Anaemia, iron deficiency and infections: new perceptions of the interaction between hepcidin, iron biomarkers, anaemia and inflammation in Malawian children
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Chapter five

Iron deficiency anaemia in children with HIV-associated anaemia: a systematic review and meta-analysis

M.O. Esan, F.A.M. Jonker, M. Boele van Hensbroek, J.C.J. Calis, K.S. Phiri

Abstract

We conducted a systematic review and meta-analysis to determine the prevalence of iron deficiency in HIV-infected children from high and low-income settings and compared it with that of HIV-uninfected controls.

We searched five major databases for primary studies reporting on anaemia and iron markers in HIV-infected children. A pooled analysis was done using random-effects models, with Forest plots and heterogeneity test estimates provided. Fifteen articles (2778 children) met the inclusion criteria. In the pooled analysis, mean overall prevalence of iron deficiency in HIV-infected children was 34\% (95\% CI 19-50\%). Prevalence rates were similar in high-income (31\%; 95\% CI 2-61\%) and low-income settings (36\%; 95\% CI 17-54\%) (p=0.14). Studies that included a HIV-uninfected control population (n=4) were only available from low-income settings and showed less iron deficiency in HIV-infected children (28\%) compared with HIV-uninfected controls (43\%); OR 0.50 (0.27-0.94); p=0.03.

The findings suggest that HIV-infected children are less likely to be iron deficient when compared with HIV-uninfected children. Possible explanations for this include HIV-induced haematosuppression and associated hypoferraemia, with adequate iron stores. Nevertheless iron deficiency is a common co-morbidity in HIV. Studies are needed to determine the role of iron deficiency in HIV-associated anaemia and the effects of iron supplementation in this population.
Chapter five | Iron deficiency anaemia in children with HIV-associated anaemia

Introduction

Anaemia is a common haematological complication of HIV infection and has been consistently found to be independently associated with HIV-disease progression and mortality.1-5 Mild to moderate anaemia is the most common presentation in HIV-infected children from both high and low-income settings, with a prevalence of 3-82% and 22-94% respectively.6 The aetiology of HIV-associated anaemia is thought to be multi-factorial with HIV-associated infections, neoplasms, drug-related side effects, and micronutrient deficiencies being the most important aetiological (sub) groups involved.7-9 Red cell production failure is often the most important underlying pathogenic mechanism.10

Iron deficiency is considered to be the most important micronutrient deficiency causing anaemia globally. In low-income settings, iron deficiency is estimated to be responsible for up to 50% of cases of anaemia seen in pregnant women and children.11 However, the contribution of iron deficiency to anaemia in HIV-infected is unclear. Poor dietary iron intake and bioavailability, as well as reduced intestinal absorption due to repeated infections could result in a diminished iron status 11, 12. On the other hand, there is evidence that iron metabolism is altered in HIV-infection, resulting in an immune-mediated relative increase in iron stores.13 Increased iron levels have been associated with advanced stages of HIV disease and mortality;14 and iron supplementation in this context may be detrimental. The purpose of this review is to determine the prevalence of iron deficiency in HIV-infected children from high and low-income settings and compare it with that of HIV-uninfected controls. The results are then used to discuss the role of iron deficiency, the use of iron markers and inflammation in HIV-associated anaemia.

Methods

Methods | Search Strategy

Primary studies reporting on haemoglobin (Hb) and markers of iron status in HIV-infected children were searched for in the following databases (excluding Web of Science) in November 2009, with an updated search done in January 2012: PubMed (1950-2012), Embase (1980-2012), Africa Index Medicus (1960-2009), Africa Journals On-line (1998-2009) and Web of Science (1975-2012). Conference abstracts were searched via conference proceedings citation index database available on Web of Science. A standardized search protocol was developed based on the Cochrane Collaboration guidelines15 using the following key words: ‘HIV’, ‘children’, ‘iron status’ and ‘anaemia’. The search strategy aimed to identify all relevant papers and conference abstracts regardless of language or publication status (published, unpublished, in press or in progress). Relevant papers were translated where necessary. Finally, references lists of all selected articles were reviewed for relevant articles. Selection of papers and data extraction was done independently by two of the reviewers (MOE and FAMJ); discrepancies were resolved by discussion.

