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ORIGINAL RESEARCH

Manifestations and Related Risk Factors of Thrombocyte Abnormalities in HIV-Positive Patients Before and After the Initiation of ART

Bei Li[1]
Leidan Zhang[2]
Ying Liu[1]
Jing Xiao[2]
Xinyue Wang[2]
Yuqing Wei[1]
Lina Fan[3]
Yujiao Duan[1]
Guoli Li[4]
Yaxian Kong[4]
Hongxin Zhao[1]

[1]Clinical and Research Center of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Department of Infection, Beijing Ditan Hospital, Peking University, Beijing, People's Republic of China; [3]Department of Infectious Disease, The Tianjin Second People's Hospital, Tianjin, People's Republic of China; [4]Institute of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, People's Republic of China

Background: At present, the thrombocyte abnormality is not well described before and after the initiation of antiretroviral therapy (ART). The purpose of this research is to investigate the dynamic changes and related risk factors of thrombocytopenia and thrombocytosis in HIV-infected individuals.

Methods: We performed a real-world observational study among 6637 HIV patients who started ART from January, 2013 to August, 2020 at the Beijing Ditan Hospital. Hazard indicators linked with thrombocytopenia and thrombocytosis were analyzed by logistic/Cox regression.

Results: The prevalence of thrombocytopenia and thrombocytosis was 2.65% and 5.85% among ART-naïve patients, respectively. Correlated risk factors: (thrombocytopenia) older age, coinfection with HBV, leucopenia, anemia, and CD4 count <350 cells/uL; (thrombocytosis) WBC level ≥4.0 x 10^9/L, anemia, NLR ≥2.0, and CD4 count ≥350 cells/uL. As for the recovery rate, it was 86.6/54.2, 83.4/46.3, 66.0/35.1, and 65.3/ 33.9 per 100 PYFU in thrombocytopenia/thrombocytosis at different treatment period (12m, 24m, 36m, and 48m). While the new-onset incidence of thrombocytopenia/thrombocytosis at different ART period (12m, 24m, 36m, 48m, 60m, 72m, and 84m) was 0.25/7.2, 0.19/6.31, 0.16/4.74, 0.16/4.55, 0.16/4.48, 0.15/4.41, and 0.15/4.39. And the driving forces of thrombocytosis were antiretroviral treatment, female, overweight, and WBC level ≥ 4.0 x 10^9/L.

Conclusion: In the medical practice, while paying attention to thrombocytopenia, clinicians should be highly vigilant about the thrombocytosis of HIV/AIDS patients, and related treatment strategies need to be further studied.

Keywords: thrombocyte abnormalities, thrombocytopenia, thrombocytosis, HIV, antiretroviral therapy

Introduction

Thrombocytes, derived from megakaryocyte cytoplasm, play a critical role in haemostasis, thrombosis and coagulation of blood.[1] The normal platelet count ranges from 100,000 to 300,000/μL in adults. During human immunodeficiency virus (HIV) infection, low or high platelets concentration is coupled with the incidence of both acquired immunodeficiency syndrome (AIDS) and non-AIDS-defining events.[2]

Hematologic abnormalities are common manifestations of advanced HIV disease and AIDS.

Unfortunately, the available information on thrombocytopenia and thrombocytosis is limited for HIV-positive individuals in China. Therefore, in this study, we systematically investigated the dynamic changes of thrombocytopenia and

Correspondence: Hongxin Zhao
Clinical and Research Center of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, No. 8 Jing Shun East Street, Beijing, 100015, People's Republic of China
Email Drzhao66@ccmu.edu.cn

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thrombocytosis before and after ART, and further analyzed the associated risk indicators, so as to provide certain guidance and basis for the optimization of clinical treatment strategies.

Materials and Methods

Study Participants

We performed a retrospective cohort study on 6637 HIV-infected members who initiated ART at the Beijing Ditan Hospital from January, 2013 to August, 2020. Subjects were excluded (1) if their age was <18 years while ART was introduced, (2) pregnant women, and (3) those with incomplete baseline data. To investigate the rate of new-onset thrombocyte abnormalities, 6074 HIV-positive individuals who were visited at least once (apart ≥12 months) after the beginning of therapy were conducted.

The protocols were approved by the ethics committees of Beijing Ditan Hospital, Capital Medical University (Approval No. 2021-022-1), and were carried out by the Declaration of Helsinki. All of clinical and laboratory data were used anonymously, so written informed consent was not required.

