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Diagnosis of Smear-Negative Pulmonary Tuberculosis in Low-Income Countries: Current Evidence in Sub-Saharan Africa with Special Focus on HIV Infection or AIDS

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1. Introduction

1.1 Background

Tuberculosis (TB) remains a major global public health problem and it persists as a major cause of human mortality and morbidity, affecting almost a third of the world's population [Sudre et al., 1992; WHO 2002]. There were 9.2 million new cases of tuberculosis worldwide in 2006, with the highest rates of disease in African countries. Despite efforts to control tuberculosis and reduce the rate of infections, the lack of accurate laboratory diagnosis hinders these efforts. The rapid spread of the human immunodeficiency virus (HIV) in sub-Saharan African countries has led to dramatic rises in incidence of TB cases and has been associated with worsening treatment outcomes, even in well functioning TB programmes [Raviglione et al., 1997]. The impact of the HIV epidemic on tuberculosis depends on the degree of overlap between the population infected with HIV and that infected with Mycobacterium tuberculosis. In sub-Saharan Africa the prevalence of both infections is high with considerable overlap between the infected populations, since the age distribution of both infections is concentrated in the 20-50-year age group. In 1994 there were an estimated 4.8 million people worldwide infected with both M. tuberculosis and HIV, of whom over 75% were reported to be living in sub-Saharan Africa (6). Worldwide estimates of the proportions of new tuberculosis cases attributable to HIV infection were 4% in 1990, 8% in 1995, projected to 14% by the year 2000 [WHO 2002]. HIV-related infection thus accounts for a relatively small but increasing proportion of the global tuberculosis burden. In sub-Saharan Africa, however, it accounts for a greater part of the burden: an estimated 30% or more of tuberculosis cases by the year 2000 [WHO 2002]. THE WORLD HEALTH

ORGANIZATION (WHO) estimated that both the number of cases of tuberculosis worldwide and the percentage attributable to coexisting HIV infection would increase substantially during the decade between 1990 and 2000 [WHO 2002]. Furthermore, most of this burden occurs among the low-income countries of the world, particularly those in sub-Saharan Africa, the region most heavily affected since the beginning of the HIV epidemic[Sudre et al., 1992].

Although both culture techniques and the introduction of nucleic acid-based tests can improve laboratory diagnosis [Perkins and Cunningham, 2007], these procedures are not widely available in most low-income countries. Instead, in most low income countries, the diagnosis of pulmonary tuberculosis (PT) still relies on the search for Acid-Fast Bacilli (AFB) in sputum smears, which has sensitivity between 50 and 80% in well-equipped laboratories [Aber et al., 1980]. In low-income countries, poor access to high-quality microscopy services contributes to even lower rates of AFB detection. Furthermore, in countries with high prevalence of both pulmonary tuberculosis and HIV infection, the detection rate is even lower owing to the paucibacillary nature of pulmonary tuberculosis in patients with HIV infection. In fact, HIV changes the presentation of smear-negative pulmonary tuberculosis from a slowly progressive disease with low bacterial load and reasonable prognosis, to one with reduced pulmonary cavity formation and sputum bacillary load, more frequent involvement of the lower lobes, and an exceptionally high mortality rate [Hopewell, 1992; Jones et al., 1993]. This means that there are many cases of PT that are not going to be diagnosed by this test, and they are denominated smear-negative pulmonary tuberculosis (SNPT). Therefore, it is often necessary to make a clinico-radiological diagnosis of smear-negative TB using an algorithm and to initiate empirical TB treatment while awaiting culture results. Therefore, early identification of persons who have TB, whether smear positive or smear negative, is desirable both to enable appropriate isolation procedures and to provide a basis for early institution of therapy. Conversely, correct prediction of persons who are unlikely to have TB is important as well to limit the expense and potential toxicity of empiric therapy. A clinical prediction rule (CPR) is defined as a "decision making tool for clinicians that includes three or more variables obtained from the history, or physical examination of the patient, or from simple diagnostic tests and that either provides the probability of an outcome or suggest a diagnostic or therapeutic course of action. Given the lack of resources to use sophisticated laboratory tests for this problem in most developing countries, we will try to develop a CPR to diagnose Smear-negative pulmonary tuberculosis.

The primary objective of this chapter will be to conduct a systematic review of the literature to gather data on evaluation of various criteria, algorithms, and clinical indicators used in low-income countries in the diagnosis of PT in people with suspected tuberculosis but repeated negative sputum smears with particular consideration of HIV infection or AIDS. This review will be of help therefore to develop it in the format of a score based on simple clinical variables for the diagnosis of Smear-negative pulmonary tuberculosis.

This article will describe the incidence, natural history and differential diagnoses of smear-negative pulmonary TB in HIV negative and HIV-positive patients. The various strategies that have attempted to address smear-negative TB will then be reviewed; highlighting plausible interventions for developing countries and areas for future research.

