Anaemia, iron and vitamin A status among South African school-aged children living with and without HIV

C Goosen,1 PhD; J Baumgartner,2 PhD; N Mikulic,2 PhD; S L Barnabas,4 PhD; M F Cotton,3 FCPaed (SA), PhD; M B Zimmermann,3 PhD; R Blaauw,1 PhD

1 Division of Human Nutrition, Department of Global Health, Stellenbosch University, Cape Town, South Africa
2 Institute of Food, Nutrition and Health, Department of Health Sciences and Technology, ETH Zurich, Switzerland
3 Family Centre for Research with Ubuntu, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa

Corresponding author: C Goosen (charleneg@sun.ac.za)

Background. Data on iron and vitamin A deficiency are scarce in school-aged children living with HIV (HIV+) compared with children without HIV (HIV−). Both deficiencies can contribute to anaemia.

Objective. To assess anaemia, iron and vitamin A status in a sample of HIV+ and HIV− school-aged children in South Africa.

Methods. In this comparative cross-sectional study, biomarkers for anaemia (haemoglobin), iron (plasma ferritin (PF), soluble transferrin receptor), vitamin A (retinol-binding protein (RBP)) and inflammatory status (C-reactive protein, α-1-acid glycoprotein) were measured in 8 - 13-year-old children from Cape Town living with (n=143) and without HIV (n=148). Measurements of PF and RBP were adjusted for inflammation using a regression-correction approach.

Results. HIV+ children had higher prevalences of anaemia (29% v. 14%; odds ratio (OR) = 2.6; 95% confidence interval (CI) 1.4 - 4.9; p=0.002), iron-deficient erythropoiesis (20% v. 9%; OR=2.5; 95% CI 1.2 - 5.0; p=0.013) and iron deficiency anaemia (11% v. 4%; OR=2.9; 95% CI 1.1 - 7.7; p=0.035) than HIV− children. Marginal vitamin A deficiency was noted in 52% of HIV+ and 57% of HIV− children (p=0.711). Subclinical inflammation was more prevalent in HIV+ than HIV− children (p=0.012).

Conclusion. Anaemia, iron-deficient erythropoiesis and iron deficiency anaemia were more prevalent in HIV+ than HIV− children. Prevalence of marginal vitamin A deficiency was high in both groups. Efforts to improve micronutrient status and mitigate nutritional determinants of anaemia in HIV+ children from resource-limited settings should be prioritised.

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Sub-Saharan Africa has the largest HIV burden globally.[11] In South Africa (SA), an estimated 260 000 children <15 years of age are living with HIV (HIV+), with 14 000 new infections recorded in this age group in 2018,[11] despite vertical HIV transmission prevention programmes.[11] Anaemia is a frequent haematological comorbidity of HIV infection, with a complex and multifactorial aetiology.[11] Although chronic inflammation and antiretrovirals such as zidovudine may cause anaemia in HIV+ individuals, nutritional determinants such as iron and vitamin A deficiencies are likely in resource-limited settings where inadequate dietary intake may be common.[4,5]

Anaemia is characterised by a lower-than-normal haemoglobin (Hb) concentration.[4,5] Iron deficiency and anaemia can prevent children from reaching their developmental and scholastic potential, thereby limiting long-term work opportunities and quality of life.[12] As anaemia is a risk factor of all-cause mortality in HIV+ individuals despite their receiving antiretroviral therapy (ART), knowledge on best strategies to abate this comorbidity is much needed.[4,5]

Iron and vitamin A deficiencies in SA school-aged children are estimated at 13.7% and 12.2%, respectively.[10] National prevalence rates are not stratified by HIV status and estimates of these nutritional deficiencies among HIV+ school-aged children derive from only a few small, independent studies.[11,12]