Definitions

Conditions were defined based on the following parameters in peripheral blood. Thrombocytopenia: platelet (PLT) count <100 x 10^9/L; thrombocytosis: platelet count >300 x 10^9/L; leucopenia: white blood cell (WBC) level < 4.0 x 10^9/L; anemia: hemoglobin (HGB) level < 110 g/L (female) or < 120 g/L (male). Hematological recovery after ART was delimited as states that the PLT counts would be within the reference range of (100–300) x 10^9/L.

Data Collection

The following demographic, clinical and laboratory data were extracted from the electronic medical record system: age, sex, HIV transmission route, WHO clinical stage, body mass index (BMI), hepatitis B virus (HBV), hepatitis C virus (HCV) serostatus, syphilis, HIV viral load (VL), CD4 T cell count, CD4/CD8 ratio at pre-ART, and initial treatment regimen. Baseline WBC count, HGB level, neutrophil/lymphocyte ratio (NLR) were also involved.

Statistical Analysis

Continuous variables were presented as the medians and interquartile ranges (IQR) due to skewed statistical distributions, while categorical variables were expressed by counts and percentages. The chi-square test was used to evaluate the difference in categorical variables. Descriptive statistics were employed to illustrate the characteristics of the participants and the overall prevalence of thrombocyte abnormalities (including thrombocytopenia and thrombocytosis) at enrollment.

To explore the risk variables independently associated with thrombocytopenia or thrombocytosis, the underlying predictors determined by univariable analysis were further entered into a multivariable logistic regression model. And the final outcomes were displayed as adjusted odds ratios (AOR) with their respective 95% confidence intervals (CI).

Normalization rates of thrombocytes after ART were evaluated as the number of recovery cases per 100 person-years follow-up (PYFU), and line charts were adopted to describe the restoration trends during the observational period. Incidence density rate of thrombocytopenia and thrombocytosis were also reported as the same way.

Cox proportional hazards models were executed to assess the impact factors on thrombocytosis in HIV-subjects after one year of ART. Characteristics that were considered clinically relevant or that performed a univariate relationship with result were fitted into multivariate analysis to control possible confounders.

Statistical calculations were performed using SPSS software (version 26.0) and GraphPad (version 7.0). All tests were two-tailed, and significance was set at 0.05.

Results

Characteristics of the Participants and Prevalence of Thrombocyte Abnormalities

From January, 2013 to August, 2020, we enrolled 6637 HIV/AIDS people in our study. The median age of cohort subjects was 30 years (IQR, 26–37), and the ratio of male to female was 22:1. The main transmission route was sexual, which accounted for 92.3% of cases. In total, 59.7% of individuals had baseline CD4 counts <350 cells/μL. The demographic, immunologic and hematological details are listed in Table 1.

Overall, the prevalence of thrombocytopenia was 2.65% (n=176), while the prevalence of thrombocytosis was 5.85% (n=388) prior to initiating ART.

Risk Factors for Thrombocyte Abnormalities Among ART-Naïve Patients

We investigated the independent hazard markers for thrombocytopenia and thrombocytosis in therapy-naïve

Table 1 Demographic Data and Clinical Characteristics of the Study Subjects at the Beginning of Antiretroviral Therapy (n=6637)

Variables	Thrombocytopenia (n=176)	Thrombocytosis (n=388)	Normal (n=6073)
Age (years)	34(29, 46)	30(25, 38)	30(26, 37)
Sex			
Male	166 (94.3)	364(93.8)	5820(95.8)
Female	10 (5.7)	24(6.2)	253(4.2)
Transmission route			
Homosexual	115 (65.3)	294(75.8)	4893(80.6)
Heterosexual	38 (21.6)	58(14.9)	733(12.1)
Other/unknown	23 (13.1)	36(9.3)	447(7.3)
WHO clinical stage			
I–II	152(86.4)	347(91.1)	5513(92.2)
III–IV	24 (13.6)	34(8.9)	469(7.8)
BMI (kg/m^2)			
18.5–24.0	88 (66.2)	186(61.4)	3136(65.6)
< 18.5	19 (14.3)	40(13.2)	472(9.9)
>24.0	26 (19.5)	77(25.4)	1171(24.5)
HBsAg			
Negative	148(85.5)	363(95.3)	5649(94.7)
Positive	25(14.5)	18(4.7)	314(5.3)
Anti-HCV			
Negative	166(96.0)	378(99.5)	5833(98.0)
Positive	7(4.0)	2(0.5)	119(2.0)
Syphilis			
Negative	105(64.4)	205(59.8)	3688(64.9)
Positive	58(35.6)	138(40.2)	1992(35.1)
Baseline VL (copies/mL)			
<100,000	88(51.5)	237(62.7)	4143(70.4)
≥100,000	83(48.5)	141(37.3)	1740(29.6)
Baseline CD4 count (cells/μL)			
<350	144(82.8)	219(56.9)	3595(60.0)
≥350	30(17.2)	166(43.1)	2397(40.0)
Baseline CD4/CD8 ratio			
<0.4	151(87.3)	272(71.0)	4238(71.9)
≥0.4	22(12.7)	111(29.0)	1658(28.1)
WBC ($\times 10^9$ /L)			
≥4.0	106(60.2)	353(91.0)	5288(87.1)
<4.0	70(39.8)	35(9.0)	785(12.9)
HGB (g/L)			
≥110(Female) or ≥120(Male)	119(67.6)	308(79.4)	5651(93.1)
<110(Female) or >120(Male)	57(32.4)	80(20.6)	422(6.9)
NLR			
<2.0	79(46.5)	168(45.8)	3589(61.2)
2.0–4.0	60(35.3)	130(35.4)	1791(30.5)
>4.0	31(18.2)	69(18.8)	488(8.3)

