Prevalence of anemia among people living with HIV: A systematic review and meta-analysis

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eClinicalMedicine
2022;44: 101283
Published online xxx
https://doi.org/10.1016/j.eclinm.2022.101283

Summary

Background Anemia is the most frequent hematologic abnormality among people living with human immunodeficiency virus (HIV) (PLWHIV) and is associated with HIV disease progression and higher risk of mortality of the patients. However, there is a wide variation of the prevalence of anemia among PLWHIV in different clinical settings. We aimed to obtain more precise estimates of prevalence of anemia and severity of anemia among PLWHIV, which may be important for patients, caregivers, researchers and health policy-makers.

Methods We systematically searched PubMed, EMBASE, Web of Science, and Cochrane Library for original articles reporting the prevalence of anemia defined using age and sex-specific hemoglobin levels according to World Health Organization criteria among PLWHIV from inception to August 31, 2021. We used DerSimonian-Laird random-effects meta-analyses to obtain pooled prevalence and 95% confidence intervals (CIs) of anemia and severity of anemia among PLWHIV. A univariable meta-regression has been conducted to assess the association between anemia prevalence and study characteristics, including study design, median year of sampling, geographical region, World Bank Income level, and proportion of antiretroviral therapy (ART).

Findings We included 63 observational studies covering 110,113 PLWHIV. The pooled prevalence of anemia was 39.7% (95% CI: 31.4%-48.0%) for children living with HIV aged <15 years, 46.6% (95% CI: 41.9%-51.4%) for adults (men and non-pregnant women) living with HIV aged ≥15 years, and 48.6% (95% CI: 41.6%-55.6%) for pregnant women living with HIV. Among adults living with HIV, the pooled prevalence of severity of anemia was 21.6% (95% CI: 19.9%-23.3%), 22.6% (95% CI: 14.8%-30.4%), and 6.2% (95% CI: 4.4%-8.1%) for mild, moderate and severe anemia, respectively. Compared with East Africa, anemia prevalence among adults living with HIV was higher in Southern Africa ($p = 0.033$).

Interpretation Anemia is prevalent among PLWHIV. Thus, policies, strategies, and programs should be considered to identify the predictors of anemia among PLWHIV to reduce the burden of anemia among patients in the ART era.

Keywords: HIV; Anemia; Severity of anemia; Antiretroviral therapy

Introduction

Globally, an estimated 37.6 million people in the world were living with human immunodeficiency virus (HIV) in 2020, and 1.5 million people were newly infected.[1] Despite a steady but slow decline in the incidence rates of HIV infection over the past two decades, with improved survival due to the scale-up of antiretroviral therapies (ART), more people are living with HIV than ever before.[2] However, in tandem with increases in life expectancy following the introduction of ART, hematological changes are one of the most common complications among PLWHIV and could impact both the length and quality of their lives.[3–5] As the most common hematologic abnormality among PLWHIV, anemia has been cited as a prognostic marker for HIV disease progression and has been associated with reduced survival.[5–8]

The causes of anemia among HIV-infected patients are multifactorial. HIV could directly and indirectly impact the survival and functioning of hematopoietic stem/progenitor cells (HSPCs) that reside in the bone marrow.[9,10] In addition, the drugs used for ART, inflammatory mediators released during HIV infection and coinfections or opportunistic infections could also affect the proliferation and differentiation of HSPCs during hematopoiesis.[9,10] Progressive depletion of HSPCs or suppression of their function could both

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Research in context

Evidence before this study

Anemia is the most frequent hematologic abnormalities among people living with human immunodeficiency virus (HIV) (PLWHIV); however, there is a wide variation of the prevalence in different clinical settings. Previous systematic reviews of prevalence of anemia among PLWHIV have focused on children below 18 years in specific regions or have included studies identifying anemia among PLWHIV not using age and sex-specific hemoglobin levels according to World Health Organization (WHO) criteria. Data are needed to establish the global burden of anemia among PLWHIV, these data are important for patients, caregivers, researchers and health policy-makers and are essential to inform normative guidance. We searched PubMed, EMBASE, Web of Science, and Cochrane Library for original articles reporting the prevalence of anemia from inception to August 31, 2021, using the term "("HIV" or "human immunodeficiency virus") and "anemia" and ("prevalence" or "incidence" or "epidemiology")". The classification of severity of anemia must be defined by using age and sex-specific Hb levels according to WHO criteria among PLWHIV. We identified 63 observational studies covering 110,113 PLWHIV for inclusion.

Added value of this study

To our knowledge, this current study is the first to assess the prevalence of anemia and severity of anemia among PLWHIV using age and sex-specific hemoglobin levels according to WHO criteria. We found that the pooled prevalence of anemia was 39.7% (95% CI: 31.4%−48.0%) for children living with HIV aged <15 years, 46.6% (95% CI: 41.9%−51.4%) for adults (men and non-pregnant women) living with HIV aged ≥15 years, and 48.6% (95% CI: 41.6%−55.6%) for pregnant women living with HIV. The pooled prevalence of severity of anemia was 21.6% (95% CI: 19.9%−23.3%), 22.6% (95% CI: 14.8%−30.4%), and 6.2% (95% CI: 4.4%−8.1%) for mild, moderate and severe anemia among adults living with HIV, respectively.

