**43**:278—84.
6. Hsu DC, Sereti I, Ananworanich J. Serious Non-AIDS events: immunopathogenesis and interventional strategies. *AIDS Res Ther* 2013;**10**:29.
7. Tan R, Westfall AO, Willig JH, Mugavero MJ, Saag MS, Kaslow RA, et al. Clinical outcome of HIV-infected antiretroviral-naive patients with discordant immunologic and virologic responses to highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2008;**47**:553—8.
8. 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**:597—612.
9. Benveniste O, Flahault A, Rollot F, Elbim C, Estaquier J, Pédron B, et al. Mechanisms involved in the low-level regeneration of CD4+ cells in HIV-1-infected patients receiving highly active antiretroviral therapy who have prolonged undetectable plasma viral loads. *J Infect Dis* 2005;**191**:1670—9.
10. Andrade BB, Hullsiek KH, Boulware DR, Rupert A, French MA, Ruxrungtham K, et al. Biomarkers of inflammation and coagulation are associated with mortality and hepatitis flares in persons coinfected with HIV and hepatitis viruses. *J Infect Dis* 2013;**207**:1379—88.
11. Lapadula G, Cozzi-Lepri A, Marchetti G, Antinori A, Chiodera A, Nicastri E, et al. Risk of clinical progression among patients with immunological nonresponse despite virological suppression after combination antiretroviral treatment. *AIDS* 2013;**27**:769—79.
12. Zoufaly A, Cozzi-Lepri A, Reekie J, Kirk O, Lundgren J, Reiss P, et al. Immuno-Virological discordance and the risk of non-AIDS and AIDS events in a large observational cohort of HIV-patients in Europe. *PLoS One* 2014;**9**:e87160.
13. van Lelyveld SF, Gras L, Kesselring A, Zhang S, De Wolf F, Wensing AM, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS* 2012;**26**:465—74.
14. Pregnancy TE, EuroCoord PHCCSGi. Prevalence and clinical outcomes of poor immune response despite virologically suppressive antiretroviral therapy among children and adolescents with human immunodeficiency virus in Europe and Thailand: cohort study. *Clin Infect Dis* 2019;**70**:404—15.
15. Lapadula G, Chatenoud L, Gori A, Castelli F, Di Giambenedetto S, Fabbiani M, et al. Risk of severe non AIDS events is increased among patients unable to increase their CD4+ T-cell counts >200+/μl despite effective HAART. *PLoS One* 2015;**10**:e0124741.
16. Pan W-H, Wu H-J, Yeh C-J, Chuang S-Y, Chang H-Y, Yeh N-H, et al. Diet and health trends in Taiwan: comparison of two nutrition and health surveys from 1993-1996 and 2005-2008. *Asia Pac J Clin Nutr* 2011;**20**:238—50.
17. Centers for Disease Control and Prevention (CDC). Revised surveillance case definition for HIV infection — United States. In: *MMWR recomm rep*, vol. 63; 2014. p. 1—10.
18. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the Evaluation and diagnosis of chest pain: a report of the American college of Cardiology/American Heart association joint committee on clinical Practice guidelines. *Circulation* 2021;**144**:e368—454.
19. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower Extremity peripheral artery disease: Executive summary: a report of the American college of Cardiology/American Heart association Task force on clinical Practice guidelines. *Circulation* 2017;**135**:e686—725.
20. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J* 2019;**41**:111—88.
21. Association AD. Standards of medical care in diabetes—2022 abridged for primary care providers. *Clin Diabetes* 2022;**40**:10—38.
22. Wang TD, Chiang CE, Chao TH, Cheng HM, Wu YW, Wu YJ, et al. 2022 guidelines of the Taiwan society of Cardiology and the Taiwan hypertension society for the management of hypertension. *Acta Cardiol Sin* 2022;**38**:225—325.
23. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical Practice guideline. *Ann Intern Med* 2013;**158**:825—30.
24. Benveniste O, Flahault A, Rollot F, Elbim C, Estaquier J, Pédron B, et al. Mechanisms involved in the low-level regeneration of CD4+ cells in HIV-1—infected patients receiving highly active antiretroviral therapy who have prolonged undetectable plasma viral loads. *J Infect Dis* 2005;**191**:1670—9.
25. Isgrò A, Leti W, De Santis W, Marziali M, Esposito A, Fimiani C, 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.
26. Fernandez S, Nolan RC, Price P, Krueger R, Wood C, Cameron D, et al. Thymic function in severely immunodeficient HIV type 1-infected patients receiving stable and effective antiretroviral therapy. *AIDS Res Hum Retrovir* 2006;**22**:163—70.
27. Zevin AS, McKinnon L, Burgener A, Klatt NR. Microbial translocation and microbiome dysbiosis in HIV-associated immune activation. *Curr Opin HIV AIDS* 2016;**11**:182—90.
28. Manner I, Baekken M, Kvale D, Oektedalen O, Pedersen M, Nielsen S, et al. Markers of microbial translocation predict hypertension in HIV-infected individuals. *HIV Med* 2013;**14**:354—61.
29. French AL, Evans CT, Agniel DM, Cohen MH, Peters M, Landay AL, et al. Microbial translocation and liver disease progression in women coinfected with HIV and hepatitis C virus. *J Infect Dis* 2013;**208**:679—89.
30. Epeldegui M, Magpantay L, Yu G, Halec G, Cumberland WG, Macatangay B, et al. A prospective study of serum microbial translocation biomarkers and risk of AIDS-related non-Hodgkin lymphoma. *AIDS* 2018;**32**:945.
31. D'Angelo C, Reale M, Costantini E. Microbiota and probiotics in health and HIV infection. *Nutrients* 2017;**9**:615.
32. d'Ettorre G, Ceccarelli G, Giustini N, Serafino S, Calantone N, De Girolamo G, et al. Probiotics reduce inflammation in antiretroviral treated, HIV-infected individuals: results of the "probio-HIV" clinical trial. *PLoS One* 2015;**10**:e0137200.
33. Lee SS, Wong NS, Wong BCK, Wong KH, Chan KCW. Combining CD4 recovery and CD4: CD8 ratio restoration as an indicator for evaluating the outcome of continued antiretroviral therapy: an observational cohort study. *BMJ Open* 2017;**7**:e016886.
34. Davy-Mendez T, Napravnik S, Zakharova O, Wohl DA, Farel CE, Eron JJ. Effectiveness of integrase strand transfer inhibitors among treatment-experienced patients in a clinical setting. *AIDS* 2019;**33**:1187—95.

