Anaemia in patients with HIV-associated tuberculosis in South Africa: predictive/prognostic value, aetiologies and treatment
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Chapter 9

Discussion
Introduction

TB remains the most important opportunistic infection in HIV/AIDS patients in sub-Saharan Africa, contributing to considerable suffering as well as nearly one in four AIDS-related deaths [1]. Despite improved collaborative HIV-TB activities over the last decade, there is still an urgent need to define new and improved strategies to address this deadly co-epidemic in sub-Saharan Africa and beyond [2]. Anaemia is the one of most frequent clinical complications of both HIV and TB disease and is associated with substantial morbidity and mortality in HIV-infected and TB patients [3-8]. While the relationship between anaemia and HIV associated TB has not been well described, anaemia may serve as a useful biomarker for HIV-associated TB that might be utilised to improve TB diagnosis and clinical management in such patients [9,10]. The work presented in this thesis therefore aims to better characterize the relationship between anaemia and HIV-associated TB among patients in South Africa.

The discussion is organized into sub-sections according to the three primary questions/objectives: 1.) *Does anaemia have predictive value for HIV-associated TB and/or mortality and can improved/rapid means of diagnosing TB in patients with HIV-related anaemia be identified?* 2.) *what are the predominant aetiologies of anaemia in patients with HIV-associated TB and what are the possible implications for treatment?* and 3.) *what are the key therapeutic interventions for anaemia in patients with HIV-associated TB?* For each sub-section, the original research findings are discussed within the context of the published literature and any recommendations/implications for clinical management and public health policy are elaborated upon. Proposed future research questions as they relate to one of the three primary questions are described at the end of each of the three sub-sections. The final portion of the discussion includes an overview of the thesis limitations as well as concluding remarks.

Part II: The predictive value of anaemia for HIV-associated TB and/or mortality and means of rapid TB diagnosis

Chapters 2 and 3 both demonstrate the high predictive value of moderate/severe anaemia for TB (both prevalent and incident TB) in HIV-infected patients [11,12]. In our setting, among ambulatory ART-naïve patients, the prevalence of previously undiagnosed, prevalent TB demonstrated strong, graded associations with anaemia and the prevalence reached 40% in those with severe anaemia (Chapter 2) [11]. We have also previously found a similar
relationship between more severe anaemia and previously undiagnosed active TB in hospitalised HIV-infected patients from the same township communities in Cape Town; however the prevalence of TB was even higher and exceeded 50% in those with severe anaemia [13]. Furthermore, a graded association between anaemia severity and incident TB during long-term ART was observed in Chapter 3 [12]. In each of these studies, anaemia was a strong independent predictor of TB [11-13]. Notably, Chapter 3 demonstrated moderate and severe anaemia (time-updated measurements) to be the strongest independent predictors of incident TB after adjusting for several possible confounding variables, including time-updated CD4 counts [12]. Our findings are consistent with previous reports demonstrating a high prevalence of TB among anaemic HIV-infected patients [14,15] as well as those that have found time-updated haemoglobin levels to be an independent predictor of TB [14,16]. We believe that our results when considered in the context of the literature strongly support routine microbiological testing for TB among HIV-infected patients (both ambulatory and hospitalised) with moderate or severe anaemia living in high TB incidence areas.

In Chapters 2 and 3 moderate and severe anaemia was highly predictive of morality in ambulatory out-patients in South Africa [11,12]. Similarly, we have also found that in hospitalised in-patients from the same Cape Town townships, moderate and severe anaemia was associated with high rates of hospital readmission, high blood transfusion requirements and identified all patients who died within 90 days of study-related admission [13]. In Chapter 3, very high mortality rates were observed within the six months following an incident TB diagnosis in those with either current moderate or severe anaemia; additionally, time-updated moderate and severe anaemia were amongst the strongest independent predictors of mortality during long-term ART [12].

