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Slower response to treatment of iron deficiency anaemia in HIV-infected pregnant women: a prospective cohort study.

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Abstract

Objective: Antenatal anaemia is associated with increased peripartum transfusion requirement in South Africa. We studied whether HIV was associated with response to treatment of iron deficiency anaemia.

Design: Prospective cohort study.

Setting: Hospital-based antenatal anaemia clinic in South Africa

Population or Sample: Equal-sized cohorts of HIV positive (HIV+) and negative (HIV−) pregnant women with iron deficiency anaemia.

Methods: Haemoglobin trajectories of women with confirmed iron deficiency anaemia (ferritin < 50 ng/mL) were estimated from initiation of iron supplementation using mixed-effects modeling, adjusted for baseline HIV status, ferritin level, maternal and gestational ages and time-varying iron supplementation.

Main Outcome Measures: Haemoglobin trajectories.

Results: Of 469 women enrolled, 51% were HIV+ of whom 90% were on antiretroviral therapy (mean CD4+ lymphocyte count 403 cells/mm^3). Anaemia diagnoses did not differ by HIV status. 400 women with iron deficiency anaemia were followed during treatment with oral or intravenous (6%) iron therapy. In multivariable analysis, haemoglobin recovery was 0.10 g/dL per week slower on average in HIV+ vs HIV− women (p = 0.001); was 0.01 g/dL per week slower in women with higher baseline ferritin (p<0.001) and 0.06 g/dL per week faster in those compliant with oral iron therapy (p= 0.002).

Conclusions: Compared to HIV− women, HIV+ women with iron deficiency anaemia had slower but successful haemoglobin recovery after iron therapy. Earlier effective management of iron deficiency could reduce the incidence of peripartum blood transfusion.

Tweetable Abstract:

Among pregnant women with iron deficiency anaemia in South Africa, HIV slows haemoglobin recovery in response to oral iron therapy.

Keywords

Iron deficiency anaemia; pregnancy; HIV

INTRODUCTION

Anaemia during pregnancy is a major global health challenge. According to the World Health Organization, up to 42% of pregnant women have anaemia although its prevalence varies by country, local parasitic diseases, altitude, ethnic group and environment factors (e.g. cigarette smoking)[1, 2]. In South Africa, as many as 40% of maternal deaths were associated with anaemia[3]. Recent studies of pregnant women showed anaemia prevalences of 43% and 33% in the Free State and KwaZulu Natal provinces of South Africa, respectively[4, 5]. Iron deficiency is thought to be the most common cause for anaemia, comprising half of the anaemic patients in the Free State study. It is recommended that all pregnant women in South Africa be treated with iron and folic acid supplements[6].

Antenatal iron deficiency anaemia confers adverse effect both on the mother and the foetus. Maternal morbidity includes intolerance of obstetric haemorrhage, cardiac failure and requirement for blood transfusion, all contributing to increased maternal mortality[7, 8]. In addition, slower post-natal recovery and fatigue are thought to be related to iron deficiency[9].

Foetal complications of maternal iron deficiency anaemia include foetal death and long-term cognitive disability given the role of iron in foetal neural development[10, 11].

South Africa has one of the world's highest prevalences of HIV infection[4]. In a large cross-sectional study of pregnant women, HIV prevalence was 25% and the prevalence of antenatal anaemia was higher among HIV+ than HIV− women(47% versus 36%)[12]. Untreated HIV infection is a risk factor for anaemia in pregnant women which may be reversed by successful antiretroviral therapy[13, 14]. In a previous study, we found that HIV was a weak but significant contributor to the odds of requiring perinatal blood transfusion[15]. In contrast, antenatal anaemia had a strong and dose related effect on transfusion requirements that was observed even at haemoglobin of 9.0 – 9.9 g/dL. Data on HIV and anaemia during pregnancy are lacking, despite our clinical impression of slower response in the treatment of iron deficiency anaemia.