Notes: Data are presented as n (%), or median (interquartile range). Variable had missing values: WHO clinical stage = 98; BMI = 1422; HBV = 120; HCV =132; Syphilis = 451; VL = 205; CD4 count = 86; CD4/CD8 ratio = 185; NLR = 232.

Abbreviations: WHO, world health organization; BMI, body mass index; HBsAg, hepatitis B surface antigen; Anti-HCV, antibody to hepatitis C virus; VL, viral load; WBC, white blood cell; HGB, haemoglobin; NLR, neutrophil-lymphocyte ratio.

patients, respectively. Multivariate logistic regression analysis demonstrated that older age (OR: 1.029, 95% CI: 1.015–1.042, $p < 0.001$), co-infection with HBV (OR: 2.825, 95% CI: 1.782–4.480, $p < 0.001$), WBC count < 4.0 x 10^9/L (OR: 2.464, 95% CI: 1.717–3.536, $p < 0.001$), HGB level < 110 g/L (female) or < 120 g/L (male) (OR: 2.962, 95% CI: 2.005–4.377, $p < 0.001$), were connected with increased odds of thrombocytopenia. On the contrary, baseline CD4 count ≥ 350 cells/uL (OR: 0.527, 95% CI: 0.338–0.821, $p = 0.005$) was negatively linked with thrombocytopenia.

As shown in Table 2, pre-ART CD4 count ≥ 350 cells/uL (OR: 1.616, 95% CI: 1.231–2.122, $p = 0.001$), HGB level < 110 g/L (female) or < 120 g/L (male) (OR: 4.012, 95% CI: 2.750–5.854, $p < 0.001$), NLR grade 2.0–4.0 (OR: 1.542, 95% CI: 1.172–2.029, $p = 0.002$) and NLR > 4.0 (OR: 2.008, 95% CI: 1.334–3.021, $p = 0.001$) were notably correlated with the presence of thrombocytosis. However, WBC count < 4.0 x 10^9/L (OR: 0.467, 95% CI: 0.291–0.750, $p = 0.002$), contrasted with WBC level ≥ 4.0 x 10^9/L, was proved with lower occurrence risk of thrombocytosis.

Normalization Rate of Thrombocyte Abnormalities After ART Introduction

Normalization rates were reckoned as the number of recovery cases per 100 person-years, and the restoration of thrombocytes was immediately observed after ART started. Longitudinally, the recovery rates of thrombocytopenia (86.6/100 PYFU) and thrombocytosis (54.2/100 PYFU) were the highest in the first year after initiating antiretroviral treatment. The restoration rates of thrombocytopenia/thrombocytosis at different treatment period (24m, 36m, and 48m) were 83.4/46.3, 66.0/35.1, and 65.3/ 33.9 (Figure 1).

Incidence Rate of Thrombocyte Abnormalities After ART Introduction

After excluding patients who lack follow-up records as well as unusual baseline thrombocyte parameters, the ultimate cohort contained 6074 HIV/AIDS patients (Figure 2). The incidence proportion of new-onset thrombocytopenia and thrombocytosis were 0.5% (31/6074) and 13.4% (814/6074). From the vertical perspective, the incidence rate of thrombocytosis reached the top (7.2/100 PYFU) after one year of ART, which was much higher than thrombocytopenia (0.25/100 PYFU, p <0.001). The specific incidence rates of thrombocytopenia/thrombocytosis at different ART period (0, 12m, 24m, 36m, 48m, 60m, 72m, and 84m) were 2.65/5.85, 0.25/7.2, 0.19/6.31, 0.16/4.74, 0.16/4.55, 0.16/4.48, 0.15/4.41, and 0.15/4.39 (Figure 2).

