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Abdominal Tuberculosis is common and Under-diagnosed in HIV Positive Adults in Zambia

BY

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DECLARATION

I declare that this dissertation represents my own work and that it has not previously been submitted for a degree, diploma or other qualification at this or another University.

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Candidate

Date.....4/07/08

Signed .....kelly.....
Supervisor

Date.....4/7/8

ABSTRACT

Abdominal tuberculosis is a common form of extra- pulmonary tuberculosis especially in HIV/AIDS patients. A high index of suspicion is required for diagnosis of abdominal tuberculosis in these patients.

A study was done at the University Teaching Hospital, Lusaka, Zambia to ascertain whether abdominal tuberculosis is common in HIV/AIDS patients, and whether under diagnosed. The inclusion criteria were fever and weight loss, with one or more of the following: diarrhoea persisting for >1 month, ascites, abdominal lymphadenopathy based on ultrasound, mesenteric masses based on ultrasound, hepatomegaly or splenomegaly, pancreatic enlargement, or unexplained focal or generalised pain/tenderness persisting over 7 days.

The exclusion criteria included: HIV negative, solely pelvic and renal abnormalities, on antituberculous treatment for more than 1 week or too sick to undergo laparoscopy or colonoscopy. 31 subjects completed the algorithm and all the subjects had abdominal ultrasound scanning of which some had laparoscopy/laparotomy while others underwent colonoscopy. In order to determine if abdominal lymphadenopathy was attributable to HIV an equivalent number to those who met the criteria was recruited as controls and had abdominal ultrasound scanning. These subjects were HIV positive and had no features of tuberculosis.

In this study 22 subjects had evidence of abdominal tuberculosis while 9 had no evidence of abdominal tuberculosis representing 71% and 29% respectively. Non of the controls had abdominal lymphadenopathy or any appreciable mass on abdominal ultrasound implying that abdominal lymphadenopathy indicate pathology.

Good history and physical examination proved to be useful in diagnosing abdominal tuberculosis. Among the physical findings, abdominal tenderness was the commonest (86%) in subjects with evidence of abdominal tuberculosis.

This study also revealed that abdominal ultrasound is an important tool in helping to make diagnosis of abdominal tuberculosis especially in poor resource set up where CT and MRI scans are not readily available. This study showed that 73% of those with evidence of abdominal tuberculosis had ascites and 54% of subjects with abdominal tuberculosis had ascites with fibrous strands.

While laparoscopic studies plus biopsy will confirm abdominal tuberculosis, this study noted that it is possible for normal looking mucosa on colonoscopy to be colonised by *Mycobacteria tuberculosis* (this was found in 1 out of 5 subjects).

No *Mycobacterium was* cultured from any of the blood samples drawn from the study subjects and positive culture of the ascitic fluid was low (13.6%). Many subjects with abdominal tuberculosis had low CD4 count (mean= 92 cell/µl).

20 subjects (HIV positive) who died of suspected pulmonary or abdominal tuberculosis had autopsy done on them. Disseminated tuberculosis was more frequent than either pulmonary or abdominal tuberculosis.

Abdominal tuberculosis in quite common in HIV positive patients. Therefore it is important to take a detailed history and elicit signs pertaining to abdominal TB.

This dissertation is dedicated to my dear wife and my son Twapelwa

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LIST OF ABREVIATIONS

TB	Tuberculosis
HIV	Human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
MTB	Mycobacterium tuberculosis
MAC	Mycobacterium Avium Complex
TNF	Tumour necrosis factor
WHO	World Heath Organisation
MGDs	Millennium Development Goals
WHA	World Heath Assembly
CT	Computed Tomography
AFB	Acid fast bacilli
ADA	Adenosine deaminase
ATT	Antituberculous treatment
UTH	University Teaching Hospital
MGIT	Mycobacterium Growth Indicator Tube
ZN	Ziehl-Neelsen
PANTA	Polymyxin B, nalidixic acid, trimethoprim, and azlocillin
USA	United States of America
PAS	Periodic acid Schiff
CD	Cluster of differentiation

Chapter 1

1.0 Background

The HIV pandemic is the most serious threat to the people of sub-Saharan Africa in post-colonial history. Its effect on productive adults is an unusual and particularly devastating feature, with profound demographic, social, and economic consequences.