Implications of all the available evidence

Our findings clearly show that anemia is prevalent among PLWHIV, especially for adults and pregnant women living with HIV. There is also a need for clinicians to pay more attention to anemia among PLWHIV in the antiretroviral therapy era. The predictors of anemia among PLWHIV to reduce the burden of anemia among patients are warranted to be studied in the future.

result in hematologic abnormalities, such as anemia, thrombocytopenia, and neutropaenia.[9,10] Of note, thrombocytopenia is often asymptomatic in HIV-infected patients and may be associated with a variety of bleeding abnormalities,[11–13] which could possibly lead to an increased risk of anemia and even aggravate anemia.[14]

Over the past three decades, an increasing number of population-based studies have evaluated the prevalence of anemia and the possibly associated factors among PLWHIV; however, there was a wide variation in the prevalence of anemia ranging from 1.3% to 95% in different clinical settings.[5,15,16] The possible explanations of the varied range of anemia prevalence among PLWHIV might be differences in criteria of anemia, progression of HIV disease, and ART status across previous studies.[5,17–22] For example, the prevalence of anemia (hemoglobin (Hb) concentration <12 g/dL for females and <13 g/dL for males) was 54.2% among PLWHIV entering pre-ART care (June 2011-June 2014) in Myanmar,[21] which was higher than that among Chinese PLWHIV receiving ART (27.7%) in 2014.[22] The prevalence of anemia that was diagnosed as Hb ≤10.5 g/dL was 42.8% among ART-naÿve children living with HIV.[20] Several previous reviews have indicated that anemia prevalence differed across studies using different definitions of anemia among PLWHIV, making comparisons difficult between studies.[5,10,23] In addition, one of the previous reviews reported that three studies conducted in Africa using the same World Health Organization (WHO) definition reported a remarkably similar prevalence of anemia among PLWHIV.[5] Therefore, we undertook a systematic review to estimate the prevalence of anemia and severity of anemia diagnosed using Hb levels according to WHO criteria for PLWHIV.[24]

Methods

Search strategy and selection criteria

We searched PubMed, EMBASE, Web of Science, and Cochrane Library for studies reporting the prevalence of anemia in HIV-infected people from inception to August 31, 2021, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[25] The protocol of this study was not preregistered. Articles were identified using the search terms "(HIV" or "human immunodeficiency virus") and "anemia" and ("prevalence" or "incidence" or "epidemiology")", without language restrictions. The detailed search strategies are presented in Supplementary Table 1.

The included studies were required to investigate PLWHIV and needed to present data that allowed us to calculate the prevalence of anemia. The prevalence of anemia and its severity were the primary and secondary outcomes of interest, and the included studies should be observational studies, including cross-sectional studies, longitudinal studies, and case control studies in which cases were representative samples of all HIV patients. Classification of severity of anemia must be determined by using age and sex-specific Hb levels

according to WHO criteria[24]: no anemia (Hb ≥130 g/L for children 6–59 months of age, ≥115 g/L for children 5–11 years of age, ≥120 g/L for children 12–14 years of age, ≥120 g/L for non-pregnant women ≥15 years of age, ≥110 g/L for pregnant women, ≥130 g/L for men ≥15 years of age), mild anemia (100–109 g/L for children 6–59 months of age, 110–114 g/L for children 5–11 years of age, 110–119 g/L for children 12–14 years of age, 110–119 g/L for non-pregnant women ≥15 years of age, 100–109 g/L for pregnant women, 110–129 g/L for men ≥15 years of age), moderate anemia (70–99 g/L for children 6–59 months of age, 80–109 g/L for children 5–11 years of age, 80–109 g/L for children 12–14 years of age, 80–109 g/L for non-pregnant women ≥15 years of age, 70–99 g/L for pregnant women, 80–109 g/L for men ≥15 years of age), and severe anemia (<70 g/L for children 6–59 months of age, <80 g/L for children 5–11 years of age, <80 g/L for children 12–14 years of age, <80 g/L for non-pregnant women ≥15 years of age, <70 g/L for pregnant women, <80 g/L for men ≥15 years of age). We excluded studies if they were reviews, animal studies, or duplicate studies (enrolling the same population in the same region around the same period) with fewer sample; or if the diagnostic methods of anemia were unclear; if baseline sample were excluded due to anemia treated previously; baseline PLWHIV were not general patients but patients with WHO stage III or IV HIV disease, special risk groups (e.g., patients with tuberculosis, Kaposi sarcoma, or hepatitis C), or patients included with criteria that would be related to anemia (e.g., patients were screened for tuberculosis or without a current TB).

Two authors (GC and YW) independently performed the literature search, screened all abstracts and titles identified in the search, and assessed the full text considered potentially relevant. Any disagreements were resolved by discussion with a third reviewer (WJ).

Data analysis

Two authors (GC and YW) extracted information about the first author's last name, year of publication, geographical location, median year of sampling, population groups (children aged <15 years, adults (men and non-pregnant women aged ≥ 15 years), and pregnant women), sample size, mean (standard deviation, SD) or median (interquartile range, IQR) age of the study population, numbers of HIV patients diagnosed with anemia overall and stratified by severity of anemia, and proportion of ART at anemia diagnosis from every eligible study. The income level of each country was further classified into low-, low-middle-, upper-middle-, or high-income according to the World Bank's country classification.[26] We extracted anemia cases at the first timepoint, when a cohort study reported several estimates of anemia cases at different timepoints, such as at baseline and after ART initiation. The two authors reached a consensus after discussing any controversial findings with a third author (WJ). The quality of the included studies was evaluated by a tool developed by Hoy and colleagues.[27,28] Each study was assessed according to 10 items, and a score of one (yes) or zero (no) was assigned for each item. Quality was assessed on a 10-point tool and classified as low (>8), moderate (6–8), and high (≤5) risk of bias.

We performed DerSimonian-Laird random-effects meta-analyses of the included studies to calculate the pooled prevalence and 95% confidence intervals (CIs) of anemia and its severity in children, adults, and pregnant women, respectively. A univariable meta-regression was conducted to assess the association between anemia prevalence and several study characteristics, including study design, median year of sampling, geographical region, World Bank Income level and ART proportion. Statistical heterogeneity among the studies was estimated using the I^2 statistic, and very low, low, moderate, and high degrees of heterogeneity were defined as ≤25%, 25% to ≤50%, 50% to ≤75%, and ≥75%, respectively.[1] Publication bias was appraised using funnel plots and Egger's test for assessing asymmetry. All analyses were performed using Stata software (version 12.0; Stata SE Corporation LP, College Station, TX, USA). A two-sided p value <0.05 was considered statistically significant.[29]

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Characteristics of included studies