For many years studies have demonstrated anaemia to be prognostic in HIV-infected individuals [17-27], including those with TB disease [5-8,28-30]. We build upon this literature by demonstrating the prognostic value of both baseline and time-updated anaemia for mortality among patients with HIV-associated TB in different clinical settings [7,11-13,31-33]. Given the high incidence of TB and its associated morbidity and mortality in our setting, a policy of systematic testing of all HIV-infected patients initiating ART or requiring acute medical hospital admission is warranted [34-36]. However, in many high TB burden settings such a strategy might not be feasible due to the high associated costs and
public health infrastructure requirements in the background of limited resources. In such settings, prioritising those with moderate/severe anaemia for routine microbiological TB testing might offer one feasible screening strategy alternative. Such a strategy may decrease costs by reducing the overall number of patients undergoing systematic testing and would not only diagnose a large proportion of TB disease, but importantly would also identify those most at risk for poor short-term outcomes and in need of immediate therapeutic interventions. Haemoglobin levels might also be used in patients with known HIV-associated TB to stratify them according to their mortality risk so that additional interventions might be undertaken to mitigate mortality risk. Therapeutic interventions for anaemic patients with HIV-associated TB are further discussed below in part IV of the discussion.

The high predictive value of anaemia for TB and poor clinical outcomes, including mortality demonstrate the value of regular haemoglobin measurements in HIV-infected patients in both in-patient and out-patient settings. Haemoglobin measurements are inexpensive and are already widely available in most clinical settings in sub-Saharan Africa as well as other limited-resource settings. Chapter 3 offers a discussion of the different options available for the measurement of haemoglobin concentrations and determination of anaemia in resource-limited settings as well as the associated strengths and weaknesses of each testing method [12]. It should be considered that the determination of haemoglobin levels (or other predictive biomarkers) potentially adds increased time, expense and requirement for a patient blood sample to any TB screening/testing algorithm – possibly increasing the complexity of an algorithm. Thus, an ideal assay would be inexpensive, durable, have no need for ongoing proprietary supplies, have good diagnostic accuracy and be able to measure haemoglobin non-invasively (no patient blood sample required). Transcutaneous spectrophotometry assays are already available and may offer an ideal solution for non-invasive, point-of-care routine haemoglobin measurements in sub-Saharan Africa [37-40]; however such assays must still undergo further development and field-based testing validation in resource-limited settings.

Improved screening and diagnostic strategies are greatly needed for the improved control of HIV-associated TB and its associated mortality [41-43]. There has been considerable progress made in the TB diagnostics field over the last five years with the introduction of the Xpert MTB/RIF assay and the Determine TB-LAM assay [42,44]. Xpert has excellent specificity and overall good diagnostic utility on both pulmonary [45] and extra-
pulmonary samples [46,47]. WHO has endorsed Xpert testing on both respiratory and non-respiratory samples for the diagnosis of HIV-associated TB [48]. While Xpert testing increases the proportion of microbiologically confirmed TB diagnoses and may decrease the time to TB treatment initiation, no randomized study to date has demonstrated a mortality impact associated with the implementation of the Xpert MTB/RIF assay [49-51].

The Determine TB-LAM assay is a low-cost, truly point-of-care, lateral flow, urine-based assay that delivers results within 25 minutes [52]; it has useful sensitivity and high specificity and identifies those with highest mortality risk [35,53-55]. Recently, a multi-country individually randomized, controlled trial in sub-Saharan Africa found that the use of the Determine TB-LAM assay in addition to standard of care TB investigations (sputum smear microscopy, chest X-ray, sputum culture, sputum Xpert) was associated with a 17% (95%CI, 4-27%) overall relative reduction in all-cause mortality at 8 weeks follow-up among HIV-positive adults requiring hospitalization; the point-of-care urine LAM assay’s implementation was associated with a nearly 30% relative mortality reduction among severely immunocompromised patients [56]. This mortality impact resulted from an increased proportion of patients being diagnosed with TB and an associated reduced time to initiation of TB treatment. On the basis of the available data regarding the utility of the urine-LAM assay (synthesized in a Cochrane review [55] as well as the above randomised study), WHO now recommends urine-LAM testing among HIV-infected hospital in-patients with ‘signs and symptoms of TB’ and who have a CD4 count \( \leq 100 \) cells/\( \mu L \) as well as HIV-infected in-patients who are ‘seriously ill’ regardless of their CD4 cell count [57].

