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The hematologic profile of Filipino HIV-infected individuals and its association with CD4 counts

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ABSTRACT

Introduction: Hematologic abnormalities are common in HIV and involve all blood cell lineages. A study on cytopenias, as correlated with disease progression, can be valuable in resource-limited settings. This study aimed to determine the hematologic profile of HIV patients and its association with CD4 count and antiretroviral (ARV) treatment.
Methods: This is a retrospective cohort study involving adult Filipino HIV patients with complete blood count (CBC) and CD4 count determinations prior to the initiation of ARV treatment and after ≥6 months of ARV treatment. Logistic regression was performed to determine the association between cytopenias and a CD4 count <200 cells/μL.
Results: The study included 302 patients. Anemia was the most common cytopenia. Anemia and leukopenia were associated with an increased likelihood of having a CD4 count <200 cells/μL in ARV-naïve patients. In ARV-treated patients, leukopenia was associated with an increased probability of having a CD4 count <200 cells/μL. An increase in hemoglobin, white blood cell (WBC) and platelet counts was observed after ≥6 months of ARV treatment.
Conclusion: Anemia and leukopenia can be used as markers of immune status in HIV-infected individuals and improvement in the CBC parameters can be used to assess response to ARV treatment. Routine monitoring of hematologic parameters is recommended.

Introduction

Infection with the human immunodeficiency virus (HIV) results in acquired immunodeficiency syndrome (AIDS), which is characterized by opportunistic infections and malignant neoplasms that rarely affect immunocompetent individuals.[1] Hematologic abnormalities are seen at every stage of HIV and involve all blood cell lineages. The hematologic profile of HIV-infected patients appears to be reflective of the level of viral replication, with severe abnormalities noted in patients having a decreased CD4 count and high viral load.[1–3] Cytopenias develop due to various mechanisms. HIV infection causes increased expression of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), trans-

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forming growth factor-beta (TGF-β) and interleukin-1 (IL-1), which results in myelosuppression and changes in the bone marrow microenvironment. Immune-mediated destruction of blood cells may also occur. Opportunistic infections, malignancies and the treatment of HIV itself may also contribute to the development of cytopenias.[1] Several studies have revealed anemia to be the most common cytopenia in HIV-infected individuals.[2–7] Studies in Brazil further determined that anemia in HIV patients was independently associated with mortality, thus making hemoglobin a useful biomarker of prognosis.[6,7]

The Philippines has the highest increase in new HIV cases in the Asia Pacific region, with 36 new cases per day recorded in 2019.[8] There are few studies on the hematologic manifestations of HIV, as correlated with CD4 counts and antiretroviral (ARV) treatment, and no studies involving the Filipino population. This study aims to determine the hematologic profile of HIV-infected individuals and its association with CD4 count and ARV treatment. The complete blood count (CBC) is a readily available monitoring test, with a cost ranging from 200 to 500 Philippine pesos (equivalent to 4.12–10.29 US dollars), at government and private hospitals. The cost of CD4 count determination is 1800–2000 Philippine pesos (equivalent to 37.06–41.17 US dollars) at government and private hospitals. If we can establish that cytopenias in HIV are associated with disease progression, we may be able to decrease the financial strains associated with monitoring.

Methods

Study setting and population

This is a retrospective cohort study that included all adult (age ≥18 years) Filipino HIV-infected patients enrolled at the HIV treatment hub of a government tertiary referral center in the Philippines. It is not a routine procedure to measure the CBC and the CD4 count of patients on the same day at our institution. As such, we limited our population to patients with the CBC and CD4 count measured within 3 months of each other at baseline, prior to the initiation of any ARV treatment, and ≥6 months after this treatment. Recommendations regarding the frequency of CD4 count monitoring are every 3–6 months, if ARV treatment is deferred, and every 3 months after the initiation of ARV treatment,[9] hence the decision to limit the time interval between the CBC and CD4 count measurement to 3 months. Pregnant patients were excluded.