A total of 4763 records were identified based on the initial search, of which 139 were selected for full-text evaluation after removal of duplications and initial screening (Figure 1). Among studies not using Hb levels according to WHO criteria to define anemia, most of them were more likely to not use age and sex-specific Hb levels or used a higher cutoff of for anemia and lower cutoff for severe anemia than that of WHO criteria.[18,30–40] After applying the inclusion criteria, 63 studies (12 cohort, 2 case-control, and 49 cross-sectional studies) covering 110,113 PLWHIV met the inclusion criteria and were included in the meta-analysis[6,17–19,21,36,41–97] (Table 1). In brief, the majority of the included studies were conducted in Africa (25 in East Africa, 8 in West and Central Africa, and 3 in Southern Africa),[6,17–19,41–43,45,48,50,51,55–58,60–62,65–68,70–74,78,79,83–85,89,92,96,97] 6 in Asia,[44,46,47,49,52,53,63,64,76,80,82,87,90,91] 5 in Europe,[21,36,59,75,86] 5 in North America,[54,77,81,93,94] 1 in

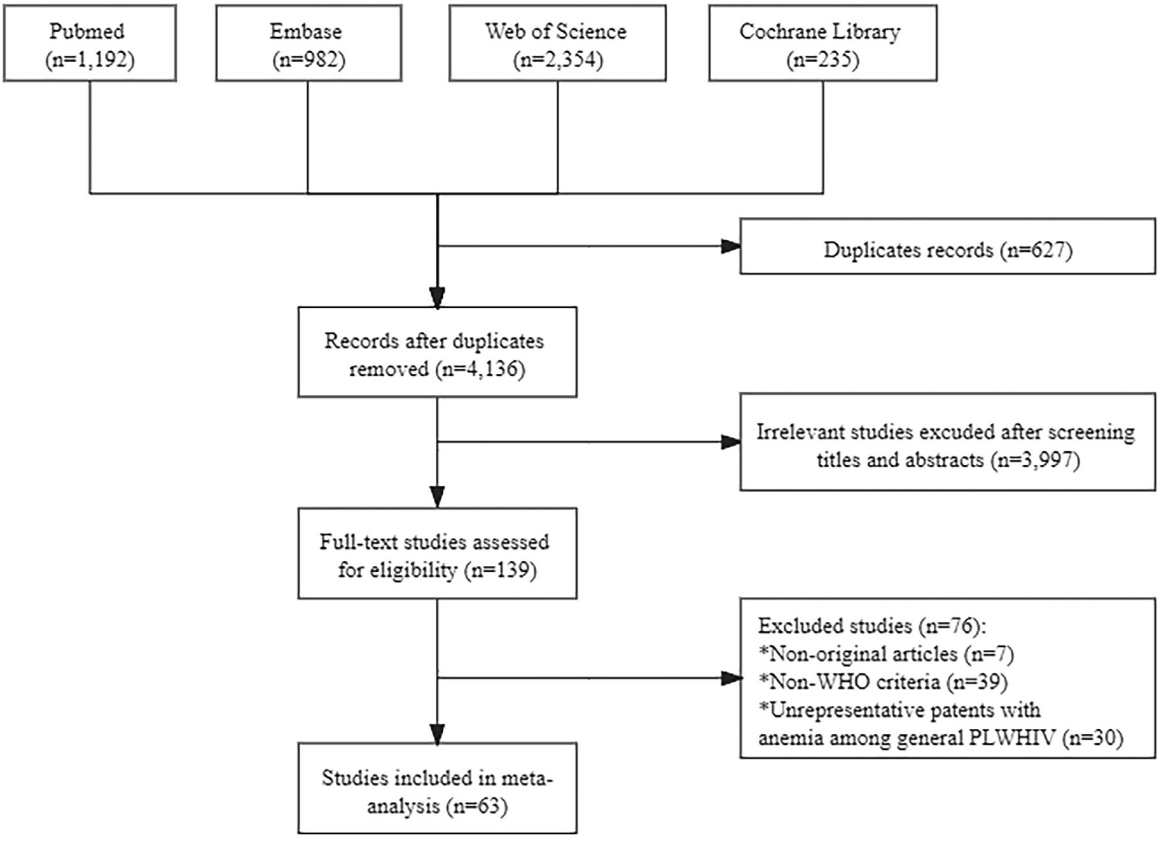

Figure 1. Study flowchart.
Note: PLWHIV=people living with human immunodeficiency virus; WHO=World Health Organization.

Oceania,[69] 1 in Latin America & Caribbean,[95] and 1 in multiple regions.[88] PLWHIV were children aged <15 years in 9 studies,[17,19,41-47] non-pregnant women and men aged ≥15 years in 51 studies,[6,18,21,36,48–94] and pregnant women in 3 studies.[95–97] All studies included in the current review were evaluated as having a moderate risk of bias (Supplementary Table 2).

Prevalence of anemia among children living with HIV

Among all the included studies, 9 studies reported cases of anemia or severity of anemia among children living with HIV aged <15 years (Table 1). Figure 2 presents the forest plot of the prevalence of anemia among children living with HIV. The pooled prevalence of anemia was 39.7% (95% CI: 31.4%–48.0%) from 8 studies, but with high heterogeneity (I^2=91.5%, p <0.001) (Figure 2). There was no evidence of publication bias based on the funnel plot and Egger's test (Supplementary Figure 1). For the severity of anemia, 1 study reported both mild and moderate anemia cases and 4 studies reported severe anemia cases among children living with HIV. The pooled prevalence of severe anemia was 3.7% (95% CI: 0.8%–6.7%) with moderate heterogeneity between studies (Supplementary Figure 2) and no evidence of publication bias (Supplementary Figure 3).

Prevalence of anemia among adults living with HIV

Figure 3 shows the prevalence of anemia among adults living with HIV aged >15 years from 47 studies included in this study. The overall estimate of anemia prevalence was 46.6% (95% CI: 41.9%–51.4%) among adults living with HIV (Figure 3). The I^2 statistic (99.5%, p <0.001) indicated substantial heterogeneity between the studies (Figure 3). The funnel plot and Egger's test did not detect any publication bias (Supplementary Figure 4). Across the severity of anemia, the pooled prevalence of anemia was 21.6% (95% CI: 19.9%–23.3%) for mild anemia from 14 studies, 22.6% (95% CI: 14.8%–30.4%) for moderate anemia from 13 studies, and 6.2% (95% CI: 4.4%–8.1%) for severe anemia from 21 studies, but with high heterogeneity (Supplementary Figure 5). No publication bias was found for the pooled prevalence of severity of anemia based on the funnel plot and Egger's test (Supplementary Figs. 6–8).