Methods | Selection Criteria

All studies that met the following criteria were included: presented data in HIV-infected children (<18 years) on mean haemoglobin/haematocrit levels and one or more of the following markers of iron status: serum ferritin, serum transferrin receptor (STIR), serum transferrin receptor-log ferritin index (STIR-F Index), zinc protoporphyrin (ZPP), serum iron, serum transferrin (Trf), total iron binding capacity (TIBC), mean cell haemoglobin concentration (MCHC), mean corpuscular volume (MCV), haemosiderin or bone marrow iron. If both haemoglobin and haematocrit values were provided, the former was used. Where more than one marker of iron status was used, bone marrow iron was considered first, but where this was not available,
peripheral blood iron markers (ferritin, Trf, STTR, TIBC, TrR-F Index) were preferred over indices of the full blood count (MCV, MCHC).16, 17 All observational and interventional studies that met the inclusion criteria were included. The following studies were excluded: individual case reports and case reviews, studies assessing restricted populations such as children with haemoglobinopathies; or studies done in children with specific HIV-related morbidities only. All other relevant non-primary articles on anaemia and iron deficiency in HIV-infected children were used for the discussion section.

Methods | Definitions
For the purpose of this review, anaemia was defined as haemoglobin of less than 11.5 g/dl or haematocrit of less than 33%. This value was derived from the cut-off values for anaemia used by the selected studies, and is the WHO cut-off for anaemia for children >5 years.11 Different markers and cut-offs for iron deficiency were used in the included studies and included ferritin (6 -40 µg/dl),2, 9, 12, 18-24 serum transferrin receptor-log ferritin >5.6 25 and >0.75, with a CRP <1.0 mg/L,26 serum iron <40 µmol/l;27 mean corpuscular volume <70 fl and mean cell haemoglobin concentration <32.4g/dl.1

After careful consideration, studies were classified into 2 broad groups: low-income and high-income settings, taking into account several factors which included socio-economic factors, accessibility/availability of health care and infection pressure. Studies done in Africa, Asia, and South America were classified as from low-income settings. Studies done in Europe and North America were classified as from high-income settings.

Methods | Statistical analysis
Comprehensive meta-analysis software version 2 (Biostat Inc., Englewood NJ, USA) and STATA version 10 (StataCorp, College Station TX, USA) were used for data analysis. Descriptive data of all identified studies are presented in Table 1. Pooled mean prevalence estimates (95% Confidence Intervals) using a random-effects model were generated for studies done in HIV-infected children using Forest plots stratified by setting (high versus low-income settings) and presented in Figure 2. A pooled analysis of available data from controlled studies (Figures 3 & 4) and of iron deficiency prevalence stratified by highly active anti-retroviral therapy (HAART) use (Figure 5) was done, with Forest plots and heterogeneity test estimates provided. A two-sample z-test was used to compare the prevalence of iron deficiency in HIV-infected children in high-income versus low-income settings, and the prevalence of iron deficiency in HIV-infected children on HAART with those not on HAART. We visually assessed for publication bias using funnel plots. Two-sided p-values of <0.05 were considered statistically significant.

Results
We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines in presenting the findings of this review.27

Results | Selection of articles
A combined search of PubMed, Web of Science and Embase databases retrieved 507 hits, which included 13 conference abstracts. Thirty-eight articles qualified using the selection criteria described above (Figure 1). Africa Index Medicus and Africa Journals On-line were excluded from the updated search as the initial search of these databases gave a low return of articles and did not provide any additional literature to that which was available on PubMed or Embase. From the 38 articles left, 23 were excluded either because they did not present relevant findings exclusively in the study target population (children <18 years) or they did not present data on iron deficiency or anaemia.
Figure 1. Systematic review flow diagram. Study results were either not reported exclusively for children <18 years or exclusively for the paediatric HIV-infected sub-population; Did not present results of iron markers for determination of iron status or haemoglobin cut-off levels for definition of anaemia in their respective study populations

