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Assessment of haematological parameters in HIV-infected and uninfected Rwandan women: a cross-sectional study

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ABSTRACT

Objectives: Although haematological abnormalities are common manifestations of HIV infection, few studies on haematological parameters in HIV-infected persons have been undertaken in sub-Saharan Africa. The authors assessed factors associated with haematological parameters in HIV-infected antiretroviral-naïve and HIV-uninfected Rwandan women.

Study design: Cross-sectional analysis of a longitudinal cohort.

Setting: Community-based women's associations.

Participants: 710 HIV-infected (HIV+) antiretroviral-naïve and 226 HIV-uninfected (HIV−) women from the Rwanda Women's Interassociation Study Assessment. Haematological parameters categorised as (abnormal vs normal) were compared by HIV status and among HIV+ women by CD4 count category using proportions. Multivariate logistic regression models using forward selection were fit.

Results: Prevalence of anaemia (haemoglobin (Hb) <12.0 g/dl) was higher in the HIV+ group (20.5% vs 6.3%; p<0.001), and increased with lower CD4 counts: ≥350 (7.6%), 200–349 (16%) and <200 cells/mm^3 (32.2%). Marked anaemia (Hb <10.0 g/dl) was found in 4.2% of HIV+ and none of the HIV− women (p<0.001), and was highest in HIV+ women with CD4 <200 cells/mm^3 (8.4%). The HIV+ were more likely than HIV− women (4.2 vs 0.5%, respectively, p=0.002) to have moderate neutropenia with white blood cells <2.0×10^3 cells/mm^3 and 8.4% of HIV+ women with CD4 <200 cells/mm^3 had moderate neutropenia. In multivariate logistic regression analysis, BMI (OR 0.87/kg/m^2, 95% CI 0.82 to 0.93; p<0.001), CD4 200–350 vs HIV− (OR 3.59, 95% CI 1.89 to 6.83; p<0.001) and CD4 <200 cells/mm^3 vs HIV− (OR 8.09, 95% CI 4.37 to 14.97; <0.001) had large independent associations with anaemia. There were large independent associations of CD4 <200 cells/mm^3 vs HIV− (OR 7.18, 95% CI 0.78 to 65.82; p=0.081) and co-trimoxazole and/or dapsone use (OR 5.69, 95% CI 0.63 to 51.45; p=0.122) with moderate neutropenia.

Conclusions: Anaemia was more common than neutropenia or thrombocytopenia in the HIV-infected Rwandan women. Future comparisons of haematological parameters in HIV-infected patients before and after antiretroviral therapy initiation are warranted.

ARTICLE SUMMARY

Article focus

Hypotheses and research question addressed

- Haematological abnormalities are common manifestations of HIV infection.
- However, few studies on haematological parameters exist in HIV-infected persons in sub-Saharan Africa.
- What are the factors associated with haematological parameters in HIV-infected antiretroviral-naïve and HIV-uninfected Rwandan women?

Key messages

- Anaemia was the most common haematological abnormality than neutropenia and thrombocytopenia in HIV-infected and HIV-uninfected Rwandan women.
- Of note, anaemia was more common in the HIV-infected than in HIV-uninfected women, especially those with greater disease progression as indicated by lower CD4 cell counts.
- Anaemia and neutropenia which are the most common haematological abnormalities in HAART-naïve HIV-infected women need to be routinely assessed for timely and adequate clinical management.

Strengths and limitations of this study

- Our study has a large sample size from which we can conclusively draw observational conclusions on occurrence and factors associated with haematological parameters.
- We assessed haematological parameters in HAART-naïve HIV-infected and HIV-uninfected women, which gives both a comparison strength with uninfected women as well as HAART-naïve group of women.
- However, our study is limited by the fact that all participants were women, and as haematological parameters differ between men and women our findings cannot be extrapolated to men.