Assessing iron and vitamin A status in HIV+ individuals is challenged by the effects of inflammation on conventional biomarkers. Plasma ferritin (PF), a positive acute-phase reactant, is elevated during inflammation and so could potentially mask depleted iron stores. Retinol-binding protein (RBP), a negative acute-phase reactant, is lowered in the presence of inflammation and so could potentially mask marginal vitamin A deficiency.[11,12] Different approaches are available for using inflammation-sensitive biomarkers to assess micronutrient status. These include raising or lowering the cut-off values that define deficiency, excluding individuals with elevated inflammatory markers such as C-reactive protein (CRP) or α-1-acid glycoprotein (AGP), arithmetic approaches with fixed categorical correction factors and, more recently, a regression correction approach.[13,14] The advantage of using a regression correction approach as suggested by the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) group is that adjustments correspond to the magnitude of inflammation (measured by CRP or AGP) and reflect acute-phase reactant estimates better than other methods.[13]

To our knowledge, iron and vitamin A status among school-aged HIV+ children have not been assessed using inflammation-adjusted biomarkers and compared with that of children without HIV (HIV−). The prevalence of iron and vitamin A deficiencies and their contribution to anaemia in HIV+ individuals therefore remain unclear. In this study, we assessed anaemia, iron and vitamin A status among a sample of HIV+ and HIV− school-aged children in SA.
Methods
Study design and participants
For this comparative cross-sectional study, we used data collected at the initial screening visits that formed part of a series of iron studies at the Family Centre for Research with Ubuntu (FAMCRU) in Cape Town, SA. Both HIV+ and HIV− children were recruited from the FAMCRU patient database, Tygerberg Hospital’s Infectious Diseases Outpatient Unit, and through word of mouth from similar communities across Cape Town. Children had to be between 8 and 13 years old, without acute illness at the time, and should not have used iron-containing supplementation in the three months prior to the study. Routine blood work records for HIV+ children were accessed on the National Health Laboratory Service’s electronic portal to confirm that they were in HIV care. The absence of HIV infection was confirmed with a rapid HIV assay (First Response HIV Card 1–2.0, Premier Medical Corporation, India) in the HIV+ group. Between September 2018 and August 2019, children were screened for the series of iron studies until a total of 293 children were included in the analyses. With an 80% power and a type I error rate of 5% assumed, the final sample size allowed for detecting a medium effect size of 0.24 between groups. Sociodemographic and selected HIV care information were collected only for the abovementioned subgroup (n=180).

Participant and sociodemographic information
Height and weight were measured using a Micro 1023 electronic platform scale and stadiometer (Scalerite, SA) and standardised techniques.[16] In the HIV+ group, the most recent HIV viral load concentrations but below the clinically used threshold for acute inflammation (i.e., CRP ≥5 mg/L or AGP >1 g/L). Subclinical inflammation was classified a priori as CRP concentrations of 0.05 - 4.99 mg/L, reflecting detectable CRP concentrations but below the clinically used threshold for acute infection.

Statistical analyses
Statistical analyses were performed using SPSS version 27 (IBM Corp., USA). Participant characteristics were summarised using descriptive statistics. Categorical variables are reported as frequencies and percentages. The prevalence of unknown parameters are reported as estimates within 95% confidence intervals (CIs).

The distribution of continuous variables was investigated using the Shapiro-Wilk test. Homogeneity of variance was tested with Levene’s test. Normally distributed continuous variables are reported as medians and interquartile ranges (IQRs).

For participant and sociodemographic information, between-group differences were assessed using the independent samples t-test or Mann-Whitney U-test for continuous variables, and Pearson’s chi-square test or Fisher’s exact test for categorical variables.

For anaemia, iron, vitamin A and inflammatory status, between-group differences were assessed using analysis of covariance (ANCOVA) for log-transformed continuous outcome variables, and binary logistic regression for categorical outcome variables, adjusting for age and sex. We report adjusted odds ratios (ORs) and 95% CIs for the logistic regression parameters. Statistical significance was set at p<0.05.

Ethical considerations
The study protocol was approved by the health research ethics committees of Stellenbosch University (ref. no. S18/06/136 and M18/05/017) and the ETH Zurich (ref. no. EK 2018-N-40). Assent was obtained from all children, and consent from their caregivers (parent or legal guardian).

Results
Participant characteristics and sociodemographic indicators
In total, 293 children were screened for participating in the series of iron studies (HIV+, n=144; HIV−, n=149) and being included in this comparative cross-sectional analysis. As one child from each group was excluded for insufficient blood volume, analyses were performed on 291 records.