One thousand five hundred and eighteen charts of Filipino HIV-infected patients were available for review, of which 302 patients fulfilled the inclusion criteria. Patients were stratified according to the CD4 count: <200 cells/μL and ≥200 cells/μL.

Definition of parameters

Anemia was defined as hemoglobin <13 g/dL for adult men and <12 g/dL for adult non-pregnant women.[10] Patients with a white blood cell (WBC) count $<4.5 \times 10^9$/L were determined to have leukopenia.[11] A platelet count $<150 \times 10^9$/L was defined as thrombocytopenia.[11]

Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range (IQR) for non-normally distributed continuous variables and mean and standard deviation (SD) for normally distributed continuous variables. The odds ratio and corresponding 95% confidence intervals (95% CI) from binary logistic regression were computed to determine the factors significantly associated with a CD4 count less than 200 cells/μL at baseline and after at least 6 months of ARV treatment. After determining the significant factors in univariate analysis, those factors underwent a stepwise method to determine the significant factors in multivariate analysis. The Wilcoxon signed rank test was used to determine the difference in CBC parameters and CD4 counts from baseline to ≥6 months of ARV treatment. All statistical tests were two-tailed. The Shapiro–Wilk test was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at the 0.05α-level of significance. STATA 13.1 was used for data analysis.

For all statistical analyses, we opted for a subset analysis of patients with the CBC and CD4 count measured on the same day at baseline, prior to the initiation of any ARV treatment, and patients with the CBC and CD4 count measured on the same day after ≥6 months of ARV treatment to account for the 3-month time interval between the CBC and CD4 count determination, this being a potential confounding variable (See Appendix A Supplementary data).

Ethical considerations

This research was approved by the Institutional Research Ethics Board. This was a retrospective cohort that only involved chart review and abstraction, with no active patient-doctor relationship. There was no follow-up of patients. The data collection tools only included de-identified information, guaranteeing strict anonymity and total confidentiality. As the data gathered did not include any personally identifiable information, the hospital's research ethics committee waived the requirement for individual written informed consent.

Results

Three hundred and two patients were included in the study. Of these, 129 patients had the CBC and CD4 count measured on the same day at baseline and 108 patients had the CBC and CD4 count measured on the same day after ≥6 months of ARV treatment. Table 1 demonstrates the demographic and clinical profile of all 302 patients at baseline. The mean age was 30.37 years (SD ± 7.5), patients were predominantly male (96.69%), single (92.05%), and employed (64.57%), with tuberculosis (41.72%) being the most prevalent opportunistic infection.

The hematologic profile and CD4 count at baseline, prior to ARV treatment and after ≥6 months of ARV treatment are presented in Table 2. A total of 166 patients (54.97%) had at

Table 1 – Demographic and clinical profile of patients at baseline (n = 302).

	Frequency (%)
Age (years)	
18–24	65 (21.52)
25–34	171 (56.62)
35–44	47 (15.56)
>45	19 (6.29)
Sex	
Male	292 (96.69)
Female	10 (3.31)
Civil status	
Single	278 (92.05)
Married	24 (7.95)
Occupation	
Employed	195 (64.57)
Unemployed	107 (35.43)
Opportunistic infections	
Tuberculosis (TB)	126 (41.72)
Pneumocystis pneumonia (PCP)	54 (17.88)
Oral candidiasis	44 (14.57)
Cryptococcosis	11 (3.64)
Toxoplasmosis	10 (3.31)
Cytomegalovirus (CMV)	7 (2.32)
Human papillomavirus (HPV)	6 (1.99)
Herpes simplex virus (HSV)	6 (1.99)
Cryptosporidiosis	6 (1.99)
Kaposi sarcoma	1 (0.33)
Mycobacterium avium complex (MAC)	1 (0.33)
Co-infections	
Hepatitis B	40 (13.25)
Hepatitis C	7 (2.32)
Prophylactic medications	
Cotrimoxazole	105 (34.77)
Azithromycin	73 (24.17)

least one form of cytopenia at baseline. Anemia was the most common cytopenia, followed by leukopenia and thrombocytopenia. A majority of the patients had a baseline CD4 count <200 cells/μL (65.89%). After ≥6 months of ARV treatment, the number of patients with anemia, leukopenia and thrombocytopenia dropped by 30.8%, 8.61% and 3.98%, respectively. The number of patients with a CD4 < 200 cells/μL decreased by 31.45%. A total of 78 patients (25.83%) had at least one form of cytopenia after ≥6 months of ARV treatment. Anemia was still the most common cytopenia, followed by leukopenia and thrombocytopenia. A majority of the patients had a CD4 count ≥200 cells/μL (65.56%) after ≥6 months of ARV treatment.