INTRODUCTION

AIDS is a systemic disorder caused by the HIV, and characterised by severe impairment and progressive damage of both cellular and humoral immune responses. Besides immunological complications of HIV disease,[1] haematological abnormalities have been documented as strong independent predictors of morbidity and mortality in HIV-infected individuals.[2] HIV replicates not only in CD4 lymphocyte cells, but also in macrophages and dendritic cells.[1 3 4] Such replication is followed by immune system depression, which can lead to life-threatening opportunistic infections. Haematological complications such as mild-to-severe anaemia are associated with HIV disease progression and subsequent reduced survival.[5]

Although numerous complications occur in HIV-infected patients,[2 6 7] the most common haematological abnormalities are anaemia and neutropenia.[6] Anaemia and neutropenia are generally caused by inadequate blood cell production because of bone marrow suppression by HIV infection mediated by abnormal cytokine expression and alteration of the bone marrow microenvironment.[5 8] Anaemia in HIV-infected persons is associated with CD4 cell depletion and progression to AIDS[9] and is one of the strongest predictors of HIV mortality and poor responses to antiretroviral therapy (ART).[2] Neutropenia is frequently observed in advanced stages of HIV infection after development of AIDS, and has been associated with certain types of antiretroviral medications used to treat HIV infection.[10] Thrombocytopenia is characterised by platelet counts below $125\times10^3/mm^3$, and also frequently occurs in HIV-infected patients.[11–13] Haematological parameters mainly anaemia and leukopaenia in HIV-infected ART-naïve patients result in poor ART-treatment outcome and otherwise strongly predict mortality.[2 14 15]

Although haematological abnormalities are common manifestations of HIV infection and AIDS, and may have considerable impact on patients' well-being, treatment and care, few studies on haematological parameters in HIV-infected persons have been undertaken in sub-Saharan Africa. Such information for HIV-infected adults in Rwanda may help to inform treatment of HIV-infected individuals in this region. We therefore assessed haematological parameters in HIV-infected antiretroviral-naïve and HIV-uninfected Rwandan women.

MATERIALS AND METHODS

Study design

Participants were from the Rwanda Women's Interassociation Study and Assessment (RWISA), a prospective observational cohort study on the effectiveness and toxicity of ART that enrolled 710 HIV-infected and 226-uninfected women in 2005. Participants from RWISA were recruited from the Women's Equity in Access to Care and Treatment (WE-ACTx) clinical site in Kigali, community-based organisations, associations of people living with HIV/AIDS, and HIV Health Center clinical care sites in Kigali. Volunteers were included if they were ART naïve except for possible exposure to single-dose nevirapine to prevent mother to child HIV transmission; were ≥25 years of age, had resided in Rwanda in 1994, and if HIV negative would be willing to undergo voluntary counselling and testing for HIV at 6-month intervals. All participants provided information on medical history, demographic characteristics, psychosocial history, experience of trauma during the 1994 Rwandan genocide and symptoms of depression and posttraumatic stress. This also includes symptoms and diagnoses that define WHO stage-IV HIV illness. A physical assessment was performed and specimens were taken for CD4 cell count, full blood count and other laboratory studies. Written informed consent was obtained from each participant in the local language (Kinyarwanda) in accordance with this study's protocols and procedures approved by the Rwanda National Ethics Committee and the Institutional Review Board of Montefiore Medical Center, Bronx, New York, USA. Details of the RWISA study procedures and informed consent process including video and individual discussion have been previously described.[16]

Laboratory data

CD4 T lymphocytes counts were determined using the Becton Dickinson FASCount system (Becton Dickinson, Singapore) at the National Reference Laboratory, Kigali, Rwanda and full blood count analyses were performed at King Faisal Hospital in Kigali using CELL-DYN 1800 automated blood analyser (Abbott). A modified methaemoglobin method was used for the colorimetric determination of haemoglobin (Hb). A portion of the lysed, diluted sample from the white blood cells (WBC) mixing chamber was used for Hb measurement. Blood samples were sent to the central laboratory within 2 h after collection where HIV-1 status and CD4 count were assessed. Blood samples were tested for HIV using the Abbott's Combo HIV Test. WBC count and platelet counts were performed using automated haematological analyser (micro Cobas; Hoffman La Roche, Basel, Switzerland).