Table 1 presents participant characteristics (N=291) and selected indicators collected from the subgroup of 180 children described above. The group of HIV+ children was older (p=0.004) and more...
Table 1. Sociodemographic characteristics of participants (N=291)

| Variables                                      | HIV+ (n=143) | HIV- (n=148) | p-value |
|------------------------------------------------|--------------|--------------|---------|
| **Sex, n (%)**                                 |              |              |         |
| Male                                           | 75 (52)      | 71 (48)      | 0.45    |
| Female                                         | 68 (48)      | 77 (52)      |         |
| **Age (years), median (IQR)**                  | 11.5 (9.9 - 12.3) | 10.8 (9.5 - 12.0) | 0.004   |
| **Age, n (%)**                                 |              |              |         |
| 8                                              | 20 (14)      | 29 (20)      |         |
| 9                                              | 16 (11)      | 23 (15)      |         |
| 10                                             | 19 (13)      | 32 (22)      |         |
| 11                                             | 42 (30)      | 28 (19)      |         |
| 12                                             | 26 (18)      | 30 (20)      |         |
| 13                                             | 20 (14)      | 6 (4)        | 0.005   |
| **Height-for-age Z-score, mean (SD)**          | -1.33 (1.01) | -0.56 (1.04) | <0.001  |
| **Stunted, n (%)**                             | 37 (26)      | 16 (11)      | 0.001   |
| **Body-mass-index-for-age Z-score, mean (SD)** | -0.41 (1.10) | -0.14 (1.32) | 0.07    |
| **Healthy weight, n (%)**                      | 124 (87)     | 117 (79)     | 0.08    |
| **Underweight, n (%)**                         | 5 (4)        | 5 (3)        | 1.00    |
| **Severe underweight, n (%)**                  | 1 (1)        | 3 (2)        | 0.62    |
| **Overweight, n (%)**                          | 9 (6)        | 16 (11)      | 0.17    |
| **Obesity, n (%)**                             | 4 (3)        | 7 (5)        | 0.39    |
| **HIV viral load, n (%)**                      |              |              |         |
| <50 copies/mL                                   | 122 (85)     | -            |         |
| ≥50 copies/mL                                   | 21 (15)      | -            |         |
| **Subgroup n=90**                               |              |              |         |
| **Age at start of antiretroviral therapy (years),* median (IQR)** | 1 (0 - 2) | - | - |
| **Current antiretroviral regimen**              |              |              |         |
| ABC-3TC-LPV/r                                   | 45 (50)      | -            | -       |
| ABC-3TC-EFV                                     | 20 (22)      | -            | -       |
| AZT-3TC-LPV/r                                   | 17 (19)      | -            | -       |
| AZT-3TC-NVP                                     | 3 (3)        | -            | -       |
| Other                                           | 5 (6)        | -            | -       |
| **Relationship status of primary caregiver, n (%)** |              |              |         |
| Single                                          | 48 (53)      | 58 (64)      | 0.13    |
| In partnership                                  | 42 (47)      | 32 (36)      |         |
| **Type of housing, n (%)**                      |              |              |         |
| Formal                                          | 53 (59)      | 62 (69)      | 0.16    |
| Informal                                       | 37 (41)      | 28 (31)      |         |
| **Individuals in household, n (%)**             |              |              |         |
| 2 - 4                                           | 37 (41)      | 23 (26)      |         |
| 5 - 8                                           | 46 (51)      | 59 (66)      |         |
| 9 - 15                                          | 7 (8)        | 8 (9)        | 0.08    |
| **Employment status of household breadwinner, n (%)** |              |              |         |
| Permanent                                       | 25 (28)      | 36 (40)      |         |
| Temporary                                       | 25 (28)      | 18 (20)      |         |
| Unemployed                                      | 40 (44)      | 36 (40)      | 0.27    |
| **Monthly household income, n (%)**             |              |              |         |
| <ZAR2 000                                       | 47 (52)      | 46 (51)      |         |
| ZAR2 000 - ZAR5 000                             | 14 (16)      | 16 (18)      |         |
| >ZAR5 000                                       | 2 (2)        | 9 (10)       |         |
| Did not disclose                                | 27 (30)      | 19 (21)      | 0.23    |
| **Household receives government grant, n (%)**  | 83 (92)      | 79 (88)      | 0.32    |
| **Child accesses school nutrition programme, n (%)** | 79 (88)  | 64 (71)     | 0.006   |

IQR = interquartile range; SD = standard deviation; ABC = abacavir; 3TC = lamivudine; LPV/r = loptinavir boosted with ritonavir; EFV = efavirenz; AZT = zidovudine; NVP = nevirapine.