We sought to investigate whether HIV infection was associated with the diagnostic category of antenatal anaemia and secondly, whether HIV infection was associated with slower response to iron therapy in cases of iron deficiency anaemia. To do so, we took advantage of a clinic that had been established specifically for the diagnosis and management of perinatal anaemia at an obstetric hospital with a high prevalence of HIV and at high altitude.

METHODS

Study design and population.

We conducted a prospective cohort study of haemoglobin recovery among women with iron deficiency anaemia in HIV+ and HIV− anaemia clinics operating on separate days at Chris Hani Baragwanath (CHB) Academic Hospital under the direction of one of us (JCH). The study population was a convenience sample of all women referred from August 2014 through October 2015 to these clinics from district hospitals and community antenatal clinics in CHB catchment area according to pre-specified referral criteria. CHB is a large public hospital in Soweto, South Africa that provides tertiary care to a large generally low-income population and has an academic affiliation to University of the Witwatersrand School of Medicine and is located at 1600 meters of altitude. The study was limited to women aged 18 years or older and with the ability to provide informed consent. In South Africa, HIV testing is performed routinely on all consenting pregnant women and antiretroviral therapy is started on those who are not already on treatment. HIV+ and HIV− women are seen at the anaemia clinic on separate days, allowing us to recruit a balanced sample with identical referral criteria.

All patients had baseline clinical data abstracted by trained research nurses using standardized data collection forms. Gestational age was assessed by last menstrual period and clinical assessment. Per clinic routine, blood samples were sent for complete blood counts and vitamin B12 levels at baseline and for complete blood count at each weekly return visit; additional iron studies were done at baseline for research. In individual patients, a clinical diagnosis of iron deficiency anaemia was defined as a hypochromic or microcytic hypochromic anaemia that responded to iron, as indicated by graphs of red blood cell volume and haemoglobin content the Advia 2110 platform[16, 17].

Per standard of care practice, after evaluation on the first clinic day, women were treated with iron and followed prospectively with weekly clinic visits and blood tests for a period that depended upon their haemoglobin response. Oral iron therapy consisted of ferrous sulfate 200 mg and, in most cases, ascorbic acid 100 mg taken three times daily with meals. Compliance was assessed by self report and recorded by the study nurse. At subsequent clinic visits, intravenous (IV) iron, initially Venofer (Iron Sucrose Nycomed Madhaus) and later Cosmofer (Cosmofer, low molecular iron Dextran, Pharmaplan, Denmark) was prescribed in cases of inadequate haemoglobin response or intolerance of oral iron. The calculated dose was based on the patient's pre-pregnancy weight and current haemoglobin level and provided sufficient iron to correct the anaemia and replace iron stores.

The study protocol was approved by the Research Ethics Committees of the University of the Witwatersrand, CHB Hospital and the University of California San Francisco prior to initiation. All enrolled women gave written informed consent. Patients were not involved in the development of the research and a core outcome set was not utilized. The study was funded by the US National Heart, Lung and Blood Institute (NHLBI). An Observational Study Monitoring Board reviewed the study protocol but NHLBI was not involved in data analysis or manuscript preparation.

Laboratory evaluation.

All tests were performed by the National Health Laboratory Service at CHB hospital and results were provided electronically to the study. Complete blood counts were performed on an Advia 2120 blood analyser (Siemens Healthcare Diagnostics, USA). For the purposes of the study, we used a lower limit of normal haemoglobin of 10.5 g/dL based upon the predominant characteristics of the study population, namely: third trimester, African ethnicity, and residence at altitude of 1600 meters, according to the formula proposed by New and Wirth[2]. Ferritin and red cell folate were measured on a Cobas E602 analyser (Roche, Germany), transferrin, serum iron, Haptoglobin and CRP levels were measured on a Cobas C701. Soluble transferrin receptor (SfTr) was measured on a Cobas Integra 400. The soluble transferrin receptor index was calculated as the SfTr divided by the $\log_{10}$ ferritin.

Statistical analysis.

For the cross-sectional analysis of anaemia diagnoses and laboratory results at baseline, descriptive statistics consisted of counts and percentages for categorical variables and means and standard deviations or medians and interquartile ranges for continuous variables. Differences in characteristics by HIV status were evaluated using chisquared tests or Wilcoxon rank-sum tests.