Logistic regression was performed to determine the association between anemia, leukopenia and thrombocytopenia with the CD4 count prior to ARV treatment (Table 3). In the univariate analysis, patients with anemia were 6.05 times more likely to have a CD4 count <200 cells/μL ($p < 0.001$). Patients with leukopenia were 4.3 times more likely to have a CD4 count <200 cells/μL ($p < 0.001$). In the multivariate analysis, anemic patients were 3.86 times more likely to have a CD4 count <200 cells/μL ($p < 0.001$) and leukopenic patients were 3.96 times more likely to have a CD4 count <200 cells/μL ($p = 0.002$).

The multivariate analysis of the subset of 129 ARV-naïve patients (See Supplementary data, Table S1), with the CBC and

Table 2 – Cytopenias and CD4 count at baseline and after ≥6 months of ARV treatment (n = 302).

	Baseline Frequency (%)	≥6 months of ARV treatment Frequency (%)
Any Cytopenia	166 (54.97)	78 (25.83)
Anemia	138 (45.70)	45 (14.90)
Hb 11–11.9 g/dL (F) or 12.9 g/dL (M)	92 (30.46)	32 (10.60)
Hb 8–10.9 g/dL	43 (14.24)	13 (4.30)
Hb <8 g/dL	3 (0.99)	0
Leukopenia	67 (22.19)	41 (13.58)
WBC 3.0–4.49 × 10^9/L	53 (17.55)	40 (13.25)
WBC 2.0–2.99 × 10^9/L	10 (3.31)	1 (0.33)
WBC <2.0 × 10^9/L	4 (1.32)	0
Thrombocytopenia	15 (4.97)	3 (0.99)
Plt 71–149 × 10^9/L	12 (3.97)	3 (0.99)
Plt 20–70 × 10^9/L	1 (0.33)	0
Plt <20 × 10^9/L	2 (0.66)	0
CD4 count		
<200 cells/μL	199 (65.89)	104 (34.44)
≥200 cells/μL	103 (34.11)	198 (65.56)

Hb: hemoglobin; M: male; F: female; WBC: white blood cell count; Plt: platelet count.

CD4 count measured on the same day, revealed that patients with anemia were 6.26 times more likely to have a CD4 count <200 cells/μL ($p < 0.001$). Patients with leukopenia were 4.75 times more likely to have a CD4 count <200 cells/μL ($p = 0.021$). The association between thrombocytopenia with a CD4 count <200 cells/μL was not significant.

All 302 patients were started on a combination of antiretrovirals. Two hundred and ninety-nine patients (99.01%) were given Lamivudine, 273 patients (90.4%) were started on Efavirenz, 229 patients (75.83%) received Tenofovir, 77 patients (25.5%) were started on Zidovudine, 28 patients (9.27%) were given Nevirapine, three patients (0.99%) received Lopinavir and Ritonavir, and one patient (0.33%) was given Stavudine. One hundred and sixty patients (52.98%) were on Cotrimoxazole and 111 patients (36.75%) were on Azithromycin after ≥6 months of ARV treatment.

Logistic regression was performed to determine the association between anemia, leukopenia and thrombocytopenia with CD4 count after ≥6 months of ARV treatment (Table 4). In the univariate analysis, anemic patients were 2.53 times more likely to have a CD4 count <200 cells/μL ($p = 0.005$). Leukopenic patients were 7.98 times more likely to have a CD4 count <200 cells/μL ($p < 0.001$). In the multivariate analysis, patients with leukopenia were 7 times more likely to have a CD4 count <200 cells/μL ($p < 0.001$).