Statistical analysis

Leucocyte values, Hb levels and platelet counts were analysed as continuous variables and compared by HIV status and CD4 cell count category (<200, 200–349 and ≥350/mm^3) in HIV-positive women. Anaemia and marked anaemia were defined as Hb <12.0[17] and <10.0 mg/dl, respectively,[18 19] and neutropenia was examined at two thresholds: WBC count <2000 and <1000 cells/mm^3 while thrombocytopenia was defined as platelets $<125.0\times10^3/mm^3$.[17] Unadjusted statistical comparisons between (1) categorical predictors and categorical outcomes were made using χ^2 tests and (2) categorical predictors and continuous outcomes were made using t tests and analysis of variance.

Multivariate logistic regression models with anaemia, neutropenia and thrombocytopenia as outcomes were fit using forward selection and a p to enter of 0.2. Statistical analyses were performed using STATA V.11.0 and SAS V.9.1.3.

RESULTS

Demographic characteristics

All 936 (226 HIV− and 710 HIV+) women who participated in the RWISA study were included in this analysis. Table 1 presents characteristics of the HIV− and the HIV+ women by CD4 count category: ≥350, 200–349 and <200 cells/mm^3. HIV-uninfected, compared with HIV+ women were older (59% vs 22% over 40 years, respectively, p<0.001), and more likely to be widowed (51% vs 42%, p=0.001). Less than half (41%) of HIV-infected women reported a prior WHO stage IV condition. Use of dapsone or co-trimoxazole in the prior 12 months was reported by 87% of HIV+ and 19% of HIV− women (<0.001).

Comparisons of haematological parameters by HIV status and CD4 level in HIV+ women

Anaemia

Anaemia was more common in HIV+ than HIV− women (20.5% vs 6.3% respectively; p<0.001) and among HIV+ women the prevalence of anaemia was higher in the lower CD4 count categories: ≥350 (7.6%), 200–349 (16.0%) and <200 (32.2%) cells/mm^3 (table 1). Marked anaemia, defined as Hb <10.0 g/dl, was found in 4.2% of HIV+ and none of the HIV− women (p<0.001), again with the highest prevalence in HIV+ women with CD4 <200 cells/mm^3 (8.4%).

Neutropenia

Mean (±SD) WBC count was lower in HIV+ than HIV− women (3.7±1.4 vs 4.5±1.4×10^3 cells/mm^3); and among HIV+ women decreased from 4.3±1.6 in those with CD4 ≥350/mm^3 to 3.3±1.4×10^3 cells/mm^3 in women with CD4 <200/mm^3 p<0.001). Neutropenia, defined as WBC <2000×10^3 cells/mm^3, was more common in HIV+ than in HIV− women (4.2 vs 0.5%, p=0.006) and most prevalent in HIV+ women with CD4 <200 cells/mm^3 (8.4%, p<0.001). Only one HIV+ and one HIV− woman had profound neutropenia, defined as WBC <1000×10^3 cells/mm^3.

Thrombocytopenia

Mean platelet count was lower in the HIV+ compared to HIV− women: 223.2±109.0×10^3/mm^3 vs 231.8±84.5×10^3/mm^3, respectively, p=0.051 with minimal differences in platelet count by category of CD4 lymphocyte count in HIV+ women (p=0.55). Thrombocytopenia was more common in HIV+ compared to HIV− women: (13.5% vs 8.6%, p=0.047), with no significant differences among the CD4 groups in the HIV+ women (=0.92).