For the prospective analysis of haemoglobin recovery, the sample was restricted to women found to have iron deficiency anaemia at intake, defined for this analysis as serum ferritin <50 ng/mL. Haemoglobin levels were evaluated as a function of covariates using a generalized linear mixed model to accommodate longitudinal data, in order to estimate mean levels at intake and rates of haemoglobin recovery (slopes) during supplementation[18]. Model covariates included baseline HIV status, ferritin category (rounded to the nearest 5 ng/mL and consolidated at 25 ng/mL), maternal age (years), gestational age (months), and

weeks of follow-up. We included interactions of HIV status and ferritin with follow-up time to allow varying recovery rates, and we modeled receipt of IV iron and compliance with oral supplemental as time-varying covariates. Gravidity and parity were not considered due to the inclusion of maternal age. Effects that were not statistically significant but improved the fit of the model per the Bayes Information Criterion were retained. Model results are illustrated via a penalized B-spline plot of the predicted values as a function of follow-up week, stratified by HIV status and baseline ferritin category. Analyses were performed using SAS version 9.4 and R version 3.5.3, with p-values less than 0.05 considered statistically significant.

RESULTS

A total of 469 pregnant women were enrolled, comprising 239 HIV+ and 230 HIV− women (Table 1). Both patient groups were predominantly of Black race/ethnicity and South African nationality; 8% were immigrants or visitors from other African countries. HIV+ patients were significantly older and had a higher gravidity and parity. The majority (56%) of initial visits occurred during the patients' third trimester; the median (Q1, Q3) gestational age was 7 (5–8) months. Almost all (90%) of the HIV+ women were on antiretroviral therapy at intake, most of whom were taking the fixed dose combination of tenofovir, emtricitabine and efavirenz commonly prescribed in South Africa.

The results of baseline laboratory evaluation are shown in Table 2. The majority of women had haemoglobin between 8.0 and 9.9 g/dL. About one-fourth had haemoglobin of 10 g/dL or higher, likely reflecting iron therapy treatment before intake at the specialty clinic and consistent with RBC indices showing a post-response pattern (data not shown). Compared to HIV− women, HIV+ women had significantly lower transferrin and red blood cell folate levels but higher C-reactive protein (all p<0.05). Based on univariate analyses, statistically significant differences by HIV status were not observed for iron, ferritin, transferrin saturation, or haptoglobin. Because of budget limitations, soluble transferrin receptor was measured in only 102 women: the median value for HIV+ vs. HIV− women was 9.71 mg/L and 10.25 mg/L respectively (p=0.79). Similarly, the median soluble transferrin receptor index was 3.77, greater than 1.5 in almost every woman and with no difference by HIV status.

A total of 442 (94%) women had a clinical diagnosis of iron deficiency anaemia with no difference by HIV status. Other diagnostic categories for anaemia included vitamin B12 deficiency (n=3), thalassemia (n=1), infection (n=3), HIV or antiretroviral related anaemia (n=2), anaemia of inflammation (n=3) and other causes (n=6). There were no cases of folate deficiency, sickle cell disease, or medication related anaemias. Infections included urinary tract infections, bacterial pneumonia and tuberculosis.

Prospective follow-up of iron deficient patients.

The subset of 400 women with ferritin < 50 ng/mL, of whom 207 were HIV+ and 193 were HIV−, were followed prospectively during their iron supplementation with oral iron and/or intravenous iron per local standard of care while monitoring haemoglobin recovery. Only 24 (6%) women received one or more doses of intravenous (IV) iron. Compliance with therapy

was noted in only 33% of women at the first return visit but increased to 65%–70% of women by the third through fifth visits, with no difference in compliance by HIV status. The median interval from first to last visits was 2 weeks among HIV− and 3 weeks among HIV+ women (p=0.0014; Table S1). Fewer than 9% and 13%, respectively, of HIV− and HIV+ women remained under follow-up beyond 6 weeks. The treatment/monitoring interval was substantially longer among women with lower baseline ferritin values and those initiating therapy in trimesters 1–2 (median, 4–5 weeks) than in trimester 3 (median, 2 weeks; Figure S1).