In Chapter 2 we evaluated the performance of the Xpert MTB/RIF assay and urine LAM point-of-care assay as well as sputum smear-microscopy among HIV-infected ambulatory patients with culture-confirmed pulmonary TB [11]. It was notable that all sputum and urine-based assays had significantly improved sensitivity in those with moderate/severe anaemia compared to those with no/mild anaemia. We have also found that among HIV-infected patients with moderate or severe anaemia and who required acute medical admission, rapid urine based-assays (urine LAM and urine Xpert) had significantly greater diagnostic yield than sputum microscopy, Xpert or culture [13,36]. This suggests that in hospitalised patients with HIV-related anaemia, urine-based screening strategies would identify a larger number of TB cases than sputum-based strategies; however this largely reflects the difficulty of obtaining sputum samples in very ill in-patients [36].
Of interest, in Chapter 2, the urine-LAM point-of-care assay had a sensitivity of 55% vs. 0% among ambulatory patients with moderate/severe anaemia and no/mild anaemia, respectively. Similar findings were observed in hospitalised patients from the same community where urine-LAM had a 4-times higher diagnostic yield in those with moderate/severe anaemia compared to in those with no/mild anaemia [13]. These findings are in agreement with previous studies identifying low haemoglobin levels as an independent predictor of LAM-positivity [44]. In sub-group analysis of a randomised study in sub-Saharan Africa, urine-LAM’s implementation (in addition to standard TB investigations) was associated with a 33% (95% CI, 13-48) relative reduction in 8-week all-cause mortality among hospitalised, HIV-infected patients with severe anaemia [56].

From the studies discussed above arise two possible policy recommendations related to the improved diagnosis of HIV-associated TB. We propose that in addition to low CD4 counts (<200 cells/μL) [58], low haemoglobin levels (moderate/severe anaemia) might also serve as a simple clinical indication for urine-LAM screening among HIV-infected patients in high TB incidence areas, especially where CD4 counts are not routinely available. Additionally, rapid sputum-based (Xpert or microscopy where resources do not permit) and urine-based (LAM and Xpert) assays should be used to systematically test for TB in high TB incidence settings among all ambulatory patients with moderate or severe anaemia prior to ART initiation [11]. Rapid urine-based screening assays should also be considered to screen for TB among HIV-infected patients with moderate or severe anaemia and who require acute medical admission (ideally within 24 hours of admission) [13,36]. Our data also indicate that systematic microbiological TB screening is highly warranted among ambulatory patients receiving long-term ART who have current evidence of moderate or severe anaemia [12]. A rapid TB screening strategy among HIV-infected patients with moderate or severe anaemia may allow for a reduction in mortality through same-day or next-day initiation of TB treatment in patients with the highest mortality risk.

Many future research questions arise from the papers presented in part II:

- What are rapid, inexpensive and accurate means for diagnosing anaemia in limited-resource settings? Can non-invasive haemoglobin tests (i.e., those not requiring blood samples) perform well in limited-resource settings?
- Does anaemia have high predictive value for TB and associated mortality in HIV-infected
as well as HIV un-infected patients in other clinical and geographical settings?

- Could haemoglobin concentrations be used in combination with current TB screening strategies (i.e., symptom-based screening or chest X-rays) to improve overall utility among HIV-infected and un-infected patients (ie, improve the ‘rule-in’ or ‘rule-out’ potential)? Could haemoglobin concentrations be used in combination with additional laboratory parameters (e.g., CD4 cell counts or C-reactive protein levels) to define new/improved screening algorithms?

- Does systematic TB testing for in HIV-infected patients with moderate/severe anaemia increase case detection rates, decrease time to diagnosis and/or treatment and reduce TB-related AIDS deaths?