Results | Description of selected studies

Fifteen articles representing 2778 children met the inclusion criteria. Eleven studies were from low-income settings: Brazil,18 Thailand,19 South Africa,2 Uganda,1,21-23 Malawi24 and India26 and four were from high-income settings: USA27,28 and Italy.12 Twelve of the studies were cross-sectional studies1,2,9,12,18,19,21,22,25,26,28,29 and three were cohort studies.3,23,24 Four of the fifteen studies presented data on iron deficiency in an HIV-uninfected control group, all from low-income settings (Figure 4).22-25

Three of the four controlled studies were cohorts of children born to HIV-infected and uninfected mothers followed from birth with blood parameters assessed periodically; HIV PCR testing was used determine which HIV-exposed children made up the HIV-infected cohort, all other children (HIV-exposed and unexposed) were used as controls.22-24 The fourth study was a case-control study in which healthy, non-severely anaemic (haemoglobin >5g/dl) community and hospital controls were recruited for HIV-infected children admitted for severe anaemia.25

All HIV-infected children from two of the studies presented were on HAART,18,29 four studies had some of their HIV-infected cohorts on HAART24,9,26,28 seven studies were done before HAART use was adopted as part of the standard of care in the countries where they were carried out 1-3,21-23,25 and two studies did not provide any information on HAART use.12,19 Four of the five studies which provided prevalence estimates for iron deficient HIV-infected children on HAART were made up of cohorts that were either followed from birth or started on HAART at an early age9,18,24,29. The fifth study cohort was made up of HIV-infected children initiated on HAART using national guidelines, adapted from WHO criteria.26 Only children on daily maintenance medications with HAART were considered for inclusion the HAART subgroup, children who received HAART only as part of peri-natal prophylaxis protocols were excluded.

Results | Anaemia

The prevalence of anaemia in HIV-infected children from high and low-income settings ranged from 15-94% and 63-100% respectively (Table 1). Prevalence of anaemia in uninfected controls from high and low-income settings ranged from 5-31% and 36-100% respectively (Table 1).
Results | Iron deficiency

The iron markers and their cut-off values used to define iron deficiency for each study are presented in Table 1. In the pooled analysis, the mean overall prevalence of iron deficiency in HIV-infected children was 35% (95% CI 18-51%). Prevalence rates were similar in high-income settings (31%; 95% CI 2-61%) and low-income settings (36%; 95% CI 17-56%) (p=0.14; Figure 2). Studies that included a HIV-uninfected control population (n=4) were only available in low-income settings and showed that HIV-infected children were less likely to be iron deficient when compared with HIV-uninfected controls [28% vs. 43%; OR 0.50 (0.27-0.94); p=0.03]; (Figures 3 and 4).

Pooled estimates of the prevalence of iron deficiency in HIV-infected children stratified by HAART use are provided in Figure 5. The prevalence of iron deficiency was significantly lower in HIV-infected children on HAART (24%; 95% CI 7-41%) when compared with those not on HAART (37%; 95% CI 17-58%) (p=0.005). Visual assessment of funnel plots for the prevalence of iron deficiency in HIV-infected children (not shown) revealed some asymmetry, with 3 outlying studies detected $^3,^{18,23}$.