The multivariate analysis of the subset of 108 patients (See Supplementary data, Table S2) treated with antiretrovirals for ≥6 months, with the CBC and CD4 count measured on the same day, revealed that patients with leukopenia were 8.21 times more likely to have a CD4 count <200 cells/μL ($p = 0.002$). The association between anemia and thrombocytopenia with a CD4 count <200 cells/μL was not significant.

There was a statistically significant increase in hemoglobin, WBC and platelet count after ≥6 months of ARV treatment (Table 5). There was also a significant increase in the CD4 count with treatment.

Table 3 – Univariate and multivariate analyses of factors associated with a CD4 count <200 cells/μL prior to ARV treatment (n = 302).

	Univariate analysis		Multivariate analysis	
	Odds ratio(95% CI)	P-value	Odds ratio(95% CI)	P-value
Anemia	6.05 (3.44–10.63)	**<0.001**	3.86 (1.94–7.68)	**<0.001**
Leukopenia	4.30 (2.03–9.09)	**<0.001**	3.96 (1.63–9.63)	**0.002**
Thrombocytopenia	0.78 (0.27–2.24)	0.638	–	–
Use of Azithromycin	–	–	–	–
Use of Cotrimoxazole	54.18 (13–225)	**<0.001**	38.68 (8.93–167)	**<0.001**
Age	1.01 (0.98–1.04)	0.596	–	–
Male	–	–	–	–
Single	1.17 (0.50–2.78)	0.715	–	–
Employed	0.53 (0.31–0.89)	**0.017**	–	–
Co-infection				
Hepatitis B	0.66 (0.34–1.30)	0.231	–	–
Hepatitis C	0.38 (0.08–1.73)	0.210	–	–
Opportunistic infections				
TB	5.61 (3.14–10)	**<0.001**	–	–
PCP	37.03 (5.04–272)	**<0.001**	13.42 (1.66–108)	**0.015**
Oral candidiasis	4.78 (1.82–12.53)	**0.001**	3.28 (1.02–10.45)	**0.045**
Cryptococcosis	–	–		–
Toxoplasmosis	–	–	–	–
CMV	3.17 (0.38–26.70)	0.288	–	–
HPV	1.04 (0.19–5.75)	0.968	–	–
HSV	0.51 (0.10–2.57)	0.415	–	–
Cryptosporidiosis	–	–	–	–
Kaposi sarcoma	–	–	–	–
MAC	–	–	–	–

ARV: antiretroviral; TB: tuberculosis; PCP: Pneumocystis pneumonia; CMV: cytomegalovirus; HPV: human papillomavirus; HSV: herpes simplex virus; MAC: *Mycobacterium avium* complex.
The p-values in bold are the ones that are statistically significant.

Table 4 – Univariate and multivariate analyses of factors associated with a CD4 count <200 cells/μL after ≥6 months of ARV treatment (n = 302).

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Anemia	2.53 (1.33–4.81)	**0.005**	–	–
Leukopenia	7.98 (3.73–17.11)	**<0.001**	7 (2.88–17.04)	**<0.001**
Thrombocytopenia	0.90 (0.08–10.09)	0.934	–	–
Use of Azithromycin	9.92 (5.72–17.17)	**<0.001**	4.91 (2.48–9.75)	**<0.001**
Use of Cotrimoxazole	9.63 (5.25–17.65)	**<0.001**	3.56 (1.69–7.49)	**0.001**
Age	0.99 (0.95–1.02)	0.400	–	–
Male	1.28 (0.35–4.64)	0.707	–	–
Single	1.63 (0.63–4.25)	0.315	–	–
Employed	0.64 (0.39–1.04)	0.071	–	–
Co-infection				
Hepatitis B	0.69 (0.33–1.44)	0.324	–	–
Hepatitis C	0.31 (0.04–2.62)	0.282	–	–
ARV regimen				
Lamivudine	–	–	–	–
Efavirenz	1.19 (0.52–2.71)	0.685	–	–
Tenofovir	0.86 (0.50–1.49)	0.599	–	–
Zidovudine	1.12 (0.65–1.92)	0.680	–	–
Nevirapine	0.89 (0.39–2.05)	0.789	–	–
Lopinavir	0.95 (0.09–10.62)	0.968	–	–
Ritonavir	0.95 (0.09–10.62)	0.968	–	–
Stavudine	–	–	–	–

ARV: antiretroviral.
The p-values in bold are the ones that are statistically significant.