1.2 Definition of smear-negative pulmonary tuberculosis

Smear-negative tuberculosis is currently defined as symptomatic illness in a patient with at least two sputum smear examinations negative for AFB on different occasions in whom pulmonary tuberculosis is later confirmed by culture, biopsy, or other investigations[WHO 2007]. Guidelines from some developing countries like Malawi through their national Tuberculosis Program recommends that the diagnosis of smear negative TB be based on four criteria of (i) cough for more than 3 weeks, (ii) three sputum smears negative for AFB, (iii) no response to an antibiotic, and (iv) a chest x-ray compatible with TB[Hargreaves et al., 2000].

The following are suggested case definitions for use in HIV-prevalent settings[WHO 2007]

Smear-Positive Pulmonary Tuberculosis

- One sputum smear examination positive for AFB **and**
- Laboratory confirmation of HIV infection **or**
- Strong clinical evidence of HIV infection*

Smear-Negative Pulmonary Tuberculosis

- At least two sputum specimens negative for AFB **and**
- Radiographical abnormalities consistent with active tuberculosis **and**
- Laboratory confirmation of HIV infection **or**
- Strong clinical evidence of HIV infection* **and**
- Decision by a clinician to treat with a full course of antituberculosis chemotherapy

OR

- A patient with AFB smear-negative sputum which is culture-positive for *Mycobacterium tuberculosis*

1.3 Impact of HIV on TB infection

Persons with HIV-1 infection are at increased risk of active TB due to reactivation of latent TB and more rapid progression to disease after TB infection. It is well known that the risk of TB is greatly increased in HIV-infected persons, and some of the underlying mechanisms are being elucidated. Effective immunity to TB involves coordination of responses between the innate and adaptive immune systems, both of which are altered by HIV[Patel and Koziel, 2009]. The strongest risk factor for developing TB disease in HIV lies in helper T-cell type 1 (Th1) adaptive immunity, specifically the progressive decline in CD4 T-cell count associated with advanced HIV [Williams and Dye, 2003]. In patients with prior TB exposure as assessed by a positive Purified protein derivative (PPD) response, the incidence of TB is 2.6%/year for those with a CD4 T-cell count greater than 350/ml, 6.5%/year for those with aCD4 T-cell count from 200 to 350/ml, and 13.3%/year for those with a CD4 T-cell count less than 200/ml [Antonucci et al., 1995]. With decline of the CD4 T-cell count, there is also a higher risk of anergy to skin test reactions, suggesting dysfunction of delayed-type hypersensitivity dependent on Th1-type immunity [Markowitz et al., 1993]. There is also in vitro evidence for qualitative dysfunction of CD4 T cells in HIV. Compared with TB-infected patients without HIV infection, peripheral blood mononuclear cells from patients coinfected

with HIV and TB have decreased proliferative T-cell responses and reduced IFN-g production to *Mycobacterium tuberculosis* in vitro, whereas anti-inflammatory IL-10 production is preserved [Zhang et al., 1994]. However, the observation that TB incidence increases shortly after HIV seroconversion, and before reduction in peripheral blood CD4 T-cell counts [Sonnenberg et al., 2005], suggests that HIV confers additional mechanisms of susceptibility to TB infection. Investigations into the progression of primary HIV infection to AIDS suggest that primary HIV infection is associated with a precipitous decrease in mucosal CD4 memory T cells [Brenchley et al., 2006a], which may set the stage for chronic immune activation and CD4 T-cell depletion through mucosal translocation of bacteria through the gut [Brenchley et al., 2006b]. Thus, mucosal CD4 memory T-cell depletion may provide a potential mechanism to account for disrupted T-cell function in early HIV infection, although whether similar events occur in the lung mucosa has not yet been established [Brenchley et al., 2008]. Indeed, primary HIV infection is associated with decreased PPD-specific IFN-secreting T cells [Sutherland et al., 2006; Geldmacher et al., 2008] and ESAT (early secreted antigenic target)-6–specific T cells [Geldmacher et al., 2008] in the blood, suggesting that early depletion of memory T cells may affect specific immunity to TB. Lung lavage enzymelinked immunospot (ELISPOT) studies also suggest decreased bacillus Calmette-Gue´rin (BCG)– or PPD-specific pulmonary CD4 T cells in asymptomatic HIV-infected persons compared with HIV-negative persons [Kalsdorf et al., 2009]. HIV–TB coinfection may also be associated with increased serum levels of IL-4, an anti-Th1 type cytokine that hinders immune response to MTb [Dheda et al., 2005]. Interestingly, alveolar lavage cells from coinfected individuals may have intact ability to secrete IFN-g in response to MTb antigens in vitro [Dheda et al., 2005], although this may not translate to equivalent cell function and cell numbers in vivo.