Risk Factors for New-Onset Thrombocytosis After 12 Months of ART

Taking into account the performances of platelets oddities throughout the observation period, we further analyzed the perilous elements of new-onset thrombocytosis after 1 year of therapy. So, all the below results precluded thrombocytopenia (n=13) from total cases (n=5208).

On the whole, the number of participants who received zidovudine (AZT)-based regimen was 133 (2.6%), tenofovir (TDF)-based regimen was 4951 (95.3%), lopinavir/ritonavir (LPV/r)-based regimen was 85 (1.6%) and integrase inhibitors (INSTIs) was 26 (0.5%) (Figure 3A).

As for thrombocytosis, the prevalence before initiation of therapy was 5.85/100 PYFU, whereas after ART, it increased to 7.20/100 PYFU. Of 7.2% of study subjects with thrombocytosis, 2.7% were taking AZT-based regimen, 2.7% were receiving LPV/r-based regimen, and 94.6% were on TDF-based regimen (Figure 3B). Table 3 displayed the ratio of thrombocythemia in each regimen after 12 months of therapy, and there was no difference among different regimens (P >0.05) (Supplementary Table).

Furthermore, we also assessed other potential burdens via univariate and multivariate Cox proportional hazard models, and the results showed that female (OR: 3.422, 95% CI: 2.418–4.843, $p < 0.001$) and BMI > 24.0 kg/m^2 (OR: 1.472, 95% CI: 1.145, 1.894, $p = 0.003$, versus normal BMI) had a statistically remarkable relation with the occurrence of thrombocythemia, while the effect of WBC count < 4.0 x 10^9/L (OR: 0.537, 95% CI: 0.349–0.824, $p = 0.004$, versus WBC level ≥ 4.0 x 10^9/L) was opposite (Table 4).

Discussion

In our study, the overall prevalence of thrombocytopenia was 2.65% prior to starting ART, which is inconsistent with the outcomes of previous reports of 4.5%-26.0%.[3–5] The discrepancy may be due to different definitions, races, disease stages, and the benefits of implementing of "treated all" strategy in recent years.

Cytopenia often affects all lineages of blood cells including anemia, leukopenia as well as

Table 2 Logistic Regression Analysis to Identify Factors Associated with Thrombocytopenia or Thrombocytosis in ART-Naïve Patients

Variables	Thrombocytopenia				Thrombocytosis			
	OR (95% CI)	*P* value	AOR (95% CI)	*P* value	OR (95% CI)	*P* value	AOR (95% CI)	*P* value
Age (years)	1.041(1.029, 1.052)	<0.001	1.029(1.015, 1.042)	<0.001	0.995(0.984, 1.005)	0.316		
Sex								
Male	Ref	–			Ref	–		
Female	1.386(0.723, 2.656)	0.326			1.517(0.985, 2.336)	0.059		
Transmission route								
Homosexual	Ref	–			Ref	–		
Heterosexual	2.206(1.516, 3.209)	<0.001			1.317(0.983, 1.764)	0.065		
Other/unknown	2.189(1.385, 3.461)	0.001			1.340(0.936, 1.920)	0.110		
WHO clinical stage								
I–II	Ref	–			Ref	–		
III–IV	1.868(1.202, 2.904)	0.005			1.152(0.800, 1.658)	0.448		
BMI (kg/m^2)								
18.5–24.0	Ref	–			Ref	–		
< 18.5	1.455(0.878, 2.412)	0.145			1.429(1.002, 2.038)	0.049		
> 24.0	0.799(0.513, 1.244)	0.321			1.109(0.843, 1.458)	0.461		
HBsAg								
Negative	Ref	–	Ref	–	Ref	–		
Positive	3.309(1.960, 4.713)	<0.001	2.825(1.782, 4.480)	<0.001	0.892(0.548, 1.451)	0.646		
Anti-HCV								
Negative	Ref	–			Ref	–		
Positive	2.067(0.950, 4.499)	0.067			0.259(0.064, 1.053)	0.059		
Syphilis								
Negative	Ref	–			Ref	–		
Positive	1.023(0.739, 1.416)	0.892			1.246(0.998, 1.557)	0.053		
Baseline VL (copies/mL)								
<100,000	Ref	–			Ref	–		
≥100,000	2.246(1.655, 3.047)	<0.001			1.417(1.142, 1.758)	0.002		
Baseline CD4 count (cells/μL)								
<350	Ref	–	Ref	–	Ref	–	Ref	–
≥350	0.312(0.210, 0.465)	<0.001	0.527(0.338, 0.821)	0.005	1.144(0.930, 1.409)	0.203	1.616(1.231, 2.122)	0.001