Table 5 – Trends in hematologic parameters following initiation of ARV treatment.

	Baseline	>6 months of treatment	P-value
	Median (IQR)		
Hemoglobin (g/dL)	13.2 (11.7–14.8)	14.65 (13.7–15.5)	**<0.001**
WBC count ($\times 10^9$/L)	5.82 (4.7–7.46)	6.2 (5.1–7.98)	**0.007**
Platelet count ($\times 10^9$/L)	260 (215–314.5)	277 (236–322)	**0.025**
CD4 count (cells/μL)	77 (22–263)	274 (152–453)	**<0.001**

ARV: antiretroviral; IQR: interquartile range; WBC: white blood cell.
The p-values in bold are the ones that are statistically significant.

Discussion

Our study revealed that anemia was the most common cytopenia, observed in 45.70% of the patients prior to ARV treatment. This is consistent with studies conducted in Brazil, Africa, and Asia.[4,6,12–15] The prevalence of leukopenia in our study was similar to that of studies performed in Africa and China.[3,4,16] Thrombocytopenia was the least common form of cytopenia noted, comparable to studies conducted in Africa and India.[2,4]

The majority of prior research has attempted to determine correlates and indicators, such as the CD4 count, of cytopenias in the HIV population.[3,4,12–17] A low CD4 count was associated with anemia in several studies of ARV-naïve and ARV-treated HIV patients.[2,3,6,13–15,17–19] However, a study in Uganda on a mixed population of ARV-naïve and ARV-treated patients and a study in Ethiopia on ARV-treated patients revealed that a low CD4 count was not significantly associated with anemia.[4,12] A low CD4 count was also observed to be correlated with leukopenia in ARV-naïve and ARV-treated patients.[3,4,16,18] Some studies revealed that a low CD4 count was an indicator of thrombocytopenia,[3,4,16] while others did not.[2,18] Our study, on the other hand, attempted to determine whether cytopenias could serve as indicators of immune suppression. Our study revealed that patients with anemia and leukopenia had an increased likelihood of having a CD4 count <200 cells/μL in ARV-naïve patients. The association of anemia and leukopenia with increased odds of having a CD4 count <200 cells/μL is likely due to the cytokine-mediated inhibitory effects on hematopoietic progenitor cells resulting from the increased HIV viral burden.[1,4] Thrombocytopenia was not common in our population, which could be a reason as to why we were not able to establish a significant association with a low CD4 count. Our study also determined that ARV-naïve patients with oral candidiasis were consistently more likely to have a CD4 count <200 cells/μL (based on the study population and subset analysis). Oral candidiasis is an opportunistic infection that is widely recognized as an indicator of immune suppression.[20] Studies have established that its occurrence is significantly associated with a CD4 count below 200 cells/μL.[21,22]

Our study also demonstrated that after a minimum of 6 months of ARV treatment, leukopenia was associated with an increased likelihood of having a CD4 count <200 cells/μL. Our findings suggest that the inhibition of leukopoiesis by HIV itself could still be the predominant etiology of leukopenia in ARV-treated patients. The number of patients with anemia decreased by as much as 30.8% after ARV treatment. Our analysis revealed that anemia was no longer associated with an increased likelihood of a low CD4 count after ≥6 months of ARV treatment. This is in agreement with the study of Woldeamanuel and Wondimu, which revealed no significant association between anemia and the CD4 cell counts after initiating ARV treatment.[12] We can surmise that anemia in ARV-treated patients may not be primarily due to HIV-associated cytokine-induced myelosuppression, but rather a result of other factors, such as nutritional deficiencies and drug effects.[1,23] Our study also consistently revealed that ARV-treated patients on Azithromycin were more likely to have a CD4 count <200 cells/μL (based on the study population and subset analysis). *Mycobacterium avium* complex (MAC) is an opportunistic infection that typically occurs when the CD4 level is <50 cells/μL.[20] At our institution, we use this CD4 count cut-off to initiate prophylaxis for MAC disease with Azithromycin. Hence, patients who were on this drug at ≥6 months of ARV treatment were the patients with a much lower starting CD4 count of <50 cells/μL, which could account for the association between Azithromycin and a low CD4 count.