Independent of CD4 T-cell count, HIV also affects the function of innate immune cells, especially alveolar macrophages (AMs), which serve as the main reservoir for MTb infection [Russell, 2001; Dheda et al., 2009]. MTb has evolved to persist within macrophages in part through prevention of MTb phagosomal fusion with lysosomes, thus preventing intracellular killing of MTb [Brown et al., 1969; Mwandumba et al., 2004]. AMs can combat intracellular parasitization by releasing immune-activating cytokines or chemokines, and by programmed cell death or apoptosis [Oddo et al., 1998; Keane et al., 2000]. Apoptosis benefits the host by promoting intracellular killing of MTb [Oddo et al., 1998; Keane et al., 2000] and improving antigen presentation by additional phagocytes to activate adaptive immunity [Schaible et al., 2003; Winau et al., 2006]. Whereas asymptomatic HIV infection does not affect the intracellular growth of MTb [Day et al., 2004; Kalsdorf et al., 2009], AMs from asymptomatic HIV-infected subjects have increased phagocytosis of MTb [Day et al., 2004; Patel et al., 2007], decreased release of specific cytokines and chemokines [Saukkonen et al., 2002], and similarly impaired MTb phagosomal maturation [Mwandumba et al., 2004] compared with AMs from healthy subjects. AMs from HIV-infected subjects also have decreased apoptosis in response to MTb [Patel et al., 2007]; the mechanism may involve increased lung levels of IL-10 in HIV, which up-regulates BCL-3 (B-cell lymphoma 3–encoded protein), an apoptosis inhibitor [Patel et al., 2009]. HIV infection of macrophages also inhibits autophagy [Kyei et al., 2009], another cellular process that may be critical for macrophage intracellular killing of MTb [Gutierrez et al., 2004].

1.4 Rationale

The focus of this chapter is on sub-Saharan Africa (SSA). Countries in the developing world and especially in sub-Saharan Africa are the most affected by the TB epidemic. Worldwide, in 2008, the estimated global TB incidence rate was 139 cases per 100,000 population, which equates to 9.4 million (range, 8.9–9.9 million) incident TB cases. This represents an 11% increase in TB incidence rate and a 40% increase in the number of TB cases, compared with estimates from 1990[WHO 2009]. This global increase in rates was attributable to increases in the SSA and was mainly driven by the HIV epidemic. Particularly in SSA, mirroring the HIV epidemic, TB incidence and TB-associated death rates have doubled, and the number of TB cases and TB-related deaths has tripled in comparison with estimated figures from 1990[WHO 2009]. The HIV epidemic has fuelled the tuberculosis epidemic in the region. Of the 9.4 million incident cases in 2009, an estimated 1.0–1.2 million (11–13%) were HIV-positive, with a best estimate of 1.1 million (12%). Of these HIV-positive TB cases, approximately 80% were in the African Region (http://www.who.int/tb/publications/global_report/2010/). The relative risk of developing TB in HIV-positive individuals, compared with HIV-negative individuals, is 21 in high HIV prevalence countries and 37 in low HIV prevalence countries[WHO 2009]. Moreover, these co-infected people have at least a 30% lifetime risk of developing active tuberculosis, thus contributing to the increase in the number of tuberculosis cases in the region. In Africa, TB is often the first manifestation of HIV infection, and accounts for a disproportionate burden of morbidity and mortality in co-infected patients [Munyati et al., 2005].

As a consequence, HIV is the single most significant risk factor for the development of TB, and HIV patients are at increased risk for primary and reactivation disease, as well as exogenous reinfection [Sonnenberg et al., 2001]. The risk of death in co-infected patients is two to four times that of HIV individuals without TB, independent of CD4 count [Whalen et al., 1995; Connolly et al., 1999]. In addition, coinfected patients have a markedly greater risk of progression to AIDS compared with HIV patients without TB [Whalen et al., 1997]. The focus of this chapter is therefore sub-Saharan Africa, the region of the world most severely affected by the HIV/TB co-epidemic.

2. Search strategy

We used a combination of systematic review, document analysis, and global expert opinion to prepare this chapter. We identified relevant publications by searches of Medline, PubMed, Embase, HealthSTAR, and Web of Science with the keywords: "tuberculosis", "*Mycobacterium tuberculosis*", "sputum negative", "smear negative", AFB negative", "negative for AFB", "HIV" , "diagnosis" and "treatment" for papers published in English between 1990 and December, 2010. Studies were included in the review if they reported on tuberculous disease in people with HIV infection or AIDS in sub- Saharan Africa and if the disease had been stratified into smear-positive and smear-negative. We reviewed data for smear-negative pulmonary tuberculosis only for patients who were also HIV positive. All retrieved titles and abstracts were scrutinised for the relevance to the topic. Analytical studies that identified demographic, clinical, radiological, or simple laboratory based indicators facilitating the diagnosis of smear-negative tuberculosis were included. An assessment of methodological quality was undertaken for each paper.

We used the WHO definition of a case of smear-negative pulmonary tuberculosis: at least two sputum specimens negative for acid-fast bacilli, abnormalities on radiography consistent with active tuberculosis, no response to broad-spectrum antibiotics, and a decision by a clinician to treat with a full course of antituberculosis chemotherapy.