In 1983-5 the first evidence of widespread infection with HIV emerged in Uganda, Zaire and Zambia. The first evidence was a change in the behaviour of Kaposi's sarcoma, then the diarrhoea-wasting syndrome known as 'slim disease' that was identified, then a reversal of all previous progress in controlling tuberculosis was noted. Over the last 20 years it has become apparent that there is a 'dual epidemic' of tuberculosis (TB) and HIV, the scale of which is disastrous. HIV infection leads to a 10 to 20 fold increased risk of TB[1]. Two of the major presenting clinical features of HIV infection, TB and persistent diarrhoea, are both potent causes of the body wasting which is such a characteristic feature of AIDS[2]. This wasting is also a very potent stigmatising factor.

However, given the greatly increased susceptibility to TB in HIV-infected adults, it is surprising that there is not more clinically apparent abdominal TB. In a systematic analysis of small intestinal biopsies in 75 Zambian patients with AIDS-related diarrhoea, no evidence of Mycobacterium avium complex (MAC) infection was found[3]. Stool samples from the same group of patients yielded 4 isolates of Mycobacterium tuberculosis (MTB) and 2 isolates of MAC[4]. Interpretation of these data has been difficult because there has been

uncertainty as to how many of these positive isolations could reflect gut excretion of swallowed acid-fast bacilli in patients with pulmonary TB.

The most thorough study of mycobacteriosis in AIDS is a post-mortem study from Cote d'Ivoire[2] in which wasting was found to be due almost as frequently to TB as to diarrhoea. Intestinal lesions of TB were found in 8.6% of 210 cadavers, and in as many as 16% with skeletal wasting. This suggests that intestinal TB may be more common than is thought. In another, as yet unexplained observation, it was found that HIV-infected patients receiving anti-tuberculous prophylaxis had a lower incidence of diarrhoeal disease, but only if the regime contained rifampicin[5]. This could be because of occult intestinal TB or because rifampicin may have antibacterial effects on other intestinal pathogens.

In HIV infection, mycobacterium tuberculosis (MTB) and mycobacterium avium complex (MAC) are important infections which occur when T cell failure is severe. One would expect to see an upsurge in intestinal/abdominal TB in AIDS, but this has not been described. Either this is because an epidemic within an epidemic has been overlooked, or because there is a biological explanation.

If there is a substantial difference between MTB isolates which are tropic for pulmonary or intestinal cellular niches, there may be a difference in the susceptibility of immunocompromised hosts to these isolates. For example, AIDS patients are susceptible to MTB but not to *Mycobacterium leprae* infection, so we know pathways of susceptibility to mycobacteria differ even though control of intracellular replication is T cell dependent for all mycobacteria.

Patients with AIDS-related gastrointestinal disease have a poor prognosis. These patients are often wasted and this is associated with severe cytokine dysregulation, in particular very greatly elevated levels of TNF[6]. There is evidence that oesophageal ulceration and possibly some colonic disease may also benefit from treatment directed at reducing TNF synthesis, possibly with drugs like pentoxifylline or spironolactone. However, it is not possible to conduct trials of these drugs in Zambia as the prevalence of abdominal TB is unknown, and inhibition of TNF could have a very adverse effect on occult TB. There is therefore an additional reason why information on gastrointestinal TB is urgently required.

1.1 Statement of the problem

Abdominal tuberculosis is a common disease entity that is under-diagnosed in HIV positive adults in Zambia.

1.2 Study justification

The prevalence of abdominal tuberculosis has never been defined in Zambia, let alone in patients with HIV/AIDS. Its clinical manifestations are not well defined especially in poor economic set up severely affected with HIV/AIDS. The study will answer the question pertaining to the easiest way of making a diagnosis of abdominal tuberculosis. The ability to define patients who are very unlikely to have gastrointestinal TB would be very helpful as it would open up the possibility of immunotherapy such as(pentoxifylline as an anti-TNF agent) in patients with a very adverse prognosis.

1.3 Hypothesis

The intestinal mycobacterial disease is common and contributes to accelerated wasting and death.

1.4 Research question

Abdominal tuberculosis is common in HIV infected patients and probably under diagnosed.

1.5.0 Objectives

1.5.1 Specific aim 1:

To evaluate frequency of abdominal tuberculosis in HIV infected patients.

1.1.2 Specific aim 2:

To assess the level of immunodeficiency in those with abdominal tuberculosis.