(*Continued*)

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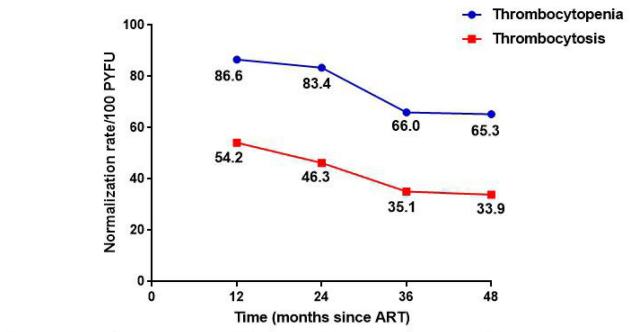
Table 2 (Continued).

Variables	Thrombocytopenia				Thrombocytosis			
	OR (95% CI)	*P* value	AOR (95% CI)	*P* value	OR (95% CI)	*P* value	AOR (95% CI)	*P* value
Baseline CD4/CD8 ratio								
<0.4	Ref	–			Ref	–		
≥0.4	0.378(0.243, 0.588)	<0.001			1.071(0.855, 1.341)	0.553		
WBC ($\times 10^9$ /L)								
≥4.0	Ref	–	Ref	–	Ref	–	Ref	–
<4.0	4.455(3.264, 6.080)	<0.001	2.464(1.717, 3.536)	<0.001	0.669(0.469, 0.954)	0.027	0.467(0.291, 0.750)	0.002
HGB (g/L)								
≥110(Female) or ≥120(Male)	Ref	–	Ref	–	Ref	–	Ref	–
<110(Female) or <120(Male)	6.265(4.494, 8.734)	<0.001	2.962(2.005, 4.377)	<0.001	3.496(2.682, 4.558)	<0.001	4.012(2.750, 5.854)	<0.001
NLR								
<2.0	Ref	–			Ref	–	Ref	–
2.0–4.0	1.521(1.082, 2.137)	0.016			1.551(1.225, 1.963)	<0.001	1.542(1.172, 2.029)	0.002
>4.0	2.885(1.884, 4.418)	<0.001			3.021(2.247, 4.060)	<0.001	2.008(1.334, 3.021)	0.001

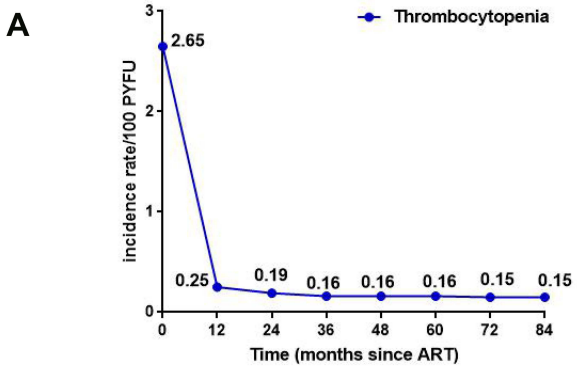
Note: Data are presented as n (%), or median (interquartile range).

Abbreviations: OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; WHO, world health organization; BMI, body mass index; HBsAg, hepatitis B surface antigen; Anti-HCV, antibody to hepatitis C virus; VL, viral load; WBC, white blood cell; HGB, haemoglobin; NLR, neutrophil-lymphocyte ratio.

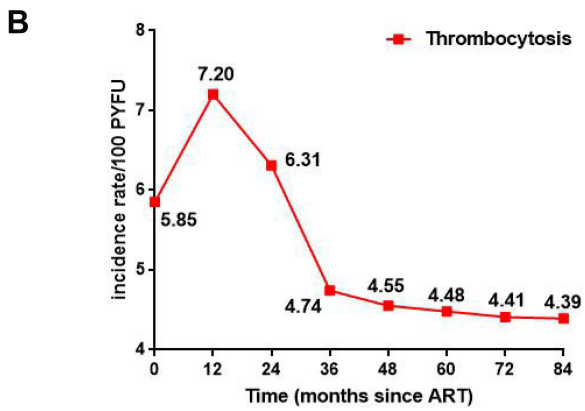


Recovery number	-	123	8	1	0
Total number	176	142	15	43	2
Recovery number	-	174	28	14	2
Total number	388	321	115	180	28

Figure 1 Recovery rate of thrombocyte abnormalities at different treatment duration. Recovery rate of thrombocytopenia and thrombocytosis after 12, 24, 36, and 48 months of antiretroviral therapy (blue: thrombocytopenia; red: thrombocytosis).