**Part III: The aetiologies of anaemia in patients with HIV-associated TB**

In anaemic patients with HIV-associated TB, the mechanisms underlying anaemia are likely multifactorial and while anaemia of chronic disease is likely the most important mechanism this had not previously been well characterized. Hepcidin is an acute phase reactant that has a central role in iron regulation and the pathogenesis of anaemia of chronic disease [59-61]. Hepcidin also has antimicrobial properties and may have an important role in the innate immune response against *Mycobacterium tuberculosis* [62-65]. However much of the existing research regarding the role of hepcidin in TB disease had previously been derived from clinical studies. In Chapter 4 we found that increased hepcidin levels were strongly associated with greater anaemia severity as well as several indices of mycobacterial burden/dissemination in both hospitalised and ambulatory patients with HIV-associated TB [66]. These results build upon previous studies suggesting hepcidin to be an important component of the host’s innate immune response to infection with *Mycobacterium tuberculosis* [64,65]. Furthermore, our findings imply that hepcidin’s expression in patients with HIV-associated TB is strongly related to mycobacterial burden/degree of disease dissemination and that anaemia may result as an undesired consequence of hepcidin’s role in the immune response to TB disease.

In Chapter 4, patients with HIV-associated TB who died within 90 days of study entry had significantly elevated hepcidin concentrations compared to those who remained alive; higher hepcidin concentrations also independently predicted mortality [66]. Elevated hepcidin levels have been found to be prognostic in other diseases including chronic kidney
disease and non-Hodgkins lymphoma [67-70]. The prognostic value of anaemia among patients with HIV-associated TB that we observed in Chapters 2 and 3 is in large part likely due to hepcidin’s inhibitory effect on ongoing erythropoiesis and the subsequent decrease in circulating haemoglobin levels [59]. This is highlighted by our finding in Chapter 4 that decreasing haemoglobin levels did not predict 90-day mortality after adjusting for hepcidin and other confounding variables. This indicates that hepcidin has greater predictive value for mortality in patients with HIV-associated TB than haemoglobin levels, which may be because hepcidin is upstream of haemoglobin and is more specifically related to active TB disease.

In Chapter 5, we sought to build on our findings presented in Chapter 4 as well as previous studies that have suggested that ACD is the predominant mechanism of anaemia in those with HIV-associated TB [71-74]. Using a published algorithm [59,75], we found that ACD was present in all anaemic HIV-TB co-infected patients (hospitalised and ambulatory). We used 7 published definitions for IDA and the overall prevalence of IDA in patients with HIV-associated TB was low (median 3%) except when microcytosis (MCV<80 fl) or hypochromia (MCHC<32 g/dL) alone were applied [76]. While the relative contributions of ACD and IDA have not previously been systematically characterized in patients with HIV-associated TB, our findings that ACD was the underlying mechanism in all patients and that IDA was very rare is consistent with reports published previously among TB patients [71-74]. A slightly higher prevalence of IDA reported among TB patients in other settings [71,74] might be accounted for by a number of factors including: differences in the definitions of IDA applied, local nutrition patterns, and high background rates of parasitic infections, but is unlikely to be due to TB disease itself.

Elevated hepcidin concentrations have previously shown good utility for predicting non-responsiveness to oral iron supplementation [77]. In Chapter 5 we observed that a very small number of patients had IDA without elevated hepcidin concentrations. This therefore demonstrates that the vast majority of anaemic patients with HIV-associated TB would be unlikely to benefit from oral iron supplementation, especially prior to combined TB treatment and ART. The mechanistic implications for therapeutic interventions for anaemia in patients with HIV-associated TB are further discussed in part IV.
The papers in part III invite further questions and have implications for future research:

- Do iron-status markers, especially hepcidin, have utility as biomarkers for HIV-associated TB, for example in identifying undiagnosed TB (‘ruling-in’), predicting TB treatment response or identifying those at increased risk for poor clinical outcomes?
- Could improved knowledge of the roles of iron and hepcidin during HIV infection and TB disease be translated into improved prevention, diagnosis and treatment strategies for TB disease in HIV-infected and un-infected individuals?
- Are the relative contributions of ACD and IDA to anaemia in HIV-associated TB patients similar in other settings?
- What proportion of anaemic patients with HIV-associated TB in other settings have iron-deficiency anaemia without elevated hepcidin concentrations and may thus be expected to benefit from oral iron supplementation?
- What additional aetiologies may contribute to anaemia among patients with HIV and/or TB in different settings, how prevalent are these additional aetiologies and how might knowledge of these aetiologies impact clinical management of anaemia in such patients?