General univariate/multivariate associations with haematological outcomes

Table 2A–C present the results of univariate and multivariate logistic regression analyses with forward selection for all participants with; anaemia (Hb <12.0 vs ≥12.0 g/dl, neutropenia (WBC <2000 vs ≥2000 cells/mm^3) and thrombocytopenia (platelets <125 vs ≥125/mm^3), respectively, as outcomes. We summarise here the results of the multivariate models. Body mass index (BMI; OR 0.87 per kg/m^2, 95% CI 0.82 to 0.93; p<0.001), CD4 200–350 cells/mm^3 vs HIV− (OR 3.59, 95% CI 1.88 to 6.83; p<0.001) and CD4 <200 cells/mm^3 vs HIV− (OR 8.09, 95% CI 4.37 to 14.97; <0.001) had large independent associations with anaemia (table 2A). Income had some independent association with anaemia, but the trend and statistical significance across categories were not consistent. There were large independent associations of CD4 <200 cells/mm^3 vs HIV− (OR 7.18, 95% CI 0.78 to 65.82; p=0.08) and co-trimoxazole/dapsone use (OR 5.69, 95% CI 0.63 to 51.45; p=0.12) with neutropenia (table 2B). Finally, CD4 >350 vs HIV− (OR 2.18, 95% CI 1.10 to 4.32; p=0.03), CD4 200–350 vs HIV− (OR 2.36, 95% CI 1.25 to 4.56; p=0.008) and CD4 <200 cells/mm^3 vs HIV− (OR 1.95, 95% CI 1.01 to 3.79; p=0.05) had large independent associations with thrombocytopenia (table 2C). Higher BMI and not being married were negatively associated with thrombocytopenia. It should be noted that despite the differences in age between HIV+ and HIV− women noted in table 1, age was not associated with our haematological outcomes of interest or otherwise did not impact on the association of HIV with these outcomes. While the use of co-trimoxazole/dapsone had large univariate associations with anaemia and neutropenia, these were confounded by HIV infection/low CD4 and diminished after the inclusion of this variable.

DISCUSSION

We assessed Hb levels, white blood cell counts and platelet counts in HIV-infected antiretroviral naïve and uninfected Rwandan women, and found that greater anaemia, neutropenia and thrombocytopenia were all associated with HIV-positive serostatus. While anaemia and neutropenia in HIV-infected women were strongly associated with lower CD4 cell counts, thrombocytopenia was not. To that end we have compared the prevalence of abnormal haematological parameters we observed in HIV-positive women with those seen in five studies in sub-Saharan Africa and Western World (table 3).

Most notably, although our findings indicated that the HIV-infected women had lower mean Hb and were more likely to have anaemia or marked anaemia than HIV-negative women, the proportions of HIV-infected (as well as uninfected) women with anaemia here were lower than those from prior published studies of women in sub-Saharan Africa and Western Countries.[18 20–22] For example, the mean Hb observed here of 13.1 g/dl for HIV+ and 14.5 g/dl for HIV-uninfected women were

Table 1 Sociodemographic and haematological characteristics by HIV status and CD4 cell count