First author, year (Country)	Median year of sampling (y)	Study design	Population group	Sample size, n	Age, y	Anemia cases by severity, n				Proportion of ART,%	Region	World Bank Income level
						Total	Mild	Moderate	Severe			
Bayleyegn et al., 2021 (Ethiopia)[41]	2020	Cross-sectional	Children	255	Median (IQR): 13 (10–14)	54				99.2	East Africa	Low
Geleta et al., 2021 (Ethiopia)[17]	2018	Cross-sectional	Children	256	Median (IQR): 12 (10–14)	98				100.0	East Africa	Low
Melku et al., 2020 (Ethiopia)[42]	2011	Cross-sectional	Children	200	NA	75	41	34		100.0	East Africa	Low
Tsegay et al., 2017 (Ethiopia)[43]	2013	Cross-sectional	Children	224	Median (IQR): 8 (NA)	66				50.0	East Africa	Low
Ahumareze et al., 2016 (Nigeria)[19]	2015	Cross-sectional	Children	164	Mean (SD): 8.3 (1.9)	89			2	100.0	West and Central Africa	Lower-middle
Shet et al., 2015 (India)[44]	2011	Cohort	Children	240	Mean (SD): 7.7 (2.6)	113			16	43.3	Asia	Lower-middle
Ezeonwu et al., 2014 (Nigeria)[45]	2005	Cross-sectional	Children	67	NA				2	71.6	West and Central Africa	Lower-middle
Kapavarapu et al., 2012 (India)[46]	2010	Cross-sectional	Children	85	Mean (SD): 9.2 (NA)	34				29.4	Asia	Lower-middle
Shet et al., 2012 (India)[47]	2008	Cross-sectional	Children	80	Mean (SD): 6.8 (NA)	42			4	36.3	Asia	Lower-middle
Damtie et al., 2021 (Ethiopia)[48]	2020	Cross-sectional	Adult	334	Mean (SD): 38.8 (9.9)	124				0.0	East Africa	Low
Butt et al., 2020 (Japan)[59]	2016	Cross-sectional	Adult	230	Mean (SD): 38.0 (14.5)	152			26	NA	Asia	High
Baye et al., 2020 (Ethiopia)[50]	2019	Cross-sectional	Adult	392	Mean (SD): 40.5 (8.5)	191				94.6	East Africa	Low
Berhane et al., 2020 (Ethiopia)[51]	2019	Case-control	Adult	212	Mean (SD): 41.68 (10.61)	80				0.0	East Africa	Low
Dobe et al., 2020 (Mozambique)[18]	2013	Cross-sectional	Adult	264	Mean (SD): 39.3 (9.8)	153				100.0	Southern Africa	Low
Khatri et al., 2020 (Nepal)[52]	2017	Cross-sectional	Adult	350	Mean (SD): 38.9 (9.1)	112				100.0	Asia	Lower-middle
Sah et al., 2020 (Nepal)[53]	2017	Cross-sectional	Adult	210	Mean (SD): 37.50 (10.57)	140	30	85	25	81.9	Asia	Lower-middle
	2002	Cross-sectional	Adult	1449		348				100.0	North America	High

Table 1 (Continued)

First author, year (Country)	Median year of sampling (y)	Study design	Population group	Sample size, n	Age, y	Anemia cases by severity, n				Proportion of ART,%	Region	World Bank Income level
						Total	Mild	Moderate	Severe			
Zanni et al., 2020 (US)[54]					Median (IQR): 49 (45–55)							
Albrecht et al., 2019 (Tanzania) [6]	2015	Cohort	Adult	1622	Median (IQR): 38 (31–46)				288	100.0	East Africa	Lower-middle
Ageru et al., 2019 (Ethiopia) [55]	2016	Cross-sectional	Adult	411	Mean (SD): 35.0 (8.9)	150	106	40	4	74.9	East Africa	Low
Tamir et al., 2019 (Ethiopia) [56]	2016	Cross-sectional	Adult	402	Mean (SD): 36.2 (9.5)	175	69	70	36	0.0	East Africa	Low
Yesuf et al., 2019 (Ethiopia)[57]	2012	Cross-sectional	Adult	404	NA	133				0.0	East Africa	Low
Ezeamama et al., 2018 (Uganda)[58]	2009	Cohort	Adult	398	Mean (SD): 35.8 (9.0)	194	113			50.0	East Africa	Low
Hentzien et al., 2018 (France)[59]	2008	Cross-sectional	Adult	1415	Mean (SD): 65.7 (5.5)	296				88.2	Europe	High
Katemba et al., 2018 (Uganda) [60]	2016	Cross-sectional	Adult	141	Mean (SD): 34 (NA)	95				0.0	East Africa	Low
Beyene et al., 2017 (Ethiopia) [61]	2013	Cross-sectional	Adult	528	Mean (SD): 33.69 (9.08)	227			37	0.0	East Africa	Low
Fiseha et al., 2017 (Ethiopia)[62]	2012	Cross-sectional	Adult	373	Mean (SD): 34.6 (10.8)	128	76	46	6	0.0	East Africa	Low
Jin et al., 2017a (China)[63]	2012	Cross-sectional	Adult	8632	Mean (SD): 47.0 (8.3)				101	100.0	Asia	Upper-middle
Jin et al., 2017b (China)[64]	2014	Cross-sectional	Adult	9402	Mean (SD): 47.8 (8.5)	2534	1788	495	251	100.0	Asia	Upper-middle
Gunda et al., 2017a (Tanzania)[65]	2016	Cohort	Adult	740	Median (IQR): 35 (27–42)	288			53	100.0	East Africa	Lower-middle
Gunda et al., 2017b (Tanzania)[66]	2015	Cross-sectional	Adult	1205	Median (IQR): 41 (32–48)	704				0.0	East Africa	Lower-middle
Melese et al., 2017 (Ethiopia)[67]	2015	Cross-sectional	Adult	377	Mean (SD): 35.21 (9.27)	290				62.9	East Africa	Low
Sahle et al., 2017 (Ethiopia)[68]	2014	Cross-sectional	Adult	172	Mean (SD): 31.95 (7.6)	89				82.6	East Africa	Low