*Data available for n=85 as start date unknown for five children.
stunted (p=0.001) than the HIV– children. Routine blood work records showed that 85% of HIV+ children had achieved viral suppression. Significantly more HIV+ than HIV– children accessed the National School Nutrition Programme (p=0.006). Other sociodemographic characteristics were similar between the two groups.

**Anaemia, iron, vitamin A and inflammatory status**

Table 2 compares the anaemia, iron, vitamin A and inflammatory status of HIV+ and HIV– children. Hb concentrations were significantly lower in HIV+ children, with anaemia presenting in 29% (95% CI 21 - 37) of this group compared with 14% (95% CI 9 - 20) of HIV– children (OR=2.6; 95% CI 1.4 - 4.9; p=0.002). The prevalence of ID (adjusted PF<15 µg/L) was 15% (95% CI 9 - 22) in the HIV+ group and 11% (95% CI 6 - 17) in the HIV– group (p=0.515). sTfR concentrations were significantly higher in the HIV+ group, with the prevalence of iron-deficient erythropoiesis at 20% (95% CI 13 - 27) in this group, compared with 9% (95% CI 5 - 15) in the HIV– group (OR=2.5; 95% CI 1.2 - 5.0; p=0.013). Of the HIV+ participants, 11% (95% CI 7 - 18) had IDA, compared with 4% (95% CI 2 - 9) of the HIV– children (OR=2.9; 95% CI 1.1 - 7.7; p=0.035). This accounted for 39% of all anaemia in the HIV+ group and 30% in the HIV– group.

Vitamin A status was similar between the HIV+ and HIV– children. Although established vitamin A deficiency was noted in 9% of both the HIV+ and HIV– children, marginal vitamin A deficiency was seen in 52% (95% CI 43 - 60) and 57% (95% CI 48 - 65) of the HIV+ and HIV– children, respectively (p=0.711). Co-existing vitamin A deficiency (marginal or established) was noted in 50 of the 61 anaemic children (82%), but there was no significant difference according to HIV status (p=0.071) (data not shown). The prevalence of co-existing ID or iron-deficient erythropoiesis and vitamin A deficiency (marginal or established) was higher in the HIV+ than the HIV– group (18% v. 9%; OR=2.2; 95% CI 1.07 - 4.6; p=0.032) (data not shown).

CRP concentrations were significantly higher in the HIV+ group and subclinical inflammation (CRP between 0.05 and 4.99 mg/L) was also more prevalent among these children (p=0.012).

**Discussion**

This comparative cross-sectional study showed a significantly higher prevalence of anaemia, iron-deficient erythropoiesis and IDA in HIV+ than in HIV– school-aged children in our sample. Marginal vitamin A deficiency was common and similar in the two groups.

The prevalence of anaemia (29% in HIV+ children; 14% in HIV– children) represents a public health problem of moderate (20 - 39.9%) and mild (5 - 19.9%) concern.11 Anaemia is a common comorbidity of HIV infection and is generally more prevalent in HIV+ than HIV– individuals,11 as also seen in our study. Promisingly, a recent systematic review and meta-analysis among HIV+ children from Ethiopia reported significantly lower HIV–anaemia comorbidity in ART-treated children compared with ART-naïve children.28

Alongside the ART programme roll-out and expansion in SA, iron status among SA school-aged HIV+ children appears to be improving. In 2009, Steenkamp et al.11 reported high prevalences of anaemia (60%), ID (30%) and established vitamin A deficiency (63%) in ART-naïve children between 1 and 10 years of age. By 2013, Kruger et al.12 reported lower prevalences of anaemia (32%) and iron-deficient erythropoiesis (15%) in children between