Multivariable modelling results are shown in Table 3 and Figure 1. Baseline haemoglobin was heterogeneous, strongly correlated with the ferritin level (p<0.0001), somewhat lower at each ferritin level among HIV-infected women (p=0.09) and somewhat higher at later gestational age ((p=0.06). During follow-up, haemoglobin recovery was about 0.10 g/dL per week slower in HIV-infected women than HIV-uninfected women (p=0.001), on average achieving haemoglobin >10 g/dL by weeks 7 and 4, respectively, regardless of baseline ferritin level. The longer recovery time in HIV-positive women was accompanied by longer supplementation: by decreasing ferritin category (25 to 5 ng/mL), the mean follow-up interval ranged from 2.0 to 3.0 weeks among HIV-positive women and from 1.6 to 2.2 weeks among HIV-negative women (data not shown). The rate of haemoglobin recovery was greater in women compliant with oral iron supplementation (p=0.002) and lesser among women with higher baseline ferritin levels (p<0.001). Haemoglobin recovery was not statistically significantly associated with IV iron therapy, gestational age, or maternal age.

DISCUSSION

Main findings.

This study of women attending an antenatal anaemia clinic in South Africa showed that anaemia was most commonly associated with iron deficiency, as demonstrated by laboratory evaluation. There were no clinically significant differences in baseline laboratory results between HIV+ and HIV− women. Among 400 women with iron deficiency anaemia, haemoglobin recovery was slower in HIV+ than HIV-women, although those followed for at least 7 weeks did eventually attain post-treatment haemoglobin levels of at least 10 g/dL. Haemoglobin recovery was also slower in women with poorer compliance and higher baseline ferritin levels.

Strengths and limitations.

While our study included a relatively large cross-sectional sample of both HIV+ and HIV− anaemic pregnant women in a major South African public hospital, restriction to women who were referred to the anaemia clinic precluded estimation of the prevalence of iron deficiency or other anaemia in the general obstetric population. In addition, some women treated with iron prior to referral to the clinic had already responded to the anaemia, which influenced baseline laboratory values and compliance with oral iron was assessed by self-report. About 25% of the patients had a baseline haemoglobin of 10 g/dL or higher but the majority of these had red cell indices consistent with a post-response pattern to iron

deficiency[16, 17]. Follow-up was based upon usual care at the anaemia clinic and therefore time under observation differed substantially by gestational age at intake and by HIV status; thus we cannot exclude biases due to differential initiation and duration of follow-up among women.

Interpretation.

Our most novel finding was a significantly slower response to iron therapy in HIV+ pregnant women when assessed by week of treatment and adjusted for ferritin level at start of iron supplementation and compliance with iron therapy. Potential explanations for this finding include ongoing inflammation and/or cytokine production affecting bone marrow formation of red blood cells secondary to either HIV infection itself or concurrent HIV-associated infections. Higher values of C-reactive protein support this hypothesis and previous studies have found lower CD4 lymphocyte count and higher erythrocyte sedimentation rate to be associated with the incidence of severe anaemia and microcytosis[19]. HIV-associated infections could include urinary tract infections, tuberculosis and viral infections, especially parvovirus; these were not evident at baseline examination but could have occurred and escaped detection during follow-up. Of note was the very rapid increase in haemoglobin of about 0.5 g/dL per week observed in HIV− women with lowest baseline ferritin and haemoglobin levels. This may reflect the effect of erythroferrone stimulated by very low levels of haemoglobin and hypoxia; erythroferrone blocks the hepcidin effect[20]. Conversely, women with highest ferritin levels may have slower haemoglobin recovery because they are already iron replete, have other unrecognized causes of anaemia or have elevated ferritin because of concurrent inflammation. It is intriguing to speculate that the prolonged haemoglobin recovery in HIV+ women could be related higher levels of hepcidin and reduced iron absorption[21].