Table 1 (Continued)

First author, year (Country)	Median year of sampling (y)	Study design	Population group	Sample size, n	Age, y	Anemia cases by severity, n				Proportion of ART,%	Region	World Bank Income level
						Total	Mild	Moderate	Severe			
Widiyanti et al., 2017 (Papua New Guinea)[69]	2015	Cross-sectional	Adult	90	NA	50				100.0	Oceania	Lower-middle
Gunda et al., 2016 (Tanzania)[70]	2012	Cross-sectional	Adult	346	Median (IQR): 41.2 (19−66)	245	105	91	49	100.0	East Africa	Lower-middle
Obirikorang et al. 2016 (Ghana)[71]	2013	Cross-sectional	Adult	319	Mean (SD): 38.9 (9.9)	76	41	19	16	68.7	West and Central Africa	High
Oo et al., 2016 (France)[21]	2013	Cross-sectional	Adult	11,454	Mean (SD): 37 (10)	6420	2184	3285	951	0.0	Europe	High
Akinyemi et al., 2015 (Nigeria)[72]	2009	Cross-sectional	Adult	14,857	Mean (SD): 36.4 (10.2)				1846	45.1	West and Central Africa	Lower-middle
Akilimali et al., 2015 (Democratic Republic of Congo)[73]	2008	Cohort	Adult	756	Mean (SD): 39.5 (9.8)	528	201	278	49	0.0	West and Central Africa	Low
Kerkhoff et al., 2015 (South Africa)[74]	2004	Cohort	Adult	1521	Median (IQR): 33 (28−33)	1203	304	469	49	0.0	Southern Africa	Upper-middle
Minchella et al., 2015 (UK)[75]	1997	Cross-sectional	Adult	196	Mean (SD): 34.3 (9.8)	110				NA	Europe	High
Mijiti et al., 2015 (China)[76]	2009	Cross-sectional	Adult	2252	Mean (SD): 36.6 (8.3)	875	433	383	59	0.0	Asia	Upper-middle
Erqou et al., 2014 (US)[77]	2004	Cross-sectional	Adult	8039	Mean (SD): 50.0 (7.3)	3933				NA	North America	High
Kerkhoff et al., 2014 (South Africa)[78]	2004	Cross-sectional	Adult	814	Median (IQR): 33 (29−39)	574	228	310	36	0.0	Southern Africa	Upper-middle
Kyeyune et al., 2014 (Uganda)[79]	2011	Cross-sectional	Adult	400	Mean (SD): 36.0 (9.0)	191				50.0	East Africa	Low
Martin et al., 2014 (Nepal)[80]	2011	Cross-sectional	Adult	319	Mean (SD): 35.6 (6.9)	178	82	84	12	73.1	Asia	Lower-middle
Santiago et al., 2014 (US)[81]	2005	Cohort	Adult	1486	Median (IQR): 40 (21−79)	616				64.4	North America	High

Table 1 (Continued)

First author, year (Country)	Median year of sampling (y)	Study design	Population group	Sample size, n	Age, y	Anemia cases by severity, n				Proportion of ART,%	Region	World Bank Income level
						Total	Mild	Moderate	Severe			
Shet et al., 2014 (India)[82]	2010	Cohort	Adult	321	Mean (SD): 37 (8)	82				0.0	Asia	Lower-middle
Tesfaye et al., 2014 (Ethiopia)[83]	2010	Cross-sectional	Adult	349	Mean (SD): 34.6 (8.5)	74				0.0	East Africa	Low
Ferede et al., 2013 (Ethiopia)[84]	2012	Cross-sectional	Adult	420	NA	138			10	0.0	East Africa	Low
Hadgu et al., 2013 (Ethiopia)[85]	2012	Cross-sectional	Adult	376	Mean (SD): 32.5 (8)	250				100.0	East Africa	Low
Khasanova et al., 2013 (Russia)[86]	NA	Cross-sectional	Adult	99	NA	30				NA	Europe	Upper-middle
Liu et al., 2013 (China)[87]	2012	Cross-sectional	Adult	276	Mean (SD): 46.7 (10.4)	74			4	94.9	Asia	Upper-middle
Zhou et al., 2013 (Western Africa, Southern Africa, Eastern Africa, Central Africa, Asian-Pacific, Caribbean, Central America, and South America)[88]	NA	Cohort	Adult	19,947	Median (IQR): 37 (31–44)	6502				100.0	–	–
Akinbo et al., 2012 (Nigeria)[89]	2011	Cross-sectional	Adult	285	NA	129				100.0	West and Central Africa	Lower-middle
Meidani et al., 2012 (Iran)[90]	2010	Cross-sectional	Adult	212	Mean (SD): 36.2 (9.1)	95				100.0	Asia	Lower-middle
De Santis et al., 2011 (France)[36]	2009	Cross-sectional	Adult	701	Mean (SD): 42 (NA)	263				82.3	Europe	High
Subbaraman et al., 2009 (India)[91]	2001	Cross-sectional	Adult	6996	Mean (SD): 33.6 (8.3)	4792				NA	Asia	Lower-middle
Erhabor et al., 2006 (Nigeria)[92]	NA	Case-control	Adult	100	Mean (SD): 35.2 (1.29)	43				NA	West and Central Africa	Lower-middle
Berhane et al., 2004 (US)[93]	1994	Cohort	Adult	2056	Median (IQR): 36 (NA)	761				100.0	North America	High

Table 1 (Continued)