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**Table 2. Status of anaemia, iron deficiency, vitamin A deficiency and inflammation among participants, according to relevant haematological markers (N=291)**

| Haematological markers for physiological status | HIV+ (n=143) | HIV– (n=148) | p-value |
|-----------------------------------------------|-------------|-------------|---------|
| **Anaemia**                                   |             |             |         |
| Haemoglobin (g/dL), median (IQR)              | 12.1 (11.6 - 12.9) | 12.5 (12.0 - 13.2) | 0.002   |
| All anaemia, n (%)                            | 41 (29)     | 20 (14)     | 0.002   |
| Mild                                         | 25 (18)     | 14 (10)     | 0.046   |
| Moderate                                     | 16 (11)     | 5 (3)       | 0.012   |
| Severe                                       | 0           | 1 (1)       |         |
| **Iron status**                               |             |             |         |
| PF (unadjusted) (µg/L), median (IQR)          | 35.6 (21.6 - 53.7) | 34.6 (23.3 - 55.8) | 0.76    |
| PF (adjusted) (µg/L), median (IQR)            | 33.0 (19.6 - 48.9) | 32.5 (22.1 - 49.7) | 0.63    |
| Iron deficiency, n (%)                        | 21 (15)     | 16 (11)     | 0.52    |
| Plasma sTfR (mg/L), median (IQR)              | 6.6 (5.6 - 8.0) | 6.1 (5.1 - 7.1) | <0.001  |
| Iron-deficient erythropoiesis, n (%)          | 28 (20)     | 13 (9)      | 0.013   |
| Iron deficiency anaemia, n (%)                | 16 (11)     | 6 (4)       | 0.035   |
| **Vitamin A status**                          |             |             |         |
| Plasma RBP (unadjusted) (µmol/L), median (IQR)| 0.95 (0.79 - 1.11) | 0.94 (0.79 - 1.10) | 0.70    |
| Plasma RBP (adjusted) (µmol/L), median (IQR)  | 0.97 (0.81 - 1.12) | 0.96 (0.80 - 1.12) | 0.91    |
| Marginal vitamin A deficiency, n (%)          | 74 (52)     | 84 (57)     | 0.71    |
| Established vitamin A deficiency, n (%)       | 13 (9)      | 13 (9)      | 0.91    |
| **Inflammatory status**                       |             |             |         |
| Plasma CRP (mg/L), median (IQR)               | 0.13 (0.02 - 1.16) | 0.04 (0.02 - 0.40) | 0.024   |
| 0.05 <CRP≤4.99 mg/L, n (%)                    | 66 (46)     | 49 (33)     | 0.012   |
| CRP ≥5 mg/L, n (%)                            | 16 (11)     | 8 (5)       | 0.11    |
| Plasma AGP (g/L), median (IQR)                | 0.58 (0.46 - 0.77) | 0.51 (0.42 - 0.78) | 0.54    |
| AGP >1 g/L, n (%)                             | 19 (13)     | 21 (14)     | 0.92    |

IQR = interquartile range; sTfR = soluble transferrin receptor; PF = plasma ferritin; RBP = retinol-binding protein; CRP = C-reactive protein; AGP = α-1-acid glycoprotein.
3 and 14 years old receiving ART. The prevalences of anaemia and iron-deficient erythropoiesis in HIV+ children in our study correspond to those of the latter study. However, the earlier studies referred to here did not compare their findings to HIV– children and our study has subsequently revealed that HIV+ children have significantly higher odds of presenting with iron-deficient erythropoiesis (OR=2.5; p=0.013) and IDA (OR=2.9; p=0.035). The prevalence of IDA was higher than national estimates (2%) for children between 7 and 9 years old in both groups.[30] This may be explained, at least in part, by the use of different definitions, as the mentioned national survey used serum ferritin as the only iron marker and values were not adjusted for inflammation, as we have done.