35. Roul H, Mary-Krause M, Ghosn J, Delaugerre C, Pialoux G, Cuzin L, et al. CD4+ cell count recovery after combined antiretroviral therapy in the modern combined antiretroviral therapy era. *AIDS* 2018;**32**:2605—14.
36. Bune GT, Yalew AW, Kumie A. The extents of metabolic syndrome among Antiretroviral Therapy exposed and ART naïve adult HIV patients in the Gedeo-zone, Southern-Ethiopia: a comparative cross-sectional study. *Arch Publ Health* 2020;**78**:40.
37. Rao MN, Lee GA, Grunfeld C. Metabolic abnormalities associated with the use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors. *Am J Infect Dis* 2006;**2**:159—66.
38. Dobrowolski P, Prejbisz A, Kuryłowicz A, Baska A, Burchardt P, Chlebus K, et al. Metabolic syndrome - a new definition and management guidelines: a joint position paper by the polish society of hypertension, polish society for the treatment of obesity, polish lipid association, polish association for study of liver, polish society of family medicine, polish society of lifestyle medicine, division of prevention and Epidemiology polish cardiac society, "club 30" polish cardiac society, and division of metabolic and bariatric surgery society of polish surgeons. *Arch Med Sci* 2022;**18**:1133—56.
39. Brahe LK, Astrup A, Larsen LH. Can we prevent obesity-related metabolic diseases by dietary modulation of the gut microbiota? *Adv Nutr* 2016;**7**:90—101.
40. Jager KJ, Zoccali C, MacLeod A, Dekker FW. Confounding: what it is and how to deal with it. *Kidney Int* 2008;**73**:256—60.

Appendix A. Supplementary data

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