Part IV: Therapeutic interventions for anaemia in patients with HIV-associated TB

HIV-infected patients with severe/life-threatening anaemia as well as symptomatic anaemia may benefit from acute stabilization of haemoglobin levels with a blood transfusion [4,78]. However, some studies have previously suggested that blood transfusions may paradoxically increase mortality in HIV-infected patients [79-81]; we investigated this issue in Chapter 6. A high prevalence of severe and life-threatening anaemia was found in HIV-infected patients requiring acute hospitalisation and a large number of patients received a blood transfusion [82]. Receipt of a blood transfusion was not independently associated with an increased risk of mortality regardless of whether it was coded as a binomial, ordinal or continuous variable and therefore we did not find any evidence to support concerns regarding the potential adverse impact of blood transfusions in HIV-infected adults in sub-Saharan Africa. However, there is a shortage of safe blood products in most settings in sub-Saharan Africa and blood transfusions are associated with increased health care costs [83-86]. The decision to administer a blood transfusion should therefore follow best practice guidelines and be based on the composite clinical picture, not haemoglobin levels alone.
Additionally, improved strategies are desperately needed for increasing the availability of safe blood products throughout sub-Saharan Africa as well as for reducing the requirement for blood products in HIV-infected and un-infected patients alike [83,88].

ART is one of the most important interventions for the prevention of HIV-associated TB and is associated with an approximately two-thirds reduction in the risk of incident TB in HIV-infected TB patients [89,90]. Previous studies have demonstrated a strong and consistent effect of ART on haemoglobin recovery among HIV-infected patients in the United States and Europe [91-95]. Data from sub-Saharan Africa appear to show a similarly positive effect of ART on anaemia resolution [96-105], but data from high TB incidence settings were limited and it was not known if patients with HIV-associated TB experienced similar haemoglobin recovery as those without TB. In Chapter 7 we investigated this question and found that a majority of HIV-infected patients have resolution of anaemia during the first year of ART without additional anaemia specific interventions [106]. Importantly, those with HIV-associated TB experienced similar haemoglobin recovery as those without TB; significant haemoglobin recovery also occurred regardless of gender, AZT exposure, and baseline CD4 cell counts and HIV viral load. Because ACD is the most important mechanism underlying anaemia in patients with HIV-associated TB (Chapters 4 and 5), by treating the active infection(s), ART’s and/or TB treatment’s efficacy for anaemia are most likely due to the down-regulation of pro-inflammatory cytokines [107,108] and normalization of hepcidin levels [74]. While normative guidelines for the management of anaemia in patients with HIV, TB and HIV-associated TB do not exist, based on the prevailing evidence we strongly recommend that ART and/or TB treatment be the key therapeutic intervention for anaemia in these patients.