The prevalence of vitamin A deficiency (whether marginal or established) did not appear to be affected by HIV status and corresponds with national estimates for children between 7 and 9 years old (marginal: 49.9%; established: 12.2%).[31] National vitamin A supplementation programmes target younger children and the vitamin A status of school-aged children largely depends on sufficient dietary intake. In our study, the majority of anaemic children had established or marginal vitamin A deficiency, whereas significantly more HIV+ than HIV– children were affected by co-existing ID or iron-deficient erythropoiesis and vitamin A deficiency. Multiple deficiencies tend to cluster in individuals with micronutrient-poor diets and the synergistic effect of these deficiencies is important in the development of anaemia.[32]

Iron-deficient erythropoiesis and IDA can result from inadequate nutrient intake and absorption-inhibiting factors in the meal matrix, as well as from inflammation-induced hepcidin upregulation, which compromises not only iron mobilisation from macrophages and hepatic iron stores but also dietary iron absorption.[8] Vitamin A deficiency can result from inadequate dietary intake and may also modulate iron metabolism and dysregulate erythropoiesis.[33] Many SA children consume a plant-based staple diet.[34] The bioavailability of non-haem iron and provitamin A (beta-carotene) in plant sources is poor, and absorption-inhibiting components such as phytic acid and polyphenols are high.[22] Although ART reduces comorbidity risk, and treatment regimens continue to improve in order to minimise side-effects, ART alone cannot ameliorate all health risks associated with HIV and persistent subclinical inflammation remain,[35] as also demonstrated by our study. Dietary intake is a modifiable factor, and it remains important to prioritise dietary interventions alongside ART to mitigate nutritional determinants of anaemia in HIV+ children.

Anthropometric assessments highlighted that stunting occurred among significantly more HIV+ than HIV– children. Irreversible height deficits often reflect chronic undernutrition during early life.[23] In cohort studies where early growth deficits affected more HIV+ than HIV– infants,[24,25] the greatest risk factors among HIV+ children were advanced maternal HIV disease, formula feeding and gastrointestinal comorbidities,[26] which conform to the basic causes of stunting, namely poor maternal health and nutrition during pregnancy and inadequate nutrition or recurring infections during early childhood.[24,25] The children in our study (8 - 13 years old) were born before the rapid scale-up of vertical HIV transmission prevention programmes, HIV testing at birth, rapid initiation of ART and consolidated breastfeeding recommendations in SA.[2] These policy changes may improve early growth outcomes by supporting maternal health, safeguarding breastfeeding practices and enabling early disease control among HIV+ children.

**Study strengths limitations**

Our findings should be interpreted in context of the study's strengths and limitations. The use of PF and sTfR to assess iron status improves the sensitivity and specificity of iron status estimates. The BRINDA regression correction approach incorporates the magnitude of inflammation measured by CRP and AGP, allowing for more precise adjustments to better reflect acute-phase protein estimates (PF and RBP).[13]

A limitation of the cross-sectional design is that observed associations cannot conclusively be used to comment on causality. Dietary intake was not included during the assessment, which could have assisted in explaining between-group differences in iron status. However, in the subsample enrolled according to HIV and iron status, where dietary intake was explored[15] and compared with HIV– peers, HIV+ children had significantly lower daily intake of highly bioavailable haem iron. Dietary vulnerability to poor iron status in the sample of children in our study therefore appears likely.

Finally, this sample represented children from an urban SA setting and findings may differ in rural and other settings, where habitual dietary intake differs.

**Conclusion**

Anaemia, iron-deficient erythropoiesis and IDA were more prevalent in HIV+ than HIV– children. The prevalence of marginal vitamin A deficiency was high in both groups. Efforts to improve micronutrient status and mitigate nutritional determinants of anaemia in HIV+ children from resource-limited settings should be prioritised. Studies in rural settings and other provinces are recommended to improve understanding of anaemia and micronutrient deficiencies among school-aged HIV+ children at country level.

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**Author contributions.** CG is the first author of the paper and was involved in all aspects of the study, from conceptualisation, acquiring funding (with input from MBZ) and developing the methodology to data acquisition, curation, analysis and interpretation. RB and JB assisted with conceptualisation and methodology development, together with input from SLB, MFC and MBZ. NM assisted with data curation and analysis, supported by JB. All authors contributed to reviewing and refining the manuscript for publication.

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**Conflicts of interest.** None.

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