3. Frequency of smear-negative pulmonary tuberculosis

Given the immunopathological spectrum seen in HIV-infected TB patients, it would be expected that the proportion of patients with smear-negative PT should increase in areas where the prevalence of HIV is high. Initial impressions were that HIV infection in sub-Saharan Africa was associated with a large and predominant increase in smear-negative PT [Harries, 1990]. It is apparent from cross-sectional studies, however, that the majority of HIV-positive PT patients are smear positive, although the proportion of smear-negative patients is greater among those infected with HIV than among those who are HIV-negative [Elliott et al., 1990; Nunn et al., 1992]. Since the advent of HIV, the annual incidence of TB has more than doubled in some African countries [De Cock et al., 1992; Wilkinson and Davies, 1997], and there has been a disproportionate increase in the reported rate of smear-negative disease. A study in Zambia [Elliott et al., 1993] of over 100 patients with culture-positive PT found that 24% of those who were HIV-seronegative had a negative sputum smear, compared with 43% of those who were HIV-seropositive. With good routine reporting systems, the national tuberculosis programmes of countries such as Malawi and the United Republic of Tanzania have reported a larger increase in new cases of smear negative than of smear-positive PT in the last 10 years [Graf 1994].

Other studies showed that the proportion of cases of smear-negative pulmonary tuberculosis in HIV-positive tuberculosis patients ranged from 10% to 61% [Affolabi et al., ; Long et al., 1991; Elliott et al., 1993; Harries et al., 1997; Behr et al., 1999; Bruchfeld et al., 2002; Zachariah et al., 2003; Kang'ombe et al., 2004; Yassin et al., 2004; Chintu and Mwaba, 2005]. The apparent variation in the incidence of negative sputum smear between these studies may be due to differences in the study populations. Some studies were conducted among patients seen at specialist institution-based centres who may be more or less likely to be smear-positive depending on the referral procedure. The level of immunosuppression among the HIV-positive patients in the various studies may also have differed. Less severely immunocompromised HIV-positive patients tend to have classic cavitary TB which is smear-positive [De Cock et al., 1992; Desta et al., 2009]. As the level of immunocompromise increases with advancing HIV disease, atypical pulmonary features predominate and smear examinations prove less sensitive It is not clear at present whether these figures reflect the true pattern of PT or whether there is an over diagnosis or under diagnosis of smear-negative cases. Reports from national tuberculosis programmes of the pattern of PT are influenced by various factors such as the criteria used to diagnose smear-negative PT, the extent to which these criteria are followed in clinical practice, and the number of other respiratory diseases that can resemble and be misdiagnosed as PT. Moreover, access to health services and DOTS in most resource-constrained settings with high HIV infection rates is restricted and services reach only a fraction of the population. If the availability of these services were increased, we expect that a much higher frequency of disease would be seen. Negative smears could also be the result of poor quality smear microscopy from inadequate sputum collection, storage, and staining, reading errors, or poor laboratory

services. In children, the diagnosis of pulmonary tuberculosis is especially difficult because the disease is paucibacillary and collection of sufficient sputum for smear microscopy and culture is difficult [Chintu and Mwaba, 2005]. HIV-positive patients with smear-negative tuberculosis are more likely to die during or before diagnosis than HIV-negative patients because of their immunosuppression, which leads to further under estimates of the magnitude of the problem.

4. Transmission of tuberculosis from smear negative patients

TB patients whose sputum smears are AFB negative are generally regarded as less infectious than those whose smears are positive. The relative TB transmission rate among patients with smear-negative, culture-positive pulmonary disease, compared with patients with smear-positive disease, was found to be 0.24 in cohort study in the Netherlands [Tostmann et al., 2008]. Overall, 17% of TB transmission events were attributable to source patients with sputum smear-negative, culture-positive disease [Tostmann et al., 2008]. These important findings are consistent with report from similar studies from San Francisco, California, and Vancouver, British Columbia [Behr et al., 1999; Hernandez-Garduno et al., 2004], collectively showing that in high-income countries, 10%–20% of TB transmission at the population level is attributable to source cases with smear-negative pulmonary TB. Tostmann and co-worker [Tostmann et al., 2008] speculated on the relevance of their data for countries in which HIV infection is endemic and rates of smear-negative TB disease are high. In these countries with a high incidence of TB, microscopic examination of sputum smear samples is often the only available diagnostic test for TB. As a result, patients with smear-negative TB do not receive a diagnosis in a timely manner; thus, disease may further develop, initiation of treatment may be delayed, and further TB transmission may occur [Siddiqi et al., 2003]. In view of these observations, one can conclude that transmission attributable to smear-negative pulmonary TB cases at the community level may be important in these regions.