First author, year (Country)	Median year of sampling (y)	Study design	Population group	Sample size, n	Age, y	Anemia cases by severity, n				Proportion of ART, %	Region	World Bank Income level
						Total	Mild	Moderate	Severe			
Semba et al., 2001 (US)[94]	1994	Cohort	Adult	361	Mean (SD): 38.1 (NA)	140				52.1	North America	High
Delicio et al., 2018 (Brazil)[95]	2007	Cohort	Pregnant women	793	Median (IQR): 28 (NA)	396				100.0	Latin America & Caribbean	Upper-middle
Manyanga et al., 2014 (Tanzania)[96]	2013	Cross-sectional	Pregnant women	420	Mean (SD): 28 (5.2)	227			21	100.0	East Africa	Lower-middle
Ezechi et al., 2013 (Nigeria)[97]	2008	Cross-sectional	Pregnant women	2318	Mean (SD): 30.5 (3.5)	985				37.1	West and Central Africa	Lower-middle

***Table 1*: Characteristics of the studies included in the systematic review and meta-analysis.**

Note: ART=antiretroviral therapy; IQR=interquartile range; NA=not available; SD=standard deviation; UK=United Kingdom; US=United States.

Prevalence of anemia among pregnant women living with HIV

This study included 3 studies that reported anemia cases among pregnant women living with HIV (Table 1). The pooled prevalence of anemia was 48.6% (95% CI: 41.6%−55.6%), but with high heterogeneity (I^2=92.6%, p <0.001) (Figure 4). No visual publication bias was found based on the funnel plot (Supplementary Figure 9).

Meta-regression of the association between anemia prevalence and study characteristics

Table 2 shows the results of the univariable meta-regression analysis of the association between anemia prevalence and study characteristics. The univariable analyses showed that geographic region was significantly associated with anemia prevalence among adults living with HIV, leading the between-study heterogeneity to be explained by 4.15%. The prevalence of anemia among PLWHIV was higher across studies conducted in Southern Africa than in East Africa (b = 22.22; 95% CI: 1.93, 42.51). The study design, median year of sampling, World Bank Income level, and ART proportion were not significantly associated with the prevalence of anemia among adults living with HIV.

Discussion

To the best of our knowledge, this current study is the first updated and comprehensive systematic review and meta-analysis of the prevalence of anemia and severity of anemia diagnosed with age and sex-specific Hb levels using WHO criteria among PLWHIV. The standardized definitions of anemia and its severity reduced heterogeneity largely because of methodologic variability and made the synthesis of prevalence possible. In addition, a meaningful standardized definition of anemia will provide the basis for better comparisons regarding the prevalence and clinical outcomes of anemia among PLWHIV.[5] Based on data from 63 observational studies covering 110,113 PLWHIV across all population groups, we found that the pooled prevalence of anemia was 39.7% for children, 46.6% for adults, and 48.6% for pregnant women living with HIV. This study found a higher prevalence of anemia among adults living with HIV in Southern Africa than in East Africa.

Our findings corroborated previously published evidence that anemia was prevalent among all population groups of PLWHIV.[5,10,98,99] HIV infects bone marrow stromal cells; however, it remains unclear to what extent hematopoietic progenitors are susceptible to HIV infection.[100,101] Moreover, HIV disrupts the bone marrow microenvironment and causes cytokine imbalance, affecting hematopoietic progenitor cells in different ways.[10] Several factors may also play a role in the development of anemia in PLWHIV, including opportunistic

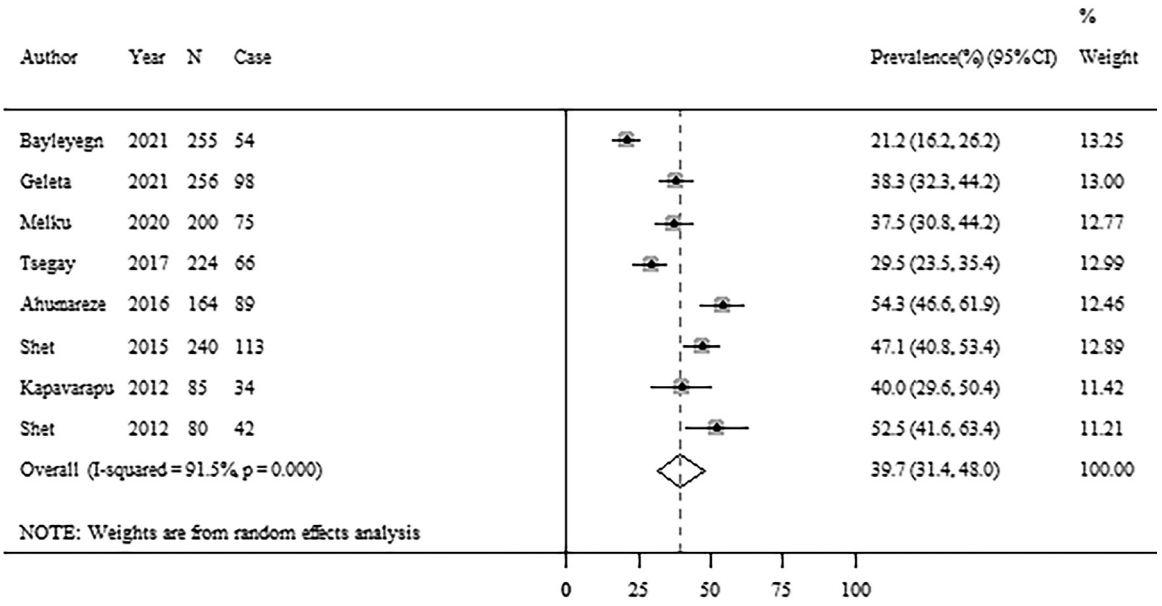

Figure 2. Forest plots of anemia prevalence among children living with HIV.
Note: CI=confidence interval; HIV=human immunodeficiency virus.

infections, chronic diseases, nutritional deficiencies, and toxicities from medications.[8,10,102] PLWHIV suffer from frequent bacterial, viral, and fungal infections, which are an important cause of anemia development and some of these infections are traditionally related to abnormal hematopoiesis.[5,100] For example, two previous studies included in this study reported a much higher prevalence of severe anemia among PLWHIV with Kaposi sarcoma[103] and tuberculosis.[104] Anemia may also be caused by drugs administered, either ART agents or agents to treat infection or lymphoma among PLWHIV.[9,100] This current review did not include studies defining anemia without using age and sex-specific Hb levels according to WHO criteria, which reported the prevalence of anemia ranging from 9.2% to 85.5%,[20,30,32–35,37–39,105–111] and the prevalence of severity of anemia ranging from 7.6% to 52.4% for mild anemia,[32,38,105,106] 1.9% to 76.1% for moderate anemia,[31,32,38,105] and 0.2% to 29.1% for severe anemia.[31-33,37,38,105,112] There were also differences in the definitions of anemia within these excluded studies, such as using different Hb cutoffs, or not using age and sex-specific Hb cutoffs, making a comparison of the results between studies difficult.