![Figure 2. Pooled analyses of prevalence of iron deficiency in HIV-infected children. 1) n=257, test for heterogeneity (random): Q=1.52; d.f.=3 (p=0.02); $I^2 =0. 2) n=964, test for heterogeneity (random): Q=4.75; d.f.=10 (p=0.01); $I^2 =0. 3) Test for overall effect (random): z=4.28 (p<0.001).](image-url)
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<th>HIV-</th>
<th>Anemia cut-off Hb (g/dl)</th>
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<th>Prevalence of Anemia (%)</th>
<th>Prevalence of Iron deficiency (%)</th>
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<td>Prior to 2002</td>
<td>13-58</td>
<td>Descriptive study on peripheral iron status in clinically stable HIV + children</td>
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<td>-</td>
<td>&lt;11</td>
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<td>TFR-P Index ≥35.6</td>
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<td>&lt;11.5</td>
<td>STR/P Index &gt;0.75 + CRP ≥1.0</td>
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<td>1987-1994</td>
<td>4-155</td>
<td>Retrospective review of bone marrow aspirates</td>
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<td>&lt;10</td>
<td>Haemosiderin: Decreased</td>
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<td>Haematological profile of asymptomatic HIV + children</td>
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<td>47</td>
<td>&lt;11</td>
<td>Haemosiderin: Decreased</td>
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<td>32.0</td>
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<td>Prior to 1995</td>
<td>1-156</td>
<td>Study assessing contribution of ID to anemia in HIV</td>
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<td>-</td>
<td>&lt;11.5</td>
<td>Serum iron &lt;10 (g/dL)</td>
<td>88.0</td>
<td>-</td>
<td>18.0</td>
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</table>
| USA  
| Gutekunst, et al                          | Prior to 2000 | <216          | Observational study classifying anemia as either due to ID or chronic disease | 16 | -    | <11.5| STR/P Index >27.8 + CRP ≥4.6 | 15.0                         | -                           | 33.0                           |                              |                              |

Table 1. Prevalence of anaemia and iron deficiency in HIV-positive children and controls. Values for serum ferritin presented in ug/L; serum iron in umol/L; MCHC in g/dL & MCV in fL. Estimate based on mean (SD) ferritin values for HIV-infected cohort at 6 months; Age specific cut-offs for anaemia and serum iron are presented. Anaemia defined as Hb <11.5g/dl for children >24months, and <10.5g/dl for children 6-24months. ID defined as serum iron <30 for children <12months; serum iron <30 for children >12months. Laboratory cut-off value for Hb not referenced by the authors.
Figure 3. Prevalence of iron deficiency in: A) HIV-uninfected controls, B) HIV uninfected controls
1) n= 291 (HIV-infected cohort), 1510; data obtained from studies on low-income settings, no data available for controlled studies from high-income settings. 2) Pooled estimates; Test of heterogeneity (random effects model): Q=1.75, d.f.=3 (p=0.04), I²=0. 3) Pooled estimates; Test of heterogeneity (random effects model): Q=2.94, d.f.=3 (p<0.001), I²=0.

Figure 4. Pooled analyses of iron deficiency prevalence in. 1) n=1801 (HIV positive: 291); compares prevalence rates of iron deficiency in HIV-infected children with controls in the four controlled studies, only studies done in low-income settings had a control group included. 2) Test of overall effect: Z=-2.17 (p=0.03).
Chapter five | Iron deficiency anaemia in children with HIV-associated anaemia

<table>
<thead>
<tr>
<th>Studies</th>
<th>mean prevalence (95% CI)</th>
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<tr>
<td>Silva, et al 1999</td>
<td>0.03 (0.03 – 0.09)</td>
</tr>
<tr>
<td>Silva, et al 2001</td>
<td>0.19 (0.03 – 0.35)</td>
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<td>Miera, et al 2005</td>
<td>0.67 (0.14 – 1.20)</td>
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<tr>
<td>Butensky, et al 2009</td>
<td>0.35 (0.17 – 0.53)</td>
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<td>Shet, et al. 2011</td>
<td>0.28 (0.14 – 0.42)</td>
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<td>Sub-total, HAART</td>
<td>0.24 (0.07 – 0.41)</td>
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<tr>
<td>Ellaurie, et al 1990</td>
<td>0.01 (-0.03 – 0.06)</td>
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<tr>
<td>Clark, et al 2002</td>
<td>0.74 (0.68 – 0.80)</td>
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<tr>
<td>Eley, et al 2002</td>
<td>0.52 (0.40 – 0.64)</td>
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<tr>
<td>Totin, et al 2002</td>
<td>0.47 (0.39 – 0.56)</td>
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<tr>
<td>Miera, et al (2), 2005</td>
<td>0.20 (-0.15 – 0.35)</td>
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<tr>
<td>Miller, et al 2006</td>
<td>0.03 (-0.001 – 0.08)</td>
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<tr>
<td>Ray, et al 2007</td>
<td>0.49 (0.41 – 0.57)</td>
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<tr>
<td>Calis, et al 2008a</td>
<td>0.42 (0.32 – 0.52)</td>
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<td>Shet, et al (2), 2011</td>
<td>0.44 (0.28 – 0.60)</td>
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<tr>
<td>Sub-total, (non-HAART)</td>
<td>0.37 (0.17 – 0.58)</td>
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Figure 5. Prevalence of iron deficiency in HIV-infected children by HAART use. ¹ Study provided data on iron deficiency for subpopulations on HAART); ² n=131 (HAART), n=155 (non-HAART). Children who received HAART only as part of peri-natal prophylaxis protocol were excluded.