Whether this is true for HIV-positive patients with pulmonary tuberculosis remains to be established. One study from Zambia concluded that patients with HIV-associated pulmonary tuberculosis were less infectious than seronegative patients [Elliott et al., 1993], whereas results from Zaire showed no difference in rates of infection among household contacts [Klausner et al., 1993]. Moreover, In sub-Saharan Africa, HIV infection has had a devastating impact on TB control [Lawn et al., 2006; WHO 2009]. In a study of a community in a township in Cape Town, South Africa, for example, the antenatal HIV seroprevalence rate is 30%, and the annual TB notification rate has increased to 11500 cases per 100,000 population [Lawn et al., 2006] almost 200-fold higher than TB rates in The Netherlands. This has been associated with a major and disproportionate increase in the rate of smear-negative disease among HIV-infected individuals [Lawn et al., 2006].

5. Diagnosis of smear negative TB in Sub-Saharan African

In the absence of rapid and simple tools to diagnose tuberculosis, health institutions should avail guidelines or algorithms to assist clinical decision-making in HIV-prevalent and resource-constrained settings, to expedite the diagnostic process and minimize incorrect diagnosis and mortality. As much as possible, patients should be correctly diagnosed and treated for smear-negative pulmonary tuberculosis; however, treatment of those without the

disease should be avoided. The diagnosis of PT in adults in most African countries is based on simple techniques such as clinical assessment, sputum smear microscopy and chest radiography. Although specificity is high [Hargreaves et al., 2001; van Cleeff et al., 2003; Apers et al., 2004], major concerns include low sensitivity [Harries et al., 1997; Hargreaves et al., 2001] and delayed diagnosis of smear-negative disease [Harries et al., 1997; Colebunders and Bastian, 2000]. The accuracy of both microscopy and radiography is reduced by HIV, and so assessment of diagnostic approaches with existing methods and continuing research into new diagnostics are necessary [Colebunders and Bastian, 2000; Kivihya-Ndugga et al., 2003; Angeby et al., 2004].

Tuberculin skin testing in adults is not useful for individual diagnosis in populations with a high prevalence of M. tuberculosis infection. In addition, for HIV-infected individuals, there is the problem that cutaneous anergy increases as the CD4 lymphocyte count declines. In Zaire, over 50% of HIV-positive PT patients with a CD4 lymphocyte count <200/4l had a negative tuberculin skin test [Mukadi et al., 1993]. Techniques that are widely available in industrialized countries for obtaining pulmonary specimens (such as induced sputum and fibre-optic bronchoscopy with bronchoalveolar lavage) and for analysing them (such as culture, antigen detection and polymerase chain reaction) are beyond the resources of most hospitals in sub-Saharan Africa.

5.1 Criteria used to diagnose smear-negative TB

5.1.1 Clinical criteria

Smear-negative tuberculosis is found to be more common in older than younger patients in a country with low prevalence of HIV infection [Samb et al., 1999]. However, countries with high HIV prevalence have an even age distribution, probably because HIV affects younger age-groups [Parry, 1993]. HIV is also more common in patients with smear-negative tuberculosis than in those with smear-positive disease. As for clinical indicators, pulmonary TB remains the most frequent form of active TB in HIV-1 infected persons, even those with low CD4 counts. Although the clinical presentation of pulmonary TB is different to the presentation of pulmonary TB in HIV-1 uninfected patients, the most common symptoms remain cough, fever, night sweats and significant weight loss [Batungwanayo et al., 1992; Bruchfeld et al., 2002]. Relative to HIV-1 uninfected patients, weight loss and fever are more common, whereas haemoptysis is less common and some studies have reported a decreased proportion of patients with cough [Selwyn et al., 1998; Kassu et al., 2007]. Although HIV-infected persons with TB may have the classic symptoms of TB (eg, productive cough, chest pain, shortness of breath, hemoptysis, fever, night sweats, and/or weight loss), many such patients have few symptoms or have symptoms that are even less specific than those mentioned. Cough persisting for longer than 3 weeks warrants AFB microscopy, according to the current WHO guidance. However, one study, in an area of high HIV and tuberculosis prevalence, confirmed smear-negative tuberculosis in 35% of patients with cough unresponsive to antibiotics of only 1–3 weeks duration [Banda et al., 1998]. Most of these patients had atypical changes on chest radiography. That study suggests that pulmonary tuberculosis should be considered in patients with short duration of cough associated with weight loss and lack of response to antibiotics, particularly those who live in overcrowded places in areas with high prevalence of HIV infection and tuberculosis. It has been noted recently that a small proportion of HIV infected patients with TB are minimally

symptomatic or asymptomatic, particularly in developing countries with a high burden of both HIV infection and TB [Bassett et al., 2009; Edwards et al., 2009].

A number of studies in Africa have tried to identify frequently occurring clinical features in smear-negative tuberculosis in areas with high prevalence of HIV infection and tuberculosis. A study, in Tanzania and Burundi, identified four clinical criteria for diagnosis of smear-negative tuberculosis [Samb et al., 1997]: presence of cough for longer than 21 days (odds ratio 5·43[1·95–15·1]); presence of chest pain for longer than 15 days (1·98 [0·77–5·12]); absence of expectoration (odds ratio for expectoration 0·42 [0·15–1·18]); and absence of shortness of breath (odds ratio for breathlessness 0·26 [0·01–0·66]). Diagnosis of smear negative tuberculosis by any two of these criteria exhibited high sensitivity but low specificity (sensitivity 85%, specificity 67%, positive predictive value 43%, and negative predictive value 94%). When three of the criteria were considered, the specificity improved while the sensitivity decreased (sensitivity 49%, specificity 86%, positive predictive value 50%, and negative predictive value 86%). The gold standard against which these clinical indicators were evaluated was Sputum culture, tissue histology, and positive clinical and radiological response to the antituberculosis therapy. However, patients with chronic lung disorders were excluded from the study, which limits the extent to which it can be generalised. The prevalence of HIV was high (71%) in both case and control groups.

