Anaemia in patients with HIV-associated tuberculosis in South Africa: predictive/prognostic value, aetiologies and treatment
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Citation for published version (APA):
Chapter 1

Introduction
Epidemiology of HIV-associated tuberculosis

Since its emergence more than three decades ago, HIV has become a major challenge to tuberculosis (TB) control efforts, especially in resource-limited settings, which have borne the brunt of the HIV and TB co-pandemics [1]. It is believed that HIV/AIDS was the strongest factor contributing the approximately 1% annual increase in global TB incidence in the 1990’s and early 2000’s [2]. At the end of 2014, 37 million people were living with HIV/AIDS and 2 million people were newly infected with HIV in that year alone [3]. In 2014, there was an estimated 9.6 million incident TB cases [4]. People living with HIV/AIDS have a nearly 30-fold increased risk of TB disease compared to those without HIV infection and for this reason, TB remains the most important opportunistic infection among HIV-infected persons [4]. Approximately 1.2 million (12%) of global incident TB cases are among people living with HIV [4]. The number of individuals dying from HIV-associated TB has been steadily declining globally since peaking in 2004 (570,000 HIV-associated TB deaths in 2004 down to 370,000 in 2014-32% reduction). However, TB remains the leading cause of death among HIV/AIDS patients and is now the leading infectious cause of death worldwide [4]. This deadly co-infection accounted for approximately one-quarter of all global HIV/AIDS and TB-related deaths, respectively [3,4].

Sub-Saharan Africa has been disproportionately burdened by this co-pandemic as nearly 80% of all cases of HIV-associated TB are from within this region [4]. This has resulted in extensive suffering among some of the world’s poorest and most vulnerable persons and has led to many millions of lives lost prematurely, especially in Southern Africa, which encompasses several countries with the world’s highest HIV prevalence and TB incidence rates.

HIV-associated TB in South Africa

With an estimated population of approximately 54 million, South Africa accounts for less than 1% of the world’s population. Yet with more than 6.3 million people living with HIV, South Africa has the world’s largest burden of HIV/AIDS, accounting for almost 20% of global HIV cases [5]. Additionally, few countries have worse TB epidemics than South Africa. It has the 6th highest number of annual incident TB cases (behind countries with much larger national populations) and the world’s 3rd highest TB incidence rate, just behind the
neighbouring countries of Swaziland and Lesotho [4]. HIV and TB disease have fuelled one another and the social, economic and environmental conditions, that to a large extent are legacies of the apartheid era, have resulted in highly favourable environments for on going HIV and TB transmission and the world’s largest HIV-associated TB epidemic [6,7]. This is epitomized by the finding that 62% of all TB is among HIV-infected individuals and that almost one in five of all global HIV-associated TB deaths occurs in South Africa [4].

Global HIV-associated TB control strategies

In 2004, the World Health Organization (WHO) and the Stop TB Partnership developed a joint interim policy on collaborative HIV and TB strategies and consisted of four core interventions [8]. These included: intensified case finding, isoniazid preventive therapy (IPT), infection control and scale-up of anti-retroviral therapy (ART). It is estimated that from 2005-2012 these collaborative activities averted 1.3 million deaths related to HIV-associated TB [9].

ART is the key intervention for the prevention of HIV-associated TB [10]. On average, ART is associated with an approximately 65% reduction in TB incidence in all HIV-infected individuals and it reduces the risk of TB across all CD4 cells counts [11]. Since the early 2000’s there has been an unprecedented scale-up of ART with more than nine million people living with HIV in Africa receiving ART [9,12]. This has contributed to millions of life-years gained and 4.8 million deaths averted in sub-Saharan Africa alone [12,13]. However, more than 60% of patients in sub-Saharan Africa are still not receiving ART and although significantly more HIV-TB co-infected patients are receiving ART [9], there is much work that remains to improve ART coverage. Additionally, even in those receiving ART for several years and with strong immune recovery, the incidence of TB in such persons remains higher than background community rates among non-HIV infected patients [14]. Hence, ART is by no means a silver bullet for TB control in HIV-infected patients and should be implemented alongside increased IPT coverage (among those eligible), improved TB infection control strategies in healthcare facilities and congregate settings as well as intensified TB case finding and improved diagnosis [8].

Diagnosing HIV-associated TB

Post-mortem studies throughout sub-Saharan Africa over the last 15 years have consistently
demonstrated a high burden of TB among AIDS patients, ranging from 33-67% (pooled summary estimate, 43.2% [95%CI 38.0-48.3%]) [15-21], approximately one half of which remained unsuspected, undiagnosed and thus untreated prior to death.