An important minority of HIV and HIV-TB co-infected patients may have persistent anaemia despite ART and/or TB and may therefore experience ongoing morbidity and increased mortality risk [98,106]. Therefore, such patients will require additional investigations and possibly additional therapeutic interventions. As anaemia is not a diagnosis but instead is a sign of underlying disease, the evaluation of anaemia in these patients should focus on identifying the underlying aetiology. Clinicians should, however, first inquire about any barriers preventing patient adherence to ART and/or TB treatment and might also consider ordering an HIV viral load as anaemia may serve as a crude marker of virological failure [109-111]. Additional investigations and therapeutic interventions that might also be considered for anaemic, HIV-infected patients are further discussed in Chapter 3.
In **Chapter 7** we identified erythrocyte microcytosis as an important risk factor for persistent anaemia, consistent with other studies from sub-Saharan Africa \[93,98,99,106\]. While non-specific, microcytosis may suggest true iron-deficiency \[112\]. Those with iron-deficiency would not be expected have resolution with ART and/or TB treatment alone, although improvement in the physical and financial wellbeing of people with HIV or HIV-associated TB receiving ART with or without TB treatment might improve nutrition (and any underlying nutritional deficiencies) independent of active iron supplementation. **Chapter 5** found that the overall proportion of patients with IDA was low regardless of definition applied \[76\]. It also highlighted that many patients with IDA likely had co-concomitant ACD and corresponding elevated hepcidin concentrations such that they would likely be non-responsive to oral iron supplementation at that time. Not only are a majority of patients unlikely to derive benefit from oral iron therapy, but in **Chapter 8** we discuss the possible harms of iron supplementation in patients with HIV and TB disease \[113\]. We also discuss the need to carefully assess which patients are likely to benefit from oral iron supplementation. A recent study demonstrated that hepcidin levels may normalize within the first two months of TB treatment and therefore at this point, those with true IDA might respond to oral iron supplementation in addition to TB treatment and ART \[74\]. Similar studies among those with HIV-associated TB are also needed.

From the studies presented **part IV**, there remain questions unanswered and implications for future research:

- What additional risk factors predict persistent anaemia in patients receiving TB treatment and/or ART and how can knowledge of such risk factors be translated into adjunct interventions for the minority of patients with anaemia despite TB treatment and/or ART?
- Could low haemoglobin levels (i.e, severe anaemia) be used as a simple indication for ART initiation in low-resource settings in HIV-infected persons who have not previously received ART?
- What strategies might be utilised to improve the availability of “safe” blood products in sub-Saharan Africa, including what strategies/interventions may reduce blood transfusion requirements among HIV-infected patients?
• At what point during TB treatment and/or ART is there sufficient down-regulation of pro-inflammatory cytokines and hepcidin so that patients with concurrent IDA may be responsive to oral iron supplementation and derive benefit?

• Is iron overload, possibly as a consequence of oral iron supplementation independently associated with poor clinical outcomes, including mortality in patients with HIV-associated TB?

Given the high prevalence of anaemia and associated mortality in HIV-infected patients (with and without TB), this thesis also highlights the need for normative, consensus guidelines for the management of anaemia in HIV-infected patients in sub-Saharan Africa and other resource-limited settings.
Limitations

This thesis presents findings from three prospective and consecutively recruited HIV-infected patient cohorts with and without TB in different clinical contexts from the same geographic catchment area in the Cape Town, South Africa townships. It however has some limitations. The large majority of the results presented in this thesis are in agreement with one another as well as the published literature, but need to be validated in other settings in sub-Saharan Africa as well as additional low-resource settings in different regions. We have demonstrated a strong and compelling relationship between HIV-associated TB and anaemia and expect that the trends and associations contained herein are generalizable to other clinical settings (both out-patient and in-patient) in sub-Saharan Africa where there is a high burden of HIV-associated TB. Point estimates (ie, prevalence and incidence) however are context specific and should not be extrapolated to other settings. For example, the prevalence of anaemia in patients with HIV-associated TB will differ with the extent of HIV and TB disease severity (ie, lower in out-patients settings and among those receiving ART and higher in in-patient settings), local nutrition patterns (iron, folate and vitamin B12 deficiency) and the local burden of parasitic diseases (malaria, hookworm, schistosomiasis, etc) among other things.