Results | Intervention studies

Only one of the studies reviewed was an intervention study, done in a high-income setting looking at the effect of oral iron therapy on iron deficiency and intestinal malabsorption in HIV-infected children.² Iron deficiency was present in 48% of the study population, and was significantly associated with intestinal malabsorption.

Discussion

In this first review on iron deficiency in paediatric HIV-infection, we observed that there is limited data on iron states in HIV-infected children. However, we identified that HIV-infected children are less likely to be iron deficient when compared with HIV-uninfected children. This comparison could only be made for children from low-income settings, since there were no studies from high-income settings reporting on the prevalence of iron deficiency in HIV-uninfected controls. We also observed that prevalence rates of iron deficiency in HIV-infected children are significantly modified by HAART use.

True versus functional iron deficiency in HIV-associated anaemia

Our results suggest that iron deficiency in HIV-infected children is a problem in both high and low-income settings, despite the increasing availability of HAART- with studies from both areas reporting similar mean prevalence rates. Our results also suggest that iron deficiency may be less common in HIV-infected children than in uninfected children. HIV-infected children are commonly malnourished due to macronutrient and multi-micronutrient deficient diets, as well as increased metabolic demands during infections.³ Iron deficiency however does not appear to be more common.

One of the studies presented in this review which looked at bone marrow aspirates in a subset of their HIV cohort found normal iron content in all 20 specimens examined- although other bone marrow studies done in children reported higher iron deficiency prevalence rates.³,⁹,²⁸ Pathophysiologic mechanisms that may explain the lower prevalence of iron deficiency seen in HIV-infected children compared with controls include a
cytokine-mediated inhibition of erythroid progenitor cells and an inflammation-induced hypoferremia, with haemoglobin levels closely correlated with low serum iron levels. These mechanisms may result in functional iron deficiency, where indices of body iron stores are relatively normal while indices of peripheral body iron are reduced. This is in contrast with true iron deficiency where iron stores (notably ferritin levels) are depleted. Functional iron deficiency, which may be seen in HIV and other chronic inflammatory disorders, may render iron unavailable for erythropoiesis resulting in anaemia but also makes it unavailable for infective organisms that require iron for growth and proliferation - thus may be protective against severe bacterial infections and malaria in regions with a high pressure of infection.

The use of iron markers in infection: the role of inflammation

The interpretation of serological markers of body iron status is unclear in areas with a high pressure of infection. Ferritin, which is commonly used to estimate body iron is also a mediator of the acute phase response and is raised in HIV-infection while serum iron and blood transferrin levels are decreased. Some of the studies identified in our search did not adequately adjust their ferritin cut-off values for inflammation - thus true iron deficiency may be present even when the indices of iron status exceed the recommended normal cut-off value. This could have contributed to the lower prevalence of iron deficiency seen in the HIV-infected cohorts of studies that used ferritin alone to assess iron status. However, two of the three controlled studies (both done in regions of high infection pressure) that used ferritin alone to assess iron status did not report a significant difference in mean ferritin values or the prevalence of iron deficiency between their HIV-infected and control populations. More importantly, the only controlled study which used serum transferrin receptor-log ferritin index to determine iron status - a marker which is less influenced by infection showed that iron deficiency was less prevalent in HIV-infected children compared with controls, further adding weight to our findings. In the absence of bone marrow iron values, ideally studies using a combination of two or more serological iron markers, preferably including a marker of inflammation in regions with a high pressure of infections should have been used but this was not possible as the number of eligible studies presenting this data was too small.