Bone marrow suppression by antiretroviral medication is another possible explanation for slower haemoglobin recovery, however this has been described mostly with zidovudine, which is not present in the fixed dose combination which the majority of women were taking[22]. HIV could also decrease iron absorption or, because of higher pill burden, reduce compliance thereby interfering with iron availability. Poor iron absorption due to HIV intestinal morbidity seems unlikely at the CD4 lymphocyte counts among the women in the study although others have shown an association between vitamin D, other micronutrients and anaemia in HIV positive women[23]. In this study, oral iron was administered with meals to reduce side effects and improve compliance and, at least among the HIV− women, this appeared to have no adverse effect on haemoglobin recovery. Although we did observe an expected effect of poor compliance with oral iron on slower haemoglobin recovery, the HIV effect was still significant after controlling for the former in our multivariable analysis. The receipt of IV iron therapy did not differ by HIV status and was surprisingly not associated with haemoglobin recovery, probably because of indication bias in that it was reserved for women with the slowest recovery. Finally, it is possible that unmeasured confounding by behavioral factors could have accounted for the HIV effect despite the circumscribed study population and multivariable modeling we performed.

Anaemia was most commonly associated with iron deficiency in those who attended the antenatal anaemia clinic and other causes of anaemia were rare. Anaemia during pregnancy is very common in South Africa but its prevalence differs according to the haemoglobin cut off utilized, the geographic region of residence (with some effect of altitude), and whether a clinic or hospital sampling frame was used. Anaemia prevalence was at least 40% in KwaZulu Natal province[4, 24, 25]. In Bloemfontein, South Africa, Weyers et al. found 33% of women to be anaemic at a haemoglobin cut off of 11.5 g/dL (adjusted for altitude) and only 40% of these had iron deficient anaemia[5]. Van den Broek and Letsky studied 150 pregnant anaemic women in Malawi and 52% were diagnosed with iron deficiency anaemia using a combination of bone marrow iron staining and the soluble transferrin receptor to ferritin ratio[26]. Although our sampling frame was not designed to measure population prevalence, the 85% proportion of iron deficiency among the anaemic women we did study suggests that anaemia that is associated with iron deficiency may be highly prevalent among pregnant women in the Soweto/Johannesburg region.

Laboratory measurements were consistent with the high degree of clinically diagnosed iron deficiency as most of these patient had a hypochromic or hypochromic microcytic anaemia that responded to iron[16, 17]. Normal levels of red blood cell folate in almost all participants contrasts with other African countries and is probably due to folate supplementation wheat and maize flour in South Africa[23]. HIV status was significantly associated with lower serum transferrin, red blood cell folate and higher C-reactive protein, although the small differences were unlikely to be clinically significant. C-reactive protein is an indicator of inflammation and has been associated with HIV infection in general and with HIV infection in pregnant women[5, 26]. In contrast to earlier studies reporting more HIV-related anaemia especially in those with low CD4 lymphocyte counts[27], the lack of associations of anaemia and most laboratory parameters with HIV status in our study is probably due to the high penetrance of antiretroviral therapy and relatively high CD4+ lymphocyte counts in our population[28].

CONCLUSION

This study documents the predominant role of iron deficiency among anaemic pregnant women in South Africa, regardless of HIV status. Slower recovery of haemoglobin during iron supplementation among HIV+ women is a new finding that needs replication and investigation to explain its pathophysiology. Practically, HIV+ women with iron deficiency anaemia may need longer treatment with oral iron and may therefore need to be identified earlier in pregnancy. Finally, and taken together with our previous findings that antenatal anaemia is strongly associated with need for a peripartum blood transfusion, the current study supports broader interventions to treat antenatal iron deficiency to reduce morbidity, peripartum transfusion and maternal mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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A) HIV Negative