In line with previous reviews,[10,113] this study found that the prevalence of anemia varied across countries and was higher in African regions. The differences in the prevalence of anemia across regions could be explained by the differences in the levels of poverty, malnutrition and the overall poor economic state, which are accentuated mainly in African countries.[10,113] In addition, we found that anemia was prevalent among adults living with HIV irrespective of ART proportion. Previous studies have reported that ART may have a protective effect on the development of anemia, through reduced disease progression.[8,71,114] Moreover, ART could improve the immunity of PLWHIV by decreasing the occurrence of multiple opportunistic infections, which are identified to potentially cause anemia.[8,102] However, ART drugs also have adverse side effects, which could cause anemia among PLWHIV.[10,115] There are ART drugs that could worsen anemia among PLWHIV, such as stavudine and zidovudine.[116,117] The association between ART and anemia among people living with HIV warrants further study. Previous evidence has shown that anemia is an established adverse prognostic marker and HIV-infected patients with anemia have a greater risk for mortality than patients without anemia.[118] Thus, prompt identification of anemia may result in improved morbidity and mortality of patients initiating ART. Anemia of chronic disease could be ameliorated if recurrent infections are prevented, either by prophylactic use of antimicrobial therapy or by improvement of the immune deficiency by effective ART among PLWHIV. For acute, severe, or life-threatening anemia, the standard treatment is blood transfusion, and the main advantage of this modality compared with drug therapy is rapid recovery from anemia with relief of symptoms. Thus, there is a need for regular screening of hematological parameters among PLWHIV and providing treatment, which could be crucial for reducing the advancement of HIV disease and its subsequent hematological complications in the ART era.

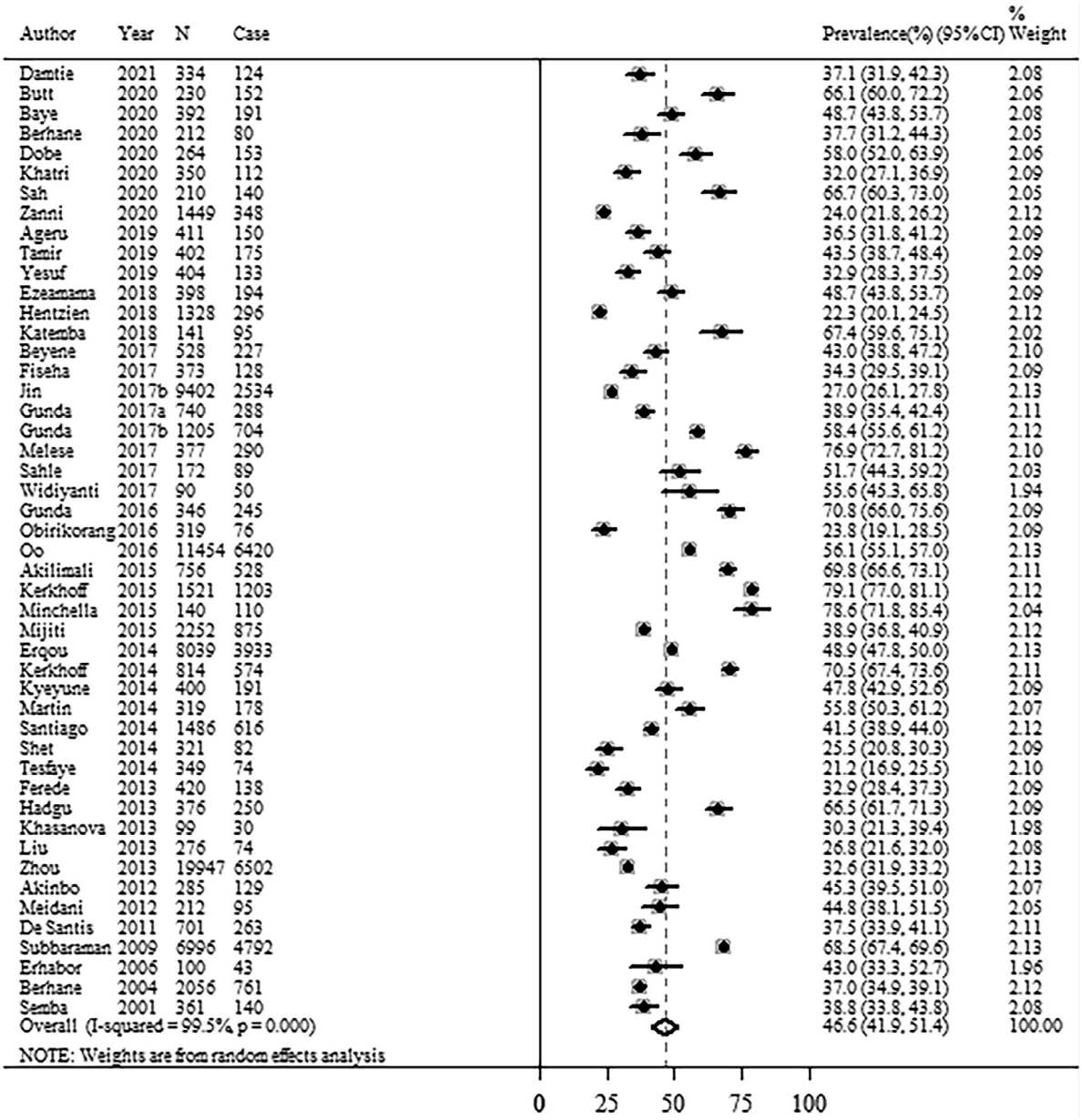

Figure 3. Forest plots of anemia prevalence among adults living with HIV.
Note: CI=confidence interval; HIV=human immunodeficiency virus.