Optimal management of HIV-associated TB is dependent on early and accurate diagnosis [22]. The diagnosis of TB in HIV-infected patients has traditionally been hampered by non-specific clinical presentation as well as high rates of extra-pulmonary/disseminated TB [23], sputum smear-negative TB [24] and radiologically non-specific disease [25]. Progress has been made in the area of TB diagnostics over the last several years with the advent of Xpert MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA) [26-28] and Determine TB-LAM Ag assay (Alere Inc. Waltham, MA, USA) [29,30] both of which hold great promise for increasing the proportion of confirmed HIV-associated TB cases, reducing times to diagnosis and initiation of TB treatment as well as possibly reducing TB-related mortality in such patients. However, the clinical impact of such assays [31-33] or others in the TB diagnostics pipeline has not yet been demonstrated and costs may be prohibitive for widespread scale-up in all high TB burden settings in sub-Saharan Africa [34]. Current evidence collectively suggests a failure of existing screening and TB diagnosis strategies. Therefore, the development of low-cost, rapid, and accurate microbiological assays as well as improved screening strategies are needed to improve the diagnosis of HIV-associated TB and reduce associated deaths [34-36].

**Biomarkers for HIV-associated TB**

Host and pathogen biomarkers for TB diagnosis, treatment monitoring and outcomes assessment are important TB research priorities [1,37,38]. A biomarker is a “characteristic that is objectively measured and assessed as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [39].” They may improve clinical management by providing information related to the pathogenic process and current health status as well as future disease risk of the patient [38]. Therefore, biomarkers for HIV-associated TB could serve several potential important purposes including, acting as a screening tool that could ‘rule-out’ patients that are unlikely to have TB as well as identify (‘rule-in’) those likely to have TB and in need of further microbiological testing. Additionally, biomarkers may give mechanistic insights to disease pathophysiology, allow for monitoring of treatment response (by identifying both TB cure
and treatment failure) and also predict those at risk for poor clinical outcomes and in need of further investigations and/or interventions, etc. Given that the large majority of TB cases occur in limited-resource settings, the ideal biomarker for HIV-associated TB would be inexpensive, available for point-of-care use and would possess several of the characteristics outlined above. Progress in this area has been slow and studies to identify and evaluate biomarkers for HIV-associated TB remain on going.

**Epidemiology of anaemia**

Anaemia (as defined by WHO as a haemoglobin concentration <13 g/dL in males and <12 g/dL in females) [40] is highly prevalent throughout the world and it is estimated that roughly one-third of the world’s population is anaemic [41]. It is one of the leading global causes of years lived with disability [41] and is associated with fatigue, impaired growth, cognitive impairment and decreased productivity. Depending on the underlying aetiology, anaemia may also be associated with high mortality rates [42]. In sub-Saharan Africa, the prevalence of anaemia among adults may exceed 60% in some regions of the continent [41]. Mechanisms underlying anaemia in African adults are likely to be multifactorial and vary across clinical settings [43], however iron-deficiency is the most important overall cause [41,44]. Hookworm, malaria and schistosomiasis as well as other chronic infectious diseases including HIV and TB are also important aetiologies of anaemia in sub-Saharan Africa [41].

**The relationship between HIV-associated TB and anaemia**

Anaemia is one of the most frequent complications of both HIV and TB disease. The association between TB disease and anaemia was described by Osler in the very early 20th century [45]. The association was further detailed by several studies published in the 1920’s and 30’s [46-48] and it was even reported at that time that TB patients with anaemia have a poor prognosis [48]. Many studies have since reported on the high prevalence of anaemia in TB patients [49-53] as well as an associated increased risk of death [53-55].

Anaemia is the most common haematological complication of HIV/AIDS. HIV-related anaemia is associated with a poorer quality of life [56], disease progression [57] and a greatly increased mortality risk [58,59]. In HIV-infected patients anaemia may be indicative of prevalent, undiagnosed TB [60-63], predict incident TB [61,64] and may also identify those at risk of TB-related mortality [65-67]. Therefore, haemoglobin concentrations may
be a useful biomarker for HIV-associated TB and the predictive value of anaemia may be underutilised as an important entry point into the TB diagnostic algorithm [68].

Despite anaemia being a well-described haematological complication of both diseases that is associated with poor prognosis, to date the relationship between anaemia and HIV-associated TB has remained poorly characterised. This thesis therefore seeks to determine the predictive value of anaemia for HIV-associated TB and associated outcomes, explore the mechanisms underlying this relationship and investigate therapeutic interventions for anaemia in these patients (including the role of ART and the likelihood of responsiveness to iron supplementation).