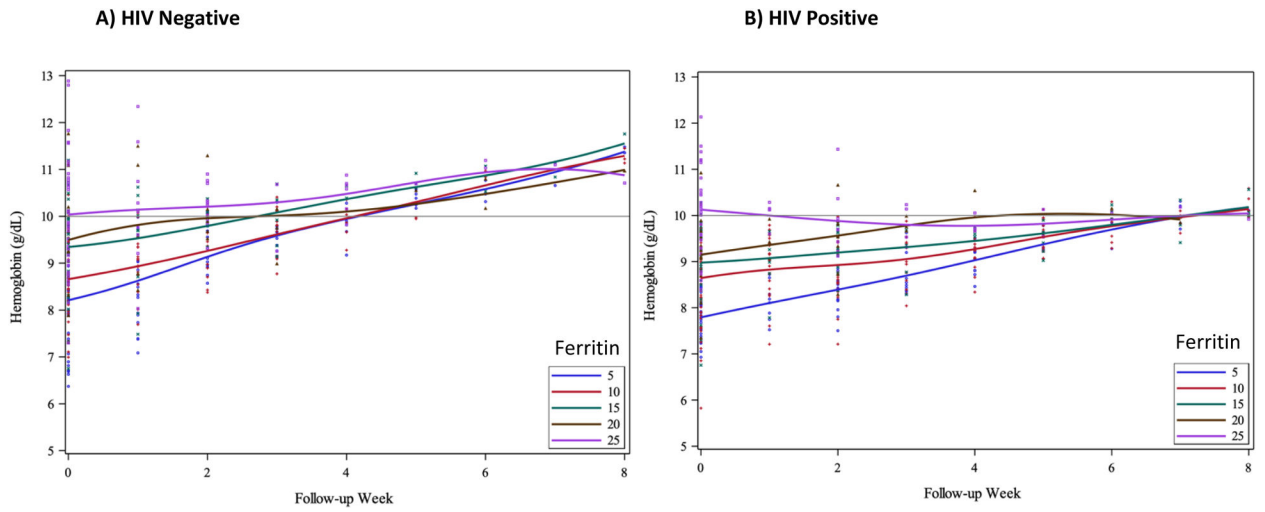**B) HIV Positive**

Figure 1.
Estimated mean haemoglobin (Hgb) trajectories, from initiation of iron therapy, stratified by HIV negative (A) and positive (B) status and baseline ferritin category, rounded to increments of 5 ng/mL with ferritin 25 ng/mL consolidated (see also Table 3). High heterogeneity among women in Hgb levels at initiation of iron supplementation diminished during follow-up.

Table 1.

Demographic and obstetric characteristics of the pregnant women, by HIV status. Except where otherwise noted, results are N (%).

	Overall (n=469)	HIV+ (n=239)	HIV− (n=230)	*p*-value
Trimester (Gestational Age)				0.55
1 (1 – 13 weeks)	28 (6.1)	14 (6.0)	14 (6.2)	
2 (14 – 26 weeks)	173 (37.8)	89 (38.0)	84 (37.5)	
3 (27 – 40 weeks)	257 (55.7)	131 (56.0)	126 (56.2)	
Missing	11	5	6	
Age				
Median (Q1, Q3)	28 (23, 33)	30 (25, 34)	25 (21, 31)	<0.001
18 – 19	27 (5.8)	8 (3.4)	19 (8.4)	
20 – 29	249 (53.7)	107 (45.2)	142 (62.6)	
30 – 39	164 (35.3)	106 (44.7)	58 (25.6)	
40 – 48	24 (5.2)	16 (6.8)	8 (3.5)	
Missing	5	2	3	
Gravidity				<0.001
1	110 (23.5)	30 (12.6)	80 (34.8)	
2	161 (34.3)	81 (33.9)	80 (34.8)	
3	121 (25.8)	80 (33.5)	41 (17.8)	
4+	74 (15.8)	47 (19.7)	27 (11.7)	
Missing	3 (0.6)	1 (0.4)	2 (0.9)	
Parity				<0.001
0	87 (18.6)	27 (11.3)	60 (26.1)	
1	170 (36.2)	90 (37.7)	80 (34.8)	
2	101 (21.5)	71 (29.7)	30 (13.0)	
3+	66 (14.1)	40 (16.7)	26 (11.3)	
Missing	45 (9.6)	11 (4.6)	34 (14.8)	
On ART Prior to Pregnancy				
Yes	NA	215 (90.0)	NA	
No		3 (1.3)		
Missing		21 (8.8)		
CD4+ T-cells (cells/mm^3)				
<200	NA	41 (17.8)	NA	
200–499		124 (53.9)		
500+		65 (28.3)		

Table 2.