We measured iron-status markers including hepcidin concentrations as well as inflammatory cytokines in three matched HIV-infected patient groups with and without TB. This allowed us to explore the role of hepcidin in anaemic patients with HIV-associated TB as well as the relative contributions of anaemic of chronic disease and iron deficiency anaemia. However, bone marrow aspirates, peripheral smears and reticulocyte counts as well as sufficient blood samples were not available that would have allowed us to systematically investigate for additional aetiologies of anaemia in such patients, including: nutritional deficiencies (folate and vitamin B12), infections (parvovirus B19, cryptococcus, cytomegalovirus, etc), malignancy (Kaposi’s sarcoma, lymphoma), haemolysis (thrombotic thrombocytopenic purpura, autoimmune haemolytic anaemia), haemoglobinopathies (sickle cell disease, thalassemia). Many of these aetiologies are thought to be decidedly less common causes of anaemia in HIV-TB co-infected patients and we have limited data to suggest as much (Kerkhoff et al. unpublished). Nevertheless, this needs confirmation in future prospective studies. Malaria, hookworm and schistosomiasis are not endemic to
Cape Town and thus did not require further investigation, however they are important causes of anaemia in other African settings [114] and their role in the pathology of anaemia should be considered in any study being undertaken in endemic areas. Additionally, while anaemia was highly predictive of mortality in our studies, additional infections, chronic kidney disease and malignancies may have similar haematological profiles as those with HIV-associated TB and may have contributed to mortality in such patients. Unfortunately, sufficient data was unavailable to determine the specific cause of death that would have allowed us to further explore these relationships. Finally, given the observational design of our studies we were only able to report on relationships and associations. Any findings, especially those related to therapeutic interventions (blood transfusions, ART, TB treatment, iron supplementation) for anaemia resolution and mortality reduction would need to be evaluated in prospective, randomised trials to properly evaluate the impact of such interventions including, efficacy and possible harms. However, for most therapeutic interventions, further evidence will likely be limited to observational studies as randomising anaemic patients with HIV and/or TB to not receive lifesaving blood transfusions, ART or TB treatment would be unethical.
Conclusions

TB remains the leading cause of death in patients with HIV/AIDS and anaemia is one of the most common clinical complications of both diseases in that as many as 90% of patients with HIV-associated TB are anaemic. Anaemia is predictive of both prevalent and incident TB among ambulatory outpatients as well as hospitalised in-patients, regardless of ART status. Among such patients, anaemia is associated with greater morbidity (hospitalisation, hospital readmission, requirement for blood transfusions) and is also a very strong independent predictor of mortality. Rapid diagnostic assays for TB (sputum- and urine-based) have improved diagnostic utility for TB in patients with moderate or severe anaemia, especially urine-based assays, including the urine-LAM point-of-care assay.

ACD is the predominant mechanism underlying anaemia in patients with HIV-associated TB; hepcidin, the key mediator of the body’s iron axis and the hormone responsible for driving the process of ACD is strongly associated with greater anaemia severity, more broadly disseminated TB disease and increased mortality risk. In patients requiring acute stabilization of haemoglobin levels, blood transfusions do not appear to confer an increased mortality risk as previously reported, but clinicians should still consider the need for a transfusions based upon the composite clinical picture and not haemoglobin levels alone. ART and TB treatment should be considered the key therapeutic intervention for anaemia in patients with HIV-associated TB as a large majority of such patients will have resolution of anaemia with combined therapy and without need for additional anaemia-specific interventions; this is likely due to down-regulation of pro-inflammatory cytokines and normalization of hepcidin levels. As IDA was decidedly uncommon and also because hepcidin concentrations are elevated in active disease (limiting duodenal iron absorption), most patients with HIV-associated TB are unlikely to derive benefit from oral iron supplementation and thus a policy of universal iron supplementation in such patients is not warranted. However, for the small minority of patients with persistent anaemia despite appropriate treatment with ART with or without TB therapy, oral iron therapy and other clinical interventions may be appropriate.

In conclusion, in high TB incidence areas in sub-Saharan Africa, all HIV-infected patients with moderate or severe anaemia should be suspected of having TB and be microbiologically tested for TB using rapid assays, regardless of symptomatology. Because
ACD, a process driven by elevated hepcidin levels, is the most common mechanism underlying anaemia in these patients, the majority can be expected to have resolution of anaemia with ART and anti-TB treatment alone. The impact of such screening and treatment strategies on HIV-associated TB in sub-Saharan is not yet known and must be evaluated in future research.
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