Number at risk	176	13	5	6	4	2	0	1
Total number	6637	5208	4181	5984	2255	1437	775	296



Number at risk	388	375	200	115	61	43	14	6
Total number	6637	5208	3907	5432	1952	1210	612	228

Figure 2 Incidence of new-onset thrombocyte abnormalities at different treatment duration. (**A**) Rate of new-onset thrombocytopenia after 12, 24, 36, 48, 60, 72, and 84 months of antiretroviral therapy. (**B**) Rate of new-onset thrombocytosis after 12, 24, 36, 48, 60, 72, and 84 months of antiretroviral therapy.

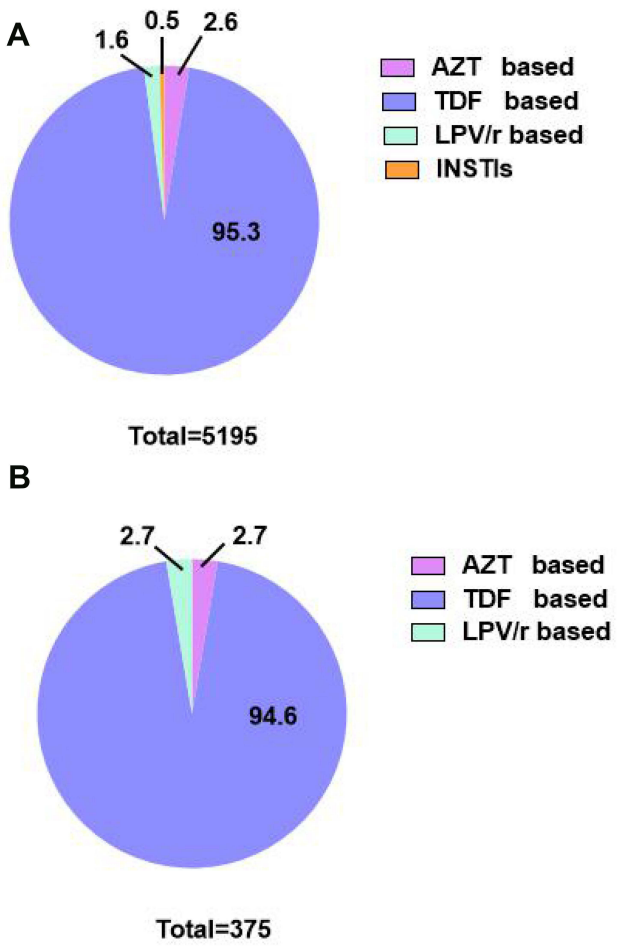


Figure 3 The proportion of different antiretroviral treatment regimens among HIV-infected patients. (**A**) The proportion of different antiretroviral treatment regimens among total subjects (n=5195). (**B**) The proportion of different antiretroviral treatment regimens in subjects with thrombocytosis (n=375).
Abbreviations: AZT, zidovudine; TDF, tenofovir; LPV/r, lopinavir/ritonavir; INSTIs, integrase inhibitors.

thrombocytopenia, and are the most common complications of treatment-naïve patients.[6,7] Higher viral loads, lower baseline CD4 levels, and advanced disease status

Table 3 The Ratio of Thrombocytosis in Each Regimen After 12 Months of Therapy

ART Regimen	Total Number	
	Normal	Thrombocytosis
TDF based	4596(92.83%)	355(7.17%)
AZT based	123(92.48%)	10(7.52%)
LPV/r based	75(88.24%)	10(11.76%)
INSTIs	26(100%)	0(0%)

Abbreviations: ART, antiretroviral therapy; TDF, tenofovir disoproxil fumarate; AZT, zidovudine; LPV/r, lopinavir/ritonavir; INSTIs, integrase inhibitors.