Laboratory results at baseline, by HIV status. Within-group results are expressed as median [IQR] for continuous characteristics and N (%) for categorical characteristics. Groups are compared using Wilcoxon rank-sum tests.

	Overall (n=469)	HIV+ (n=239)	HIV− (n=230)	*p* value	*# missing*
Haemoglobin (g/dL)	9.10 [1.9]	9.00 [1.85]	9.10 [1.98]	0.09	0
5.4–7.9	95 (20%)	54 (23%)	41 (18%)		
8.0–9.9	248 (53%)	130 (54%)	118 (53%)		
10.0–14.1	126 (27%)	55 (23%)	71 (31%)		
Iron (µg/L)	6.00 [9.7]	5.80 [8.10]	6.60 [14.4]	0.24	28
Ferritin (ng/mL)	12.0 [15.0]	11.5 [12.2]	14.0 [19.0]	0.24	30
Ferritin < 50 ng/mL	400 (91%)	207 (91%)	193 (92%)		
Ferritin < 25 ng/mL	334 (84%)	179 (86%)	155 (80%)		
Transferrin (mg/L)	4.27 [0.95]	4.20 [1.09]	4.31 [0.84]	0.02	27
Transferrin saturation (%)	5.0 [12.0]	5.0 [10.0]	6.0 [15.0]	0.35	28
Haptoglobin (g/L)	1.06 [0.60]	1.07 [0.57]	1.08 [0.63]	0.26	74
RBC folate (µmol/L)	3.16 [1.46]	2.84 [1.32]	3.35 [1.56]	0.001	151
C-reactive protein (mg/L)	6.00 [7.50]	7.00 [9.00]	5.00 [6.00]	<0.001	30
CRP>5 (n(%))	112 (25%)	54 (24%)	58 (27%)	0.51	
Reticulocyte haemoglobin (CHR; pg)	26.4 [6.17]	26.6 [5.83]	25.6 [6.90]	0.06	83

Normal ranges: Iron: 9–30.4 umol/L; Transferrin: 2.5–3.8 g/L; Transferrin saturation: 15–50%; Haptoglobin: 0.3–2 g/L; RBC folate: 1426–3294 nmol/L; CRP normal < 10% but we present >5% as per Weyers et al.[5] ; CHR: range not reported but analogous to mean corpuscular haemoglobin range of 27–32 pg.

Table 3.

Results of a multivariable model measuring associations of patient characteristics with haemoglobin (Hgb) level at the baseline visit and weekly changes during iron supplementation (see also Figure 1). Effects are relative to HIV− women with mean Hgb at <u>baseline</u> of 7.8 g/dL and mean <u>weekly change</u> in Hgb of 0.43 g/dL.

Patient characteristic	Mean (95% CI) <u>baseline</u> difference in Hgb per unit change in each covariate	Type-3 p-value
HIV+ vs HIV−	−0.25 (−0.53, 0.037)	0.088
Ferritin, per 5 ng/mL increment	0.098 (0.078, 0.12)	<0.001
Gestational age, per month	0.052 (−0.003, 0.11)	0.063
Maternal age, per year	0.003 (−0.012, 0.018)	0.70
	Mean (95% CI) <u>weekly change</u> in Hgb per unit change in each covariate	Type-3 p-value
HIV+ vs HIV−	−0.098 (−0.16, −0.041)	0.001
Ferritin, per 5 ng/mL increment	−0.013 (−0.017, −0.009)	<0.001
Compliant with oral iron [*]	0.057 (0.021, 0.093)	0.002
IV iron documented [*]	−0.031 (−0.092, 0.031)	0.33

[*] Modeled as a time-varying covariate