In another hospital-based study in Ethiopia, the most frequent symptoms in patients with pulmonary tuberculosis (both smear positive and smear negative) than in those without pulmonary tuberculosis were loss of appetite, weight loss, fever, night sweats, chest pain, haemoptysis, and breathlessness were more common [Tessema et al., 2001]. However, patients with smear-negative tuberculosis had night sweats for a longer time. Smear-positive patients were more likely to have fever and weight loss than the smear negative group (odds ratios 4·1 [1·2–15·0] and 6·4 [2·3–17·8], respectively). The diagnosis by a group of tuberculosis physicians, which may have been due to lack of resources, although the authors do not clarify the reason in the paper, was used as the gold standard for diagnosis of pulmonary tuberculosis. However, in an area with low prevalence of HIV infection and high prevalence of tuberculosis, one study based in Senegal found no clinical features differentiating smear-negative from smear-positive tuberculosis other than the absence of cough (odds ratio 10·0 [1·96–50·0]) [Samb et al., 1997]. Limitations of this study were that it had a small sample size and that the diagnosis was confirmed by means of sputum culture in only 20% of cases. The overall prevalence of HIV in both case and control groups was 8·9%. Our search could only retrieve one study that included subjects from a population with low prevalence of both HIV infection and tuberculosis [Kanaya et al., 2001]. Cough with expectoration was considered as a negative predictor of smear-negative tuberculosis (odds ratio 0·3 [0·1–0·6]). This study could not identify any other differentiating clinical features, possibly owing to the small sample size.

5.1.2 Radiographic criteria

Although the classical radiographic hallmarks of PT are cavitation, apical distribution, bilateral distribution, pulmonary fibrosis, shrinkage and calcification, no pattern is absolutely diagnostic of tuberculosis. Interpretation of chest X-rays of individuals suspected to have PT is difficult. In the pre-HIV era, there was considerable inter- and intra-observer variation in chest X-ray interpretation by radiologists and chest physicians [Thoman 1979].

In sub-Saharan Africa with limited microbiological services, the problem is compounded because there are few trained radiologists or chest physicians, and in most district hospitals chest X-rays are interpreted by relatively inexperienced medical officers or paramedics., survey in Malawi showed that medical officers misdiagnosed a third of clinical vignettes, which described typical radiographic signs of tuberculosis [Nyirenda et al., 1999]. The nonspecific findings of pulmonary infiltrates, in the middle or lower lobes, in HIV positive PT patients adds to the difficulties of correct radiographic diagnosis. It is now well recognized in industrialized countries [Pedro-Botet et al., 1992; Greenberg et al., 1994] and countries in sub-Saharan Africa [Simooya et al., 1991; Abouya et al., 1995] that the chest X-ray can appear normal in HIV-positive PT patients.

Studies in sub-Saharan Africa revealed that tuberculous patients with HIV infection are more likely to have atypical chest radiographic appearances (pulmonary infiltrates with no cavities, lower-lobe involvement, intrathoracic lymphadenopathy, and even normal appearance) than tuberculous patients without HIV infection [Harries et al., 1998b; Banda et al., 2000]. In areas of high HIV and tuberculosis prevalence, 75% of patients with smear-negative tuberculosis are likely to have atypical chest radiographic findings [Tessema et al., 2001]. Patients with smear-negative tuberculosis are less likely to have cavities on the chest radiograph (odds ratio 2·56) than patients with smear positive tuberculosis [Samb et al., 1999]. In addition, smear-negative patients can also present with normal or only slightly abnormal chest radiographs [Harries et al., 1998a]. A study confirmed pulmonary tuberculosis by sputum culture in 21% of patients with suspected tuberculosis and negative smears and normal or slightly abnormal chest radiographs. 47% of such patients were found to have typical radiographic features after 3 months. A third of the culture-negative patients also developed typical radiographic signs of tuberculosis during follow-up. Authors from that study suggested that close monitoring of smear-negative patients with suspected tuberculosis and normal or slightly abnormal chest radiographs is useful in areas with high prevalence of HIV infection and tuberculosis.