Iron states in HIV-associated anaemia: is intervention needed?

The results of this review casts some doubt as to the role of iron deficiency in the aetiology of anaemia of HIV-infection, and raises important questions on how HIV-associated anaemia should be managed. It is known that anaemia in HIV disease is associated with an increased risk of death. and anaemia treatment is associated with an improved survival and quality of life in HIV-infected persons. However, it is unknown if iron deficiency plays a major role in the aetiology of anaemia in HIV-infected children, with the results suggesting that it is less common when compared with uninfected children. An important question remains - if the WHO policy of iron supplementation for the prevention and treatment of anaemia is favourable in HIV-infected children, especially in the era of increased availability of HAART. Castaldo et al demonstrated that iron supplementation is beneficial in HIV-infected children; however the six patients that received iron in this study were neither randomised nor blinded, and there was no control group with which to compare their findings - thus their results were subject to selection and measurement bias. They also did not report if there were any untoward effects seen as a result of iron supplementation. The detrimental effects of iron supplementation for the treatment of anaemia in iron-replete children have been clearly demonstrated in previous studies, with the results showing an increased risk of severe infections and death in populations with a high prevalence of malaria. Given the increased risk of susceptibility to infections in HIV-infected children, this evidence is needed to inform management, especially in regions with a high prevalence of infections, including malaria.
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In trying to assess the impact of important factors that could have affected our results, we examined the effect of HAART on our prevalence estimates. We observed that routine HAART use in HIV-infected children was associated with a lower prevalence of iron deficiency when compared with HIV-infected children not on HAART. The explanation for this observation is unclear, but it may be related to the beneficial effect of HAART on anaemia and haematopoiesis, where a reduction in viral load results in reversal of cytokine-mediated haematosuppression. A recent study carried out in India by Shet et al in which a cohort of HIV-infected children managed according to national guidelines were followed for 6 months reported that HAART when given with iron supplementation was associated with a better haemoglobin response than either HAART or iron given alone, without any serious adverse effects seen. These observations make a strong case for the conduct of studies examining the effects of HAART on iron status in HIV-infected children.

Other factors that could potentially have had an impact on our findings include poor dietary intake and bioavailability of iron, inadequate HIV disease monitoring and management in resource-limited settings, prevention and treatment of opportunistic infections, and management of co-morbidities such as malnutrition and parasitic infections- especially in regions with a high pressure of infection. We have tried to limit the impact of these factors by classification of the studies included in this review; however their importance cannot be understated, especially in low-income settings.

Limitations of this review
The number of studies identified by our search was small and heterogenous, restricting the differential analytic power of the meta-analysis. We partly corrected for this by doing sub-group analyses using high and low income settings. However, as we found some asymmetry on visual assessment of funnel plots (not presented), we cannot rule out publication bias which is not uncommon with diagnostic studies.

None of the studies from high-income settings provided data on iron deficiency in HIV-uninfected controls, thus it was not possible to compare findings in controlled studies from different geographic (socio-economic) settings. There were no randomized clinical trials on iron supplementation in HIV-infected children with anaemia identified in our search.

Clinical impact and areas for future research
Our findings suggest that iron deficiency may be less common in HIV infected children compared with HIV-uninfected children. Studies examining the role of iron deficiency in the aetiology of HIV-associated anaemia are needed. There is a need for more studies in which the iron status of HIV-infected children is correctly defined, ideally using bone marrow iron estimates, and also for studies examining the effect of HAART on iron status. There is a need for randomized clinical trials evaluating the safety and benefit of iron supplementation in the treatment of HIV-associated anaemia, especially in low-income settings.
Conclusions

Though the data available was limited, the findings suggest that HIV-infected children are less likely to be iron deficient when compared with HIV-uninfected children. Iron deficiency however remains a common co-morbidity. Studies are needed to determine the role of iron deficiency in HIV-associated anaemia and to assess the safety and benefit of iron supplementation. This information is required to guide management, especially in low-income settings with a high prevalence of infections, including malaria.

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