Characteristics	Among all women N (%)			Among HIV+ women only N (%)			
	HIV− (N=226)	HIV+ (N=710)	p Value	HIV+ CD4 >350 cells/µl (N=197)	HIV+ CD4 200–349 cells/ µl (N=268)	HIV+ CD4 <200 cells/µl (N=245)	p Value
Age/years N (%)							
<30	34 (15%)	158 (22%)	<0.001	51 (26%)	50 (19%)	57 (23%)	0.35
30–40	59 (26%)	393 (55%)		107 (54%)	151 (56%)	135 (55%)	
40+	133 (59%)	159 (22%)		39 (20%)	67 (25%)	53 (22%)	
Income (Rwf)							
<10000	92 (45%)	251 (36%)	0.02	66 (34%)	98 (37%)	87 (37%)	0.41
10000–35000	79 (39%)	347 (50%)		105 (54%)	131 (50%)	111 (47%)	
>35000	33 (16%)	97 (14%)		22 (11%)	35 (13%)	40 (17%)	
Level of education N (%)							
No schooling	67 (32%)	156 (22%)	0.02	46 (24%)	58 (22%)	52 (22%)	0.89
Some primary school	69 (33%)	269 (38%)		78 (40%)	99 (37%)	92 (38%)	
Secondary or University	76 (36%)	277 (39%)		71 (36%)	110 (41%)	96 (40%)	
Marital status N (%)							
Legally married/partner	80 (38%)	256 (36%)	0.004	86 (44%)	97 (36%)	73 (30%)	0.034
Widowed	108 (51%)	296 (42%)		71 (36%)	118 (44%)	107 (44%)	
Other	25 (12%)	153 (22%)		38 (19%)	53 (20%)	62 (26%)	
Body mass index (kg/m^2)							
Mean±SD	(21.3±3.8%)	(21.6±3.9%)	0.22	(21.9±3.9%)	(21.9±3.9%)	(21.1±3.7%)	0.15
Alcohol use N (%)	56 (28%)	144 (21%)	0.04	39 (21%)	53 (21%)	52 (22%)	0.98
Smoking N (%)							
Yes	7 (3%)	18 (3%)	0.58	4 (2%)	7 (3%)	7 (3%)	0.86
WHO stage 4 N (%)							
Yes	Not applicable	288 (41%)		59 (30%)	105 (39%)	124 (51%)	<0.001
Co-trimoxazole/dapsone use in prior year N (%)							
Yes	41 (19%)	612 (87%)	<0.001	145 (75%)	247 (92%)	220 (91%)	<0.001
Employed N (%)							
Yes	51 (25%)	171 (25%)	0.99	50 (26%)	63 (24%)	58 (25%)	0.84
Haemoglobin (g/dl)							
N	223	669	<0.001	180	251	238	<0.001
Mean±SD	14.3±1.4	13.1±1.6		13.5±1.3	13.1±1.7	12.7±1.7	
Anaemia N (%)	14 (6.3%)	137 (20.5%)		15 (7.6%)	43 (16.0%)	79 (32.2%)	<0.001
Marked anaemia N (%)	0	28 (4.2%)	<0.001	4 (1.1%)	6 (2.4%)	20 (8.4%)	<0.001
White blood cell count, ×10^3 cells/mm^3							
N	223	670		181	251	238	
Mean±SD	4.5±1.4	3.7±1.4	<0.001	4.3±1.6	3.8±1.3	3.3±1.4	<0.001
Neutropenia N (%)							
<2000 cells/mm^3	1 (0.45%)	28 (4.2%)	0.006	2 (1.1%)	6 (2.4%)	20 (8.4%)	<0.001
<1000 cells/mm^3	1 (0.45%)	1 (0.15%)					
Platelet count (×10^3/mm^3)							
N	208	654	0.05	179	246	229	0.55
Mean±SD	231.8±84.5	223.2±109.0		225.9±106.7	222.9±109.9	221.4±110.3	
Thrombocytopenia	18 (8.6%)	88 (13.5%)	0.0547	24 (13.4%)	36 (14.6%)	31 (13.5%)	0.92

Anaemia is defined as haemoglobin <12.0 g/dl; Marked anaemia is defined as haemoglobin <10.0 g/dl; Thrombocytopenia is defined as platelet counts <125.0×10^3/mm^3. The HIV+ and HIV− women were compared using chi-square (X^2) test, and similarly CD4+ cell count categories within HIV+ women were compared the χ^2 test. Rwf, Rwandan Francs.

each about a full point higher in both the HIV-infected and the HIV-uninfected women compared with 2056 HIV-infected (Hb 12.3 g/dl) and 569 HIV-uninfected (Hb 13.0 g/dl) participants in the Women's Interagency HIV Study (WIHS).[18] Lower Hb levels in HIV-infected than uninfected individuals are nearly universally observed, and our finding is similar to prior studies from sub-Saharan Africa, for example, HIV-infected women were more likely to be anaemic than HIV negative women (23.6% vs 12.8%; p=0.031) in a Ugandan study.[20] In a recent Rwandan study of 200 HIV-infected (of whom 50 were on ART) and 50 uninfected women,

