Anaemia in patients with HIV-associated tuberculosis in South Africa: predictive/prognostic value, aetiologies and treatment
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Chapter 10

Summary
Background

While progress has been made over the last decade in the control of HIV-associated tuberculosis (TB) as evidenced by a 33% reduction in related mortality since 2004, TB remains the leading cause of death in people living with HIV and still accounts for one in four AIDS-related deaths globally. Sub-Saharan Africa bears a disproportionate burden of this co-pandemic and post-mortem studies throughout the continent have consistently demonstrated that between 33% and 67% (pooled summary estimate, 43.2% [95%CI 38.0-48.3%]) of HIV/AIDS-related deaths were caused by TB, much of which was undiagnosed at the time of death. In such patients the clinical presentation is often so non-specific that much TB remains ‘below the radar’ and is unsuspected, undiagnosed and therefore remains untreated. Anaemia is highly prevalent throughout sub-Saharan Africa, is one of the most common complications of both diseases, and is associated with substantial morbidity and mortality. Haemoglobin concentrations may be a useful biomarker in patients with HIV-associated TB and anaemia may have predictive value that is underutilised as an important entry point into the TB diagnostic algorithm. The relationship between anaemia and HIV-associated TB has not been previously well characterized. This thesis therefore attempts to better characterize this relationship in South African cohorts of patients and is organized according to three main parts: the predictive value of anaemia for HIV-associated TB and associated outcomes, the aetiologies of anaemia in patients with HIV-associated TB and therapeutic interventions for anaemia in such patients.

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

In Chapter 2, we sought to determine the predictive value of anaemia for underlying, prevalent TB. Ambulatory, ART-naïve out-patients were consecutively enrolled, anaemia was classified according to World Health Organization (WHO) criteria and patients were systematically tested for TB using culture, Xpert MTB/RIF and fluorescence microscopy on sputum as well as using the Determine TB-LAM assay for the presence of lipoarabinomannan (LAM) in urine. A high prevalence of previously undiagnosed TB was found in those with moderate or severe severe anaemia and moderate or severe anaemia both independently predicted TB disease and was present in all patients who died within 90 days. All TB assays (both sputum- and urine-based) had improved diagnostic sensitivity in
patients with moderate or severe anaemia compared to those with no or mild anaemia, especially the urine LAM point-of-care test. **Chapter 3** assessed the predictive value of current anaemia severity for incident TB and mortality in patients receiving ART for up to 8 years in a large community-based clinic. Prospectively collected data including time-updated haemoglobin concentrations and CD4 counts, TB diagnoses and deaths were retrospectively analyzed. Among 1,521 patients receiving ART for a median of 5.0 years, strong, graded associations were observed between time-updated (current) anaemia severity and both incident TB and mortality; extraordinarily high TB incidence and mortality rates were observed among those with current (time-updated) severe anaemia. In multivariable Poisson regression analysis, moderate and severe anaemia (time-updated) during long-term ART were the strongest independent predictors for incident TB and mortality and notably were stronger predictors than advanced immunosuppression (low CD4 counts). These two studies both strongly suggest that HIV-infected patients with moderate or severe anaemia living in high TB incidence areas should be prioritized for routine microbiological investigation using rapid diagnostic assays and given such a high mortality risk, may require additional clinical interventions.

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

This section sought to better understand the aetiologies of anaemia in patients with HIV-associated TB and both studies (**Chapter 4 & 5**) were nested within prospective cohort studies of patients enrolled into studies evaluating new TB diagnostics. **Chapter 4** explores the relationship between hepcidin (the ‘master regulator’ of iron homeostasis and central to the pathogenesis of anaemia of chronic disease [ACD]) and anaemia severity, mycobacterial burden/dissemination and mortality in patients with HIV-associated TB. All patients were systematically tested for TB and three patient groups were included: hospital in-patients with HIV-associated TB and HIV-positive ambulatory out-patients (with or without TB). Hepcidin concentrations were strongly associated with greater severity of anaemia and several indices of greater mycobacterial burden/dissemination in both TB patient groups. TB patients who died within 90 days of follow-up had higher hepcidin concentrations and in multivariable survival (Cox regression) analysis increasing hepcidin concentrations were found to be an independent predictor of 90-day mortality. In **Chapter 5** the relative contributions of ACD and iron deficiency (IDA) to anaemia in two patient groups
(hospitalised in-patients and ambulatory out-patients) with HIV-associated TB were assessed. Haemoglobin levels, iron-status markers, hepcidin and pro-inflammatory cytokines were measured and the prevalence of ACD as well as IDA (using 7 different published definitions of IDA) was determined. More than 80% of HIV-associated TB patients were anaemic and ACD was universally present in all anaemic patients; in contrast, however, the overall prevalence of IDA remained low across a range of published definitions. Those with IDA and without elevated hepcidin concentrations (predictive of possible responsiveness to oral iron supplementation) were also very low. Collectively these studies suggest that ACD is the predominant mechanism underlying anaemia in patients with HIV-associated TB and that hepcidin is an important mediator of anaemia in such patients, especially in those with disseminated disease. Regardless of definition applied, IDA was very uncommon in this patient population and thus few anaemic patients with HIV-associated TB in this setting are unlikely to benefit from oral iron supplementation.

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

HIV-infected patients with severe/life-threatening anaemia may require acute haemoglobin stabilization with a blood transfusion, however it has previously been reported that transfusions may paradoxically increase short-term mortality in HIV-infected patients; this issue was investigated in Chapter 6. Consecutive HIV-infected adults requiring acute medical admission to a district hospital were recruited and receipt of transfusions and mortality within 90 days were determined. Of 578 patients enrolled, nearly one-third had severe or life-threatening anaemia and a large number of such patients received blood transfusions. While blood transfusions were associated with increased risk of mortality in univariable analysis, in multivariable Cox regression analyses receipt of blood transfusions, regardless of whether it was coded as a binomial, ordinal or continuous variable was not associated with increased mortality risk. Chapter 7 examines the effect of anti-retroviral therapy (ART) on the resolution of anaemia in the first year of ART in a patient cohort with a high prevalence and incidence of TB. Time-updated haemoglobin concentrations and CD4 counts as well TB diagnoses were retrospectively analysed. Among 814 ART-naive patients anaemia was very common; however, approximately two-thirds had resolution of anaemia after one year of ART and haemoglobin recovery did not differ among those with prevalent or incident TB. A
minority of patients had persistent anaemia despite ART and such patients may require additional clinical interventions. In Chapter 8, we discuss the possible harms and benefits of oral iron therapy in HIV and TB disease in sub-Saharan Africa and the need for further studies to define both the proportion of patients who may benefit from oral iron supplementation and at what time point during treatment they may become responsive to oral iron supplementation. The studies in this section suggest that ART and TB-therapy (i.e., treatment of the underlying infection) should be the key therapeutic interventions for anaemia in patients with HIV-associated TB. A minority of patients may require additional interventions including blood transfusions and oral iron therapy but these (and other interventions) should be considered on a case-by-case basis.

Chapter 9 offers a general discussion of the findings presented in this thesis. This includes clinical and public health policy implications of the research, thesis limitations, research questions that remain unanswered and overall conclusions drawn from this work.