Table 4 Cox Proportional Hazard Regression Analysis to Identify Risk Factors Related to Thrombocytosis After 12 Months of Treatment

Factors	Thrombocytosis (n=375)		Normal (n=4820)		Univariate Analysis		Multivariate Analysis	
	N	%	N	%	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)								
<30	195	52	2433	50.5	Ref	–		
≥30	180	48	2387	49.5	0.897(0.733, 1.099)	0.295		
Sex								
Male	333	88.8	4654	96.6	Ref	–	Ref	–
Female	42	11.2	166	3.4	2.746(1.992, 3.786)	<0.001	3.422(2.418, 4.843)	<0.001
Transmission route								
Homosexual	282	75.2	3908	81.1	Ref	–		
Heterosexual	66	17.6	551	11.4	1.640(1.254, 2.143)	<0.001		
Other/unknown	27	7.2	361	7.5	1.043(0.702, 1.547)	0.836		
WHO clinical stage								
I–II	344	91.7	4352	90.3	Ref	–		
III–IV	23	6.1	388	8.0	0.674(0.442, 1.029)	0.067		
BMI (kg/m^2)								
18.5–24.0	173	46.1	2503	51.9	Ref	–	Ref	–
< 18.5	23	6.1	354	7.3	0.995(0.618, 1.475)	0.835	0.984(0.636, 1.524)	0.943
>24.0	96	25.6	887	18.4	1.437(1.119, 1.844)	0.004	1.472(1.145, 1.894)	0.003
HBsAg								
Negative	352	93.9	4494	93.2	Ref	–		
Positive	17	4.5	258	5.4	0.785(0.482, 1.277)	0.329		
Anti-HCV								
Negative	367	97.9	4639	96.2	Ref	–		
Positive	4	1.1	100	2.1	0.462(0.173, 1.238)	0.125		
Syphilis								
Negative	241	64.3	3008	62.4	Ref	–		
Positive	113	30.1	1617	33.5	0.847(0.678, 1.059)	0.146		
Baseline VL (copies/mL)								
<100,000	248	66.1	3312	68.7	Ref	–		
≥100,000	119	31.7	1361	28.2	1.097(0.882, 1.366)	0.405		
Baseline CD4 count (×10^9 /L)								
<350	205	54.7	2862	59.4	Ref	–		
≥350	164	43.7	1900	39.4	1.214(0.989, 1.491)	0.064		
Baseline CD4/CD8 ratio								
<0.4	267	71.2	3329	69.1	Ref	–		
≥0.4	95	25.3	1351	28.0	0.943(0.746, 1.192)	0.626		
CD4 count at 1 year of ART (×10^9 /L)								
<350	73	19.5	1014	21.0	Ref	–		
≥350	226	60.3	2781	57.7	1.150(0.884, 1.496)	0.297		
WBC (×10^9 /L)								
≥4.0	342	91.2	4196	87.1	Ref	–	Ref	–
<4.0	33	8.8	624	12.9	0.634(0.443, 0.906)	0.012	0.537(0.349, 0.824)	0.004

(*Continued*)

Table 4 (Continued).

Factors	Thrombocytosis (n=375)		Normal (n=4820)		Univariate Analysis		Multivariate Analysis	
	N	%	N	%	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HGB (g/L)								
≥110(Female) or ≥120(Male)	348	92.8	4506	93.5	Ref	–		
<110(Female) or >120(Male)	27	7.2	314	6.5	1.032(0.697, 1.526)	0.876		
NLR								
<2.0	237	63.2	2867	59.5	Ref	–		
2.0–4.0	101	26.9	1460	30.3	0.863(0.682, 1.090)	0.216		
>4.0	31	8.3	369	7.7	1.060(0.733, 1.534)	0.755		

Notes: Data are presented as n (%), or median (interquartile range). Variable had missing values: WHO clinical stage = 88; BMI = 1159; HBV = 74; HCV =85; Syphilis = 216; VL = 155; CD4 count = 64; CD4/CD8 ratio = 153; CD4 count at 1 year of ART = 1101; NLR = 130.

Abbreviations: HR, hazard ratio; CI, confidence interval; WHO, world health organization; BMI, body mass index; HBsAg, hepatitis B surface antigen; Anti-HCV, antibody to hepatitis C virus; VL, viral load; WBC, white blood cell; HGB, haemoglobin; NLR, neutrophil-lymphocyte ratio.

are the driving forces for cytopenia among HIV/AIDS individuals.[3,8,9] Just as our study observed, patients with lower WBC, HGB and CD4 counts had an increased occurrence of thrombocytopenia.

Moreover, we also found that thrombocytopenia was remarkably associated with older age and HBV-infected. Populations of our cohort ranged from 18 to 83 years with a median age of 30 years (IQR: 26–37), which prompted the fact that young people with sexually active were vulnerable to HIV.[10] Besides, it also may be due to a higher prevalence of myelodysplasia in older persons.[11] HIV infection promoted hepatitis B activity, while liver impairments damaged thrombopoietin production, they worked together to accelerate the thrombocytopenia.[12,13]

Antiretroviral therapy can effectively recover the amounts of platelets.[14,15] Considering the myelosuppressive effects of AZT,[16,17] Ditan Hospital has gradually adopted TDF+3TC+EFV as the preferred regimen for HIV-infected patients since 2009. Nowadays, AZT-related thrombocytopenia has been relatively rare.