Table 2

Variable	Univariate model OR (95% CI)	p Value	Multivariate model* OR (95% CI)	p Value
Panel A: logistic regression analyses for modelling anaemia, haemoglobin (g/dl) <12 vs ≥12				
HIV status, HIV+ vs HIV−	3.84 (2.17 to 6.82)	<0.001	NA†	
HIV+, CD4 >350 vs HIV−	1.27 (0.59 to 2.75)	0.54	1.47 (0.68 to 3.21)	0.33
HIV+, CD4 200–350 vs HIV−	3.09 (1.64 to 5.81)	<0.001	3.59 (1.88 to 6.83)	<0.001
HIV+, CD4 <200 vs HIV−	7.42 (4.05 to 13.58)	<0.001	8.09 (4.37 to 14.97)	<0.001
Age (years), 30–40 vs <30	0.84 (0.54 to 1.31)	0.44		
Age (years), 40+ vs <30	0.65 (0.40 to 1.06)	0.08		
10–35 k Rwf vs <10 k	0.67(0.46 to 0.98)	0.04	0.68 (0.45 to 1.03)	0.07
>35 k Rwf vs <10 k	0.80 (0.47 to 1.38)	0.43	0.94 (0.52 to 1.70)	0.85
Some primary school	0.96 (0.61 to 1.51)	0.87		
Secondary or university	1.00 (0.65 to 1.56)	0.98		
BMI (per kg/m^2) per unit	0.87 (0.82 to 0.92)	<0.001	0.87 (0.82 to 0.93)	<0.001
Alcohol 1–4 drinks/week	0.97 (0.42 to 2.25)	0.95		
Alcohol >4 drinks/week	1.09 (0.68 to 175)	0.71		
Co-trimoxazole or dapsone use	2.45 (1.54 to 3.89)	0.0002		
WHO stage 4 illness, Yes vs No	2.40 (1.68 to 3.43)	<0.001		
Widowed vs married/partner	0.99 (0.67 to 1.47)	0.96		
Other vs married/partner	1.29 (0.80 to 2.07)	0.30		
Smoking vs not smoking	0.98 (0.33 to 2.92)	0.98		
Employed vs not employed	1.07 (0.71 to 1.63)	0.73		
Panel B: logistic regression analyses for modelling neutropenia WBC (cells/mm^3) <2000 vs ≥2000				
HIV status, HIV+ vs HIV−	9.68 (1.31 to 71.58)	0.03	NA†	
HIV+, CD4 >350 vs HIV−	2.51 (0.23 to 27.89)	0.45	1.03 (0.08 to 13.15)	0.98
HIV+, CD4 200–350 vs HIV−	5.44 (0.68 to 45.51)	0.12	1.86 (0.78 to 65.82)	0.60
HIV+, CD4 <200 vs HIV−	20.37 (2.71 to 153.1)	0.003	7.18 (0.78 to 65.82)	0.08
Age (years), 30–40 vs <30	0.77 (0.33 to 1.77)	0.54		
Age (years), 40+ vs <30	0.28 (0.08 to 0.92)	0.04		
10–35 k Rwf vs <10 k	1.07 (0.47 to 2.42)	0.87		
>35 k Rwf vs <10 k	1.41 (0.48 to 4.14)	0.53		
Some primary school	1.05 (0.39 to 2.80)	0.92		
Secondary or university	1.20 (0.46 to 3.09)	0.71		
BMI (per kg/m^2) per unit	0.96 (0.86 to 1.06)	0.40		
Alcohol 1–4 drinks/week	0.71 (0.09 to 5.43)	0.74		
Alcohol >4 drinks/week	1.07 (0.40 to 2.89)	0.89		
WHO stage 4 illness yes vs no	3.36 (1.57 to 7.21)	0.002		
Co-trimoxazole or dapsone use	12.18 (1.65 to 90.0)	0.014	5.69 (0.63 to 52.5)	0.12
Widowed vs married/partner	1.15 (0.50 to 2.66)	0.74		
Other vs married/partner	1.19 (0.43 to 3.34)	0.74		
Smoking vs not smoking	1.28 (0.17 to 9.83)	0.81		
Employed vs not employed	0.36 (0.11 to 1.22)	0.10		
Panel C: logistic regression analyses for thrombocytopenia, platelets (mm^3) <125 vs ≥125				
HIV status, HIV+ vs HIV−	1.64 (0.96 to 2.80)	0.07	NA†	
HIV+, CD4 >350 vs HIV−	1.66 (0.87 to 3.16)	0.13	2.18 (1.10 to 4.32)	0.03
HIV+, CD4 200–350 vs HIV−	1.81 (0.99 to 3.29)	0.05	2.36 (1.25 to 4.45)	0.008
HIV+, CD4 <200 vs HIV−	1.47 (0.79 to 2.75)	0.23	1.95 (1.01 to 3.79)	0.05
Age (years), 30–40 vs <30	1.33 (0.74 to 2.37)	0.34	1.29 (0.72 to 2.33)	0.40
Age (years), 40+ vs <30	1.61 (0.88 to 2.95)	0.12	2.32 (1.20 to 4.50)	0.01
10–35 k Rwf vs <10 k	0.89 (0.58 to 1.38)	0.61		
>35 k Rwf vs <10 k	0.74 (0.38 to 1.45)	0.38		
Some primary school	0.66 (0.40 to 1.11)	0.12		
Secondary or university	0.77 (0.47 to 1.26)	0.29		
BMI (per kg/m^2) per unit	0.96 (0.90 to 1.01)	0.12	0.95 (0.89 to 1.00)	0.06
Alcohol 1–4 drinks/week	0.17 (0.02 to 1.22)	0.08		
Alcohol >4 drinks/week	0.87 (0.49 to 1.53)	0.62		
WHO stage 4 illness vs No	0.78 (0.50 to 1.22)	0.28		