5.1.3 Sputum smear microscopy

Microscopy for the detection of AFB is rapid, low cost, and detects the most infectious cases of tuberculosis, but needs maintenance of equipment, consistent supply of reagents, and proper training in interpretation of the slides [Foulds and O'Brien, 1998]. International guidelines recommend the microscopic examination of three serial sputum specimens for acid-fast bacilli (AFB) in the investigation of pulmonary TB suspects, and define a positive case as a case with at least two smear-positive results [WHO 2003]. Recent studies have shown that under routine conditions, evaluating TB suspects with two sputum smears is as effective as with three sputum smears and is accompanied with less laboratory work and thus reductions in the cost related to the TB workup [Ipuge et al., 1996; Gopi et al., 2004]. This strategy could leave more time for the examination of each slide, should the workload dictate a reduction in the number of examinations. For a smear to be positive, there must be at least 5000-10 000 acid-fast bacilli per mL sputum, but these bacilli could be released only intermittently from cavities [WHO 2004]. If the sensitivity of smear microscopy could be improved, it would be a valuable instrument for TB control [Angeby et al., 2004] and would improve the diagnosis of tuberculosis in both adults. Many investigators have suggested sputum liquefaction and concentration through centrifugation to improve detection of AFB

in negative smears through direct microscopy. Liquefaction of sputum with sodium hypochlorite and concentration by either centrifugation or sedimentation is the most widely studied procedure [Angeby et al., 2004]. Studies carried out in developing countries have shown an increase of almost two fold in the sensitivity of AFB detection compared with direct microscopy [Gebre et al., 1995; Habeenzu et al., 1998]. A systematic review also showed that studies that used sputum processing with chemicals including bleach and centrifugation yielded a mean 18% increase in sensitivity and an incremental yield (positives with bleach minus positives with Ziehl-Neelsen stain only) of 9% [Steingart et al., 2006]. Specificity ranged from 96% to 100% with the bleach method alone and from 95% to 100% with the Ziehl-Neelsen method alone [Angeby et al., 2004]. In HIV-positive patients, sensitivity increased from 38·5% to 50·0% after concentration [Bruchfeld et al., 2000]. This improvement was less remarkable when compared with the sensitivity of direct microscopy supported by clinicians' judgment in diagnosing pulmonary tuberculosis. The main disadvantages of the bleach method are the additional processing time, the technique lacks standardisation, and its advantages over other sputum concentration methods are not clear [Colebunders and Bastian, 2000].

Fluorescence microscopy increases the probability of detecting AFB, especially if the sputum contains few bacteria, and hence improves the sensitivity of microscopy in HIV-positive patients. A systematic review of studies that used fluorescence microscopy showed that on average, in comparison with Ziehl-Neelsen microscopy, fluorescence microscopy showed a 10% increase in sensitivity and 9% incremental yield, and this improvement was not affected by HIV status [Kivihya-Ndugga et al., 2003; Steingart et al., 2006]. The methods had similar specificity, but fluorescence microscopy done on one or two specimens was more cost effective than the Ziehl-Neelsen method used on three sputum specimens [Kivihya-Ndugga et al., 2003].

6. Differential diagnosis of smear-negative TB

There have been a number of research studies in sub-Saharan Africa, using either induced sputum or fibre-optic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy, to determine the range of pulmonary diseases found in patients with respiratory illness and negative AFB sputum smears. AFB microscopy lacks sensitivity compared with culture. In patients with culture-confirmed pulmonary TB, the sensitivity of AFB microscopy ranges from 22 to 80% [Kim et al., 1984]. In the setting of low income countries as elsewhere, there are a number of factors that influence the diagnosis of smear negative tuberculosis. These factors include the prevalence of tuberculosis in the population, the prevalence of HIV infection, and finally, the prevalence of other infections that may mimic tuberculosis. In under-resourced, over-worked TB control programmes, laboratories cannot cope with the influx of diagnostic and follow-up smear examinations, and smears may not be done at all. For example, in Botswana in 1992, 48% of patients reported with pulmonary tuberculosis had no smear examinations performed [De Cock and Wilkinson, 1995]. Alternatively, the sputum specimens collected may be inadequate in quality or number. Ipuge et al. [Ipuge et al., 1996] found that 83.4% of smear-positive cases were detected on the first specimen, 12.2% on the second, and 4.4% on the third, by Ziehl-Neelsen staining under routine programme conditions in Tanzania. Finally, the performance of the smears may be technically inadequate. Declining quality of smear examination is a particular problem in

overburdened laboratories in HIV-endemic countries. When, as part of an epidemiological study of TB and HIV in Tanzania, Chum et al. [Chum et al., 1996] compared the sputum microscopy results obtained in local and reference laboratories, 29% of new smear-negative cases (on the basis of local microscopy) were found to be smear-positive by the reference laboratory. False-negative results can be due to inadequate staining, under- or over-decolourisation, or inspection of too few fields (i.e., a minimum of 100 fields of a Ziehl-Neelsen smear must be examined before reporting a negative result and this examination takes about 5–10 minutes) [WHO 1998].