Research setting
The ART service at the Hannan Crusaid Treatment Center is a large community-based clinic in Gugulethu township, Cape Town, South Africa and has been previously described in detail [69-71]. It serves a district of over 300,000 people who are principally African and live in conditions, reflecting low socioeconomic status. The antenatal HIV seroprevalence is approximately 30% and the annual TB incidence routinely exceeds 1000/100,000. All patients included in the studies were referred to the ART programme from primary care clinics for initiation of treatment according to prevailing national treatment guidelines.

GF Jooste Hospital is a public sector, district level hospital located in the Mananberg area of Cape Town, South Africa and served underprivileged township communities of approximately 1.3 million people; the patients served by this hospital are heavily reliant on the public health system. In 2013, the antenatal HIV sero-prevalence was 37%. ART has been available free of charge in the public health sector since 2004. During the study period, patients were eligible to start ART if they had a CD4<200 cells/μL (<350 cells/μL if they were pregnant or had TB) or if they had any WHO stage 4 illness. During the end of the study period the criteria expanded to include all patients with a CD4 count ≤350 cells/μL or with a WHO stage 3 or 4 disease.
Thesis aim and objectives

Overall aim: To characterise the relationship between anaemia and HIV-associated TB in South Africa

Specific objectives

1.) To determine the predictive value of anaemia for HIV-associated TB and mortality and to identify optimum means of TB diagnosis TB in patients with HIV-related anaemia
   • Determine the prevalence of anaemia among HIV-infected patients
   • Determine the prevalence of active TB in patients with HIV-related anaemia and stratified according to anaemia severity.
   • Determine the predictive value of anaemia for undiagnosed prevalent TB.
   • Determine the predictive value of time-updated (current) anaemia for incident TB among during long-term ART.
   • Determine the clinical outcomes of patients with anaemia and HIV-associated TB.
   • Determine which TB assays have greatest diagnostic accuracy and utility for detection of TB among HIV-infected patients with anaemia.

2.) To investigate the aetiologies of anaemia in patients with HIV-associated TB
   • Investigate the relationship between hepcidin, anaemia severity, mycobacterial burden/disease dissemination and mortality in patients with HIV-associated TB.
   • Characterize the relative contributions of anaemia of chronic disease and iron deficiency anaemia to anaemia in patients with HIV-associated TB.

3.) To explore the methods of treatment for anaemia in patients with HIV-associated TB, including the effect of ART and the likely role of oral iron supplementation.
   • Determine if blood transfusions are associated with increased short-term mortality in HIV-infected patients.
   • Determine the effect of ART and TB treatment on the haemoglobin recovery in patients with HIV-associated anaemia.
   • Determine what factors are independently associated with persistent anaemia during ART.
Thesis outline

Part II: The predictive value of anaemia for HIV-associated TB and/or mortality and means of rapid TB diagnosis (Chapters 2 and 3).
In this section the predictive value of anaemia for HIV-associated TB as well as mortality is investigated and strategies for rapidly diagnosing TB among patients with HIV-related anaemia are explored. Chapter 2 investigates the predictive value of anaemia for undiagnosed prevalent TB and associated short-term mortality among ambulatory patients presenting for ART-initiation as well as evaluates means of rapid TB diagnosis among such patients. In Chapter 3, the predictive value of current haemoglobin levels for incident TB and mortality among patients receiving long-term ART (up to 8 years) is investigated.

Part III: The aetiologies of anaemia in patients with HIV-associated TB (Chapters 4 and 5)
This section sought to explore and characterize the most common causes of anaemia among patients with HIV-associated TB with the aim of informing more accurate/informed treatment strategies. In Chapter 4 the relationship between hepcidin, the key iron-regulating hormone, and anaemia severity, mycobacterial burden and mortality is explored among patients with HIV-associated TB. Chapter 5 characterizes the relative contributions of anaemia of chronic disease and iron-deficiency to anaemia in patients with HIV-associated TB in this setting as well as determines what proportion of anaemic patients may benefit from oral iron supplementation.

Part IV: Therapeutic interventions for anaemia in patients with HIV-associated TB (Chapters 6-8)
In this section treatment strategies for anaemia in patients with HIV-associated TB are explored. Chapter 6 investigates blood transfusion requirements among hospital in-patients with HIV-related anaemia and determines if blood transfusions paradoxically increase short-term mortality risk as has previously been reported. Chapter 7, reports on the impact of ART on haemoglobin levels in anaemic HIV-infected patients with and without TB as well as risk factors for persistent anaemia during ART. Finally, Chapter 8 discusses the benefits and
possible harms associated with oral iron therapy and the need for greater understanding of the aetiologies of anaemia in patients with HIV, TB and other chronic infectious diseases in sub-Saharan Africa to better inform treatment strategies.

Discussion (Chapter 9)
This chapter discusses and summarizes the findings of the research contained within this thesis, the implications of this research, future research needed, thesis limitations and ends with concluding remarks.
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