Compared with thrombocytopenia, thrombocytosis was often overlooked and the relevant data was limited. In our study, its prevalence was 5.85% among treatment-naïve patients. It can be divided as two types: primary/secondary thrombocythemia.[18] The latter is the most common in nowadays whose causes usually include acute/chronic infection, inflammation, hemorrhage/iron deficiency, drugs, and so on.[19,20]

The causes of thrombocytosis in HIV infection are complex. HIV virus itself,[21] immune activation factors (such as interleukins-1, IL-6, and tumor necrosis factor), anemia, protease inhibitors and others all contribute to its occurrence. IL-6 has thrombopoietic-like activity,[22] can cause a rise in thrombopoietin and the development of reactive thrombocytosis,[23] while erythropoietin has a structural similarity to thrombopoietin and could directly stimulate thrombopoietin receptors.[24] Moreover, protease inhibitors play a critical role in platelets storage by improving platelet survival time and reduce platelet aggregation.[25,26] With the therapy prolongs, HIV viremia is suppressed, the degree of immune activation is decreased, and anemia is rectified. It seems the reason why the incidence rate of thrombocytosis is higher within short-time ART, and lower after long-time ART.

In agreement with the above description, our consequences showed that patients with higher baseline CD4 counts, anemia, and elevated NLR were more susceptible to thrombocytosis. NLR was an indication of systemic inflammation and interrelated with all-cause mortality among HIV-infected people.[27,28]

Our data also reflected that anti-retroviral treatment had dual effects on thrombocytosis.[29–31] On the one hand, it can partially recover the quantity of PLTs; on the other hand, it promotes the appearance of thrombocytosis. Additionally, females and overweight were related to thrombocytosis in the process of ART. The possible explanations were anemia (such as menorrhagia, iron deficiency) and overnutrition.[32] Megakaryocyte proliferation was the reason for PLT count increased in iron deficiency anemia.[22,33]

HIV-1 infection increased the level of platelets activation.[34] A variety of cytokines including IL-1, IL-6,

TNF-α, TGF-β, and sCD14 were released by activated platelets promoted the occurrence of systemic inflammation,[31,35] then triggered multiple NAD (cardiovascular events, neurocognitive disorders, renal fibrosis).[34,36] Thrombocytosis further accelerated this process, and platelets activation still persisted despite successful ART.[34]

Objectively speaking, thrombocytopenia, which often causes critical situations that need to take medical action immediately (such as gastrointestinal hemorrhage, cerebral hemorrhage), has attracted deep attention. From the classification of WHO clinical stages to the formulation of clinical diagnosis and treatment strategies,[37] thrombocytopenia has always been an important consideration. While, the effects of thrombocytosis tend to be ignored in the clinical practice despite the consensus that it is an abnormal indicator. To make matters worse that PLT play a part in certain chronic disease (such as ischemic thrombosis and cardiovascular events[34]) which will bring patients with fatal trouble.

Our results showed that the incidence of thrombocytosis was much higher than that of thrombocytopenia, whether in ART-naïve patients or during ART. Simultaneously, the recovery rate of thrombocytosis by antiviral therapy was far less than thrombocytopenia. Therefore, while paying attention to thrombocytopenia, we should be highly vigilant about the thrombocytosis, and multidisciplinary collaboration is needed if necessary. It was reported that as classic antiplatelet drugs, clopidogrel and low-dose aspirin also have anti-inflammatory and anti-activation effects.[38,39] The clinical applications of them in HIV infection and pathogenesis remain further study.

This study has some limitations. Firstly, based on the inherent weakness of the retrospective study. Secondly, observational research restricts the discussion of mechanisms. Nevertheless, this large cohort investigation still likely reflects the actual circumstances of thrombocyte abnormalities of Chinese HIV-infected adults.

Conclusion

In the medical practice, while paying attention to thrombocytopenia, clinicians should be highly vigilant about the thrombocytosis of HIV/AIDS patients, and related treatment strategies need to be further studied.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation; and took part in drafting, revising or critically reviewing the article. Furthermore, all authors gave final approval for the version to be published; have agreed on the journal to which the article has been submitted.

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Disclosure

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