Other diseases identified in patients suspected of having TB include bacterial pneumonia due to a wide range of pathogens, Pneumocystis carinii pneumonia (PCP), Kaposi's sarcoma, nocardiosis and fungal infections with Cryptococcus neoformans and Aspergillus fumigatus. Bacterial pneumonia is the main differential diagnosis in HIV-positive and HIV-negative individuals, while PCP, cryptococcosis, and nocardiosis are of increased importance in HIV-positive subjects. The reported rates of PCP in African HIV-positive patients with respiratory symptoms vary between 0 and 33%. [Abouya et al., 1992; Kamanfu et al., 1993; Batungwanayo et al., 1994; Greenberg et al., 1995; Malin et al., 1995; Daley et al., 1996; Grant et al., 1998].

This variation has not been fully explained, but has been attributed to differences in patient selection, the level of immunodeficiency of HIV-positive patients in Africa, the limited availability of specialized laboratory diagnostics, the failure to diagnose PCP in the presence of multiple other infections, and geographic differences in the prevalence of PCP [Batungwanayo et al., 1994; Malin et al., 1995]. HIV-associated nocardiosis may also be under diagnosed. Lucas et al. [Lucas et al., 1994] conducted an autopsy study of 247 HIV-positive cases in Abidjan, Ivory Coast, and found one case of nocardiosis for every nine TB cases. These medical conditions account for significant morbidity and mortality in patients presenting with ‘smear-negative pulmonary disease’ in HIV- and TB endemic developing countries. However, the pre-eminent position of TB as the major pathogen in these circumstances must be emphasised. Moreover, it is necessary to emphase the importance of appropriate diagnosis of smear negative tuberculosis, both in terms of public health to identify early infectious sources more rapidly, and in terms of individual health, to identify specific diseases that can be treated. "In areas of high prevalence of tuberculosis, the most common disease that occurs in someone with the clinical signs of tuberculosis but has a negative sputum smear is still tuberculosis

7. Conclusion and future perspective

Smear-negative pulmonary TB is an increasing clinical problem in developing countries affected by the dual HIV/TB epidemic. It is clear that in sub-Saharan Africa more information is required to help solve some of the problems surrounding the diagnosis of smear negative TB. Clear diagnostic criteria need to be developed and agreed upon, and these may vary from country to country according to the availability of diagnostic facilities. Management algorithms that have been validated by local studies should improve case detection. Where current WHO guidelines have been implemented, clinical audits have the potential to improve the quality of diagnosis of smear-negative tuberculosis. Wider use of sputum induction and evaluation of novel sputum processing techniques may also improve the investigation of these patients. Some authors have argued for the wider availability of

TB culture facilities in developing countries; however, these Utopian interventions will require increased financial and technical support from the international community. The contribution of false negative sputum smears to the overall burden of smear-negative TB and the deficiencies in the system that lead to false-negative results need to be addressed. Rates of misdiagnosis of smear-negative tuberculosis can be reduced by development of diagnostic tools, which incorporate the diagnosis of other non-tuberculosis pulmonary disorders. Extensive basic research to develop rapid, simple, and accurate tuberculosis diagnostic tools that can be used in laboratories and remote locations is essential. Increased political commitment, greater scientific interest, and massive investment are needed. At the same time, innovative means need to be sought to address the human resources issues in the diagnosis problem, such as strategic efforts to train adequate and efficient laboratory staff at all levels. New diagnostic techniques are required in addition to AFB microscopy for the identification of smear-negative tuberculosis. These need to be appropriate for use in low income countries. Research into development of more cost-effective microbiological and serological diagnostic solutions is under way. However, until such tests are widely available, diagnostic scoring systems and algorithms must be developed and validated to assist clinicians working in resource-poor settings. Research collaboration is required between countries with similar HIV prevalence to address these research needs and to develop joint management guidelines, which can be applied and evaluated in different situations.

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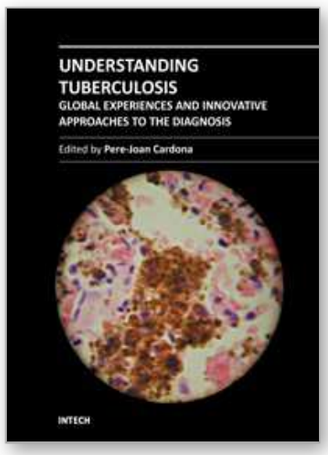
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Understanding Tuberculosis - Global Experiences and Innovative Approaches to the Diagnosis

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Mycobacterium tuberculosis is a disease that is transmitted through aerosol. This is the reason why it is estimated that a third of humankind is already infected by Mycobacterium tuberculosis. The vast majority of the infected do not know about their status. Mycobacterium tuberculosis is a silent pathogen, causing no symptomatology at all during the infection. In addition, infected people cannot cause further infections. Unfortunately, an estimated 10 per cent of the infected population has the probability to develop the disease, making it very difficult to eradicate. Once in this stage, the bacilli can be transmitted to other persons and the development of clinical symptoms is very progressive. Therefore the diagnosis, especially the discrimination between infection and disease, is a real challenge. In this book, we present the experience of worldwide specialists on the diagnosis, along with its lights and shadows.

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