Continued

Table 2 Continued

Variable	Univariate model OR (95% CI)	p Value	Multivariate model* OR (95% CI)	p Value
Co-trimoxazole or dapsone use	1.10 (0.69 to 1.74)	0.69		
Widowed vs married/partner	0.63 (0.40 to 0.98)	0.04	0.49 (0.29 to 0.80)	0.005
Other vs married/partner	0.62 (0.34 to 1.10)	0.10	0.59 (0.32 to 1.07)	0.08
Smoking vs not smoking	0.71 (0.16 to 3.09)	0.65		
Employed vs not employed	1.15 (0.71 to 1.86)	0.57		

*By Stepwise selection with overall p=0.05 to enter and p=0.10 to remain for the entire variable. Only the variables selected into the final model are included.
†HIV+ status was fit into the multivariate model by CD4 category with HIV− as baseline.
BMI, body mass index; WBC, white blood cells.

the prevalence of anaemia was similar to our study (29% and 8%, respectively).[23] Poor nutritional status may also cause anaemia,[17] which may be reflected in the association of anaemia with lower BMI in this urban Rwandan population.

The higher Hb levels in the Rwandan women, with and without HIV infection, than elsewhere may be attributable to the higher altitude of Rwanda, a mountainous country, with an elevation above sea level of 1500 m in Kigali, the capital city and site of this study.[24] The high Hb observed in this cohort of Rwandan women may be due to acclimatisation to higher altitude ensuring that women living in high-altitude regions of Rwanda have similar physiological adaptations as those living at lower-altitude levels.[25] High-altitude adaptations to fall in partial pressure of oxygen reduces the driving pressure needed for diffusion of oxygen across the alveolar-capillary barrier, and thus a fall in arterial partial pressure of oxygen. This results in reduction of oxygen delivery to body tissues and thus potential cellular hypoxia and organ dysfunction.[26] Thus, living in higher altitude may have resulted in a fall of arterial oxygen content and reduced oxygen tissue delivery. This may have resulted in participants' adaptation to ensure restoration of arterial oxygen saturation, which increases Hb concentration in individuals who habitually reside in high-altitudes areas, a principle used by endurance athletes.[27]