We also sought to determine the trends in hematologic parameters after the initiation of ARV treatment to determine if any significant patterns would emerge that could be useful during the follow-up of our patients. A statistically significant increase was noted in hemoglobin, WBC and platelet counts after ≥6 months of ARV treatment. This was consistent with studies conducted in Africa, which observed an increase in these hematologic parameters with ARV treatment.[12,24,25] This result is likely due to the positive effect of ARV treatment on the differentiation and survival of hematopoietic cells. The decrease in opportunistic infections, inflammation and immune phenomenon due to a decreasing viral burden, as a consequence of ARV therapy, all play a role in the improvement of hematologic parameters.[12]

We opted to include in our study all 302 patients who had the CBC and CD4 counts measured within 3 months of each other prior to ARV treatment and after ≥6 months of ARV treatment, as this was reflective of practices at our institution. Our subset analysis of patients with the CBC and CD4 count measured on the same day was consistent with the analysis made on all 302 patients, in terms of the associations between anemia, leukopenia and thrombocytopenia with the CD4 count. Thus, the results of our study can be applied to our patients, whose CBC and CD4 counts were measured within 3 months of each other.

The findings of this study are limited by its retrospective design and involvement of only one HIV treatment hub. The CBC and CD4 counts were performed at different diagnostic centers, hence differences in automated cell counters could

have led to some variability in results. Males comprised the majority of the study population, which is reflective of the epidemiology of HIV in the Philippines, where males are disproportionately affected, accounting for 94% of the total HIV population. This can be attributed to sexual contact among males who have sex with males (MSM) as the predominant mode of HIV transmission (85%) in the Philippines.[8] Since the population studied was predominantly male, the results of this study may not be generalizable to females with HIV. Several studies have identified ethnicity, age, sex, body mass index, tuberculosis and oral candidiasis as factors associated with cytopenias in HIV.[3,4,13–16] Some of these factors are interdependent and can exacerbate each other.[15] Our study did not determine the different etiologies of cytopenias in the Filipino HIV population. Hence, we recommend further studies to determine how demographic factors, opportunistic infections, drugs and nutrition, which are known to contribute to the development of cytopenias, could impact the association of anemia and leukopenia with the CD4 count. Nevertheless, our study does reveal that anemia and leukopenia can be used as markers of immune status in HIV-infected individuals, which is very valuable in resource-limited settings with rapidly increasing new HIV cases, such as in the Philippines.

Conclusion

Anemia and leukopenia are associated with an increased likelihood of having a CD4 count <200 cells/μL in ARV-naïve patients infected with HIV. In ARV-treated patients, the presence of leukopenia is associated with an increased probability of having a CD4 count <200 cells/μL. The presence of anemia and leukopenia in HIV-infected individuals can serve as indicators of disease progression and improvement in CBC parameters can be used to assess response to ARV treatment. The routine monitoring of hematologic parameters should thus be implemented for HIV-infected patients, as it can serve as an accessible and inexpensive indicator of their clinical-immunologic status.

Authors' contributions

PPMV, IRST, CLRA, TED contributed to the conception and design of the study.

PPMV, IRST, JRMC performed the data collection, analysis and interpretation of data.

PPMV drafted the manuscript. IRST, JRMC, CLRA, TED revised it critically for important intellectual content. All authors approved the final manuscript for publishing.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.htct.2020.10.964.

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