This current systematic review and meta-analysis included studies using Hb levels according to WHO criteria to define anemia and the severity of anemia, making the results of the included studies comparable and producing reliably pooled estimates in this study. However, some limitations in this study should also be acknowledged. First, there is the possibility of duplicate PLWHIV within studies. We included one study with a large sample of PLWHIV from multiple countries[88]; thus, duplicate patients may potentially exist within the included studies. Second, the high heterogeneity between the studies reduced the precision of our pooled effect size estimates, urging some caution in our interpretation of the prevalence of anemia. Third, the limited number of included studies for other common causes of anemia among PLWHIV increased the uncertainty of our pooled prevalence estimates, and the sources of heterogeneity could only be explored by subgroup analysis in a limited set of population groups. Finally, unmeasured or residual confounding in the source studies could not be addressed in this meta-analysis using only published data.

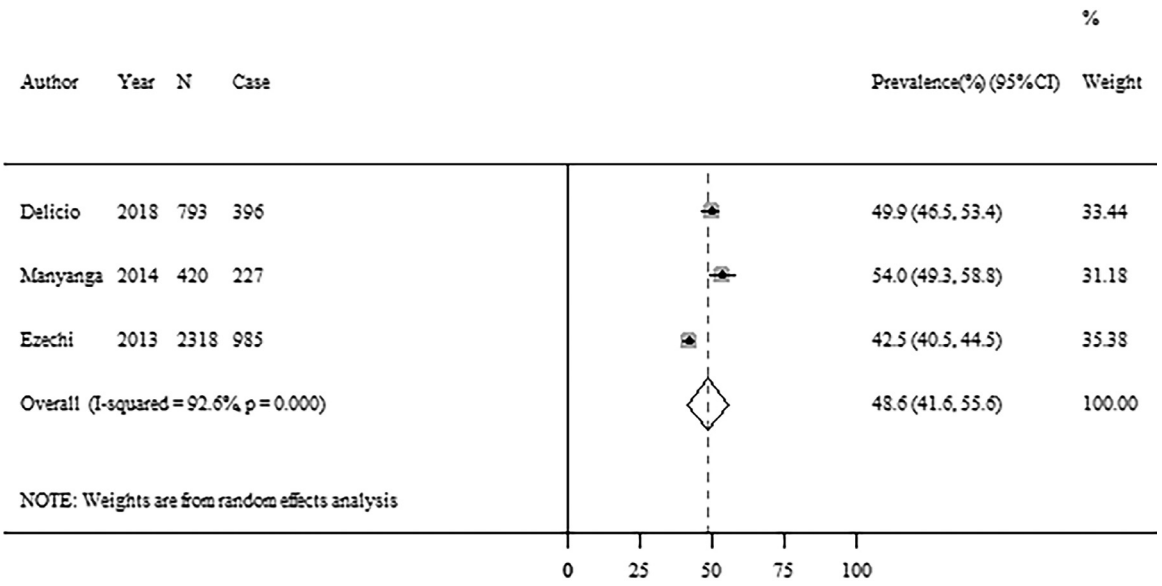

Figure 4. Forest plots of anemia prevalence among pregnant women living with HIV.
Note: CI=confidence interval; HIV=human immunodeficiency virus.

In conclusion, this systematic review and meta-analysis found that anemia was prevalent among PLWHIV. Thus, clinicians should pay more attention to anemia among PLWHIV in the ART era. Policies, strategies, and programs should be considered to identify the predictors of anemia among PLWHIV to reduce the burden of anemia among patients.

Study Characteristic	Number of studies, n	Coefficient (95% CI)	*p* value	R^2
Study design				−3.41%
Cross-sectional	36	Ref.		
Cohort	10	−2.57 (−14.60, 9.47)	0.669	
Case-control	2	−7.15 (−32.16, 17.87)	0.677	
Median year of sampling (y)	45	0.06 (−1.22, 1.34)	0.922	−2.36%
Geographic region				4.15%
East Africa	19	Ref.		
West and Central Africa	4	−1.48 (−19.62, 16.66)	0.870	
Southern Africa	3	22.22 (1.93, 42.51)	0.033	
Asia	10	−1.94 (−14.74, 10.86)	0.761	
Europe	5	−2.17 (−18.67, 14.33)	0.792	
North America	5	−9.03 (−25.40, 7.33)	0.271	
Other	1	8.48 (−26.40, 43.36)	0.490	
World Bank Income level				−4.39%
Low-income	19	Ref.		
Lower-middle-income	11	2.18 (−10.77, 15.13)	0.736	
Upper-middle-income	6	−2.23 (−18.18, 13.73)	0.780	
High-income	11	−4.85 (−17.75, 8.04)	0.452	
ART proportion,%				−3.78%
<20	16	Ref.		
20–79.9	9	−0.32 (−14.10, 13.45)	0.963	
≥80	17	−3.63 (−15.16, 7.89)	0.528	

***Table 2*: Univariable meta-regression of anemia prevalence and study characteristics among adults living with HIV.**
Note: ART=antiretroviral therapy; CI=confidence interval.

Data sharing statement

All data used in this manuscript can be found in the online versions of the studies that were accessed. Our own data synthesis of these manuscripts is available upon reasonable request.

Contributors

GC and ML were responsible for the conception and design of the study; GC, YW and WJ performed data acquisition; GC performed data analyses; GC and ML interpreted the results; GC drafted the manuscript; and all authors critically revised the manuscript and approved the final version.

Declaration of interests

Authors declare no conflict of interest with the content of this article.

Funding

This work was supported by the National Natural Science Foundation of China (grant number: 71934002, 71874003) and National Key Research and Development Program of China (grant number: 2020YFC0846300).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101283.

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