We have reported higher prevalence of neutropenia in the HIV-infected than uninfected Rwandan women, a common finding in sub-Saharan Africa.[20 21 28] Neutropenia may be due to HIV suppression of bone marrow resulting in abnormal granulopoesis. Antigranulocyte antibodies have been described in HIV-infected persons,[29] and neutropenia observed in HIV-infected adults may be attributed to decreased production of granulocyte colony-stimulating factor.[30] It should be noted that one study from Nigeria among HIV-infected persons found a mean WBC count that was higher than the mean values for HIV-infected women in our study.[21] This difference could be attributed to different stages of HIV illness in the study populations and the fact that participants in our study were ART-naïve, which was not true for the Nigerian study.

In our study, neutropenia observed in HIV-infected women was of higher prevalence in women with CD4 lymphocyte count <200 cells/µl. Similarly, the WIHS found baseline neutropenia, defined as <2000 cells/mm^3, in 44% of women participants and a longitudinal analysis found that worsening HIV disease was associated with subsequent neutropenia.[10] Neutropenia in an Ivory Coast study was observed in 21% of HIV-infected patients starting co-trimoxazole prophylaxis, but low-grade neutropenia was not associated with adverse clinical consequences[31] as is also the case in other sub-Saharan African countries. Neutropenia in our study was independently associated with low CD4 lymphocyte count, and this suggests that the stage of HIV-infection is an important determinant to pre-treatment neutropenia.

We observed a higher prevalence of thrombocytopenia (platelets ≤125.0×10^3/µl) in HIV-infected compared to HIV-uninfected women, but no association between thrombocytopenia and CD4 count within HIV-infected women. In developed countries, thrombocytopenia is

Table 3 Prevalence of anaemia, neutropenia and thrombocytopenia in HIV-infected women in five studies

Study (N)	Anaemia Hb <12.0	Hb <11.0	Hb <10.0	Neutropenia WBC <2000	WBC <1000	Thrombocytopenia Platelets <125 000
RWISA (710) (Rwanda)	20.3%		4.9%	4.2%	0.1%	13.5%
WIHS (2059) (North America)	37.0%		7.2%	44%	7%	14.6%
Uganda (123)		23.6%				
APS (2197) (North America)	32.3%		6.8%			
PEARLS (Africa, Asia and Americas)					~15%	

Uganda[20]
APS, Anemia Prevalence Study[22]; PEARLS, prospective evaluation of ART in resource limited settings[28]; WIHS, Women's Interagency HIV Study.[10 18]

generally infrequent in healthy asymptomatic HIV-infected patients, and is associated with very advanced HIV disease and comorbidities.[32] However, thrombocytopenia has been shown to be one of the common haematological abnormalities in patients before HAART initiation in sub-Saharan countries.[28] Although HIV-infected women in our study were HAART-naïve, the majority was asymptomatic and few reported WHO stage IV illness, and as noted may not have had advanced HIV disease.

Our study has some limitations. Its non-randomised cross-sectional design makes it structurally impossible to determine temporal direction or causality including inability of multivariate models to adjust for all confounding. Second, all participants in this study were women, and as Hb levels differ between men and women, our findings cannot be extrapolated to men. Finally, the small number of women with WBC <2.0 cells/mm^3 resulted in inadequate power to assess predictors of neutropenia. It is possible, or even likely, that the large OR for the associations of co-trimoxazole use (OR=5.69 CI 0.63 to 51.45) and CD4 count <200 cells/mm^3 (OR=7.18 CI 0.78 to 65.82) with neutropenia would be significant with a larger sample size.

In conclusion, we observed high prevalence of anaemia in HIV-infected and uninfected Rwandan women. Anaemia was more common in the HIV-infected than in uninfected women, especially those with greater disease progression as indicated by lower CD4 cell counts. Neutropenia and thrombocytopenia were more common in the HIV-infected than in uninfected Rwandan women. As anaemia and neutropenia are the most common haematological abnormalities in HAART-naïve HIV-infected women, it is important to routinely assess these parameters for timely and adequate clinical management.

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