1.1.3 Specific aim 3:

To identify useful diagnostic markers of abdominal tuberculosis in a poor resource setting.

1.1.4 Specific aim 4:

To evaluate the frequency of pulmonary tuberculosis co-existing with gastrointestinal tuberculosis.

1.1.5 Specific aim 5:

To define specificity of abdominal ultrasound findings by looking at HIV positive controls

Chapter 2

2.0 Literature review

2.1 History

Tuberculosis is one disease that has existed and affected man for a very long time. In fact the Greek called it phthisis, emphasizing its wasting nature if remained untreated. It was noted to be a problem of epidemic proportions during industrialisation and urbanisation in the seventeen and eighteenth centuries. It was a common cause of death in Europe particularly England and Wales in 1650, accounting for at least 20% of all deaths[7]. In the same vein, United States of America was not spared and particularly the Eastern part that recorded annual mortality rate in the nineteenth century of 400 per 100,000 population[7].

The actual cause of tuberculosis caused a lot of debate until Robert Koch discovered that actually it was a tubercle bacillus responsible for the wasting disease[7]. The discovery took place in 1882 and it was leant that improvement in the socioeconomic conditions led to the reduction of the cases. Isolation of the infectious patients in the sanitoria also proved to be helpful in the first half of twentieth century. Some of these measures led to the reduction of mortality in Europe and United States even before the introduction of antimycobacterial drugs[7].

Natural history of tuberculosis as shown by various studies indicated that before the advent of chemotherapy the disease was fatal[8]. A bout a third of patients

died within a year if left untreated and one half died within 5 years. Those that survived at 5 years 60% under went remission but the remainder were still infectious[8].

2.2 Epidemiology

Tuberculosis is a killer disease and results in the death of about three million people globally each year. It is estimated that between 2000 and 2020, 1 billion people will be infected; 200 million will become sick and if control is not strengthened 35 million people will die of the disease[9].

In 5 out of 6 World Heath Organisation (WHO) regions, a survey in 2004 revealed that per capital tuberculosis incidence was stable or falling[9]. The exception was the African region, which recorded an increase in the incidence of tuberculosis following the spread of HIV. However there has been a decline in case notification from African region probably as a result of decline in HIV epidemic.

The 10th WHO annual report on surveillance, planning and financing for global tuberculosis comprises data concerning notifications, treatment outcomes, TB activities, budgets, cost and expenditures[9].

In East Europe (mostly countries of the former Soviet Union), incidence per capital increased during the 1960s, but peaked around 2001, and has since fallen[9].

Eleven consecutive years of data (1994-2004) are now available to assess progress towards the Millennium Development Goals (MDGs) for TB control, and towards targets set by the World Heath Assembly (WHA) and stop TB partnership.

WHA targets were to detect, by 2005 70% of new sputum smear- positive cases and to successfully treat 85% these cases[9]. There were 9 million new TB cases and approximately 2 million TB deaths in 2004. More than 80% of all TB patients live in Sub-Saharan Africa and Asia.

Overall, one third of the world's population is infected with the TB bacillus, but not all infected individuals have clinical disease.

The bacteria cause disease when the immune system is weakened, as in older patients, HIV patients and other immune lowering diseases. The control of TB has become challenging because of natural history of the disease and the varying pattern in which it manifests in different groups.

The HIV epidemic in sub-Saharan Africa has contributed to an increased incidence of pulmonary tuberculosis (TB), but a similar rise in abdominal TB has not been widely noted. The annual risk of developing active TB, when co-infected with HIV, is 20 to 30 times the risk in seronegative individuals[10,11].

The percent of TB cases attributable to HIV infection is especially high in the African region (31%) and in the United States (26%)[10]. The importance of co-infection is evident, and is particularly important in developing countries, where in HIV/AIDS patients, TB of any organ is the most common life-threatening opportunistic infection[10]. In Africa, TB is the leading cause of mortality and morbidity in HIV infected patients,[10] causing up to 41% of deaths in Zaire[10]. Globally, 11% of deaths in HIV positive individuals are attributed to TB[12]. In Zambia, the number of newly diagnosed cases of TB increased from 8,246

(124/100,000) in 1985 to 38,863 (409/100,000) in 1996 and 52,000 (512/100,000) in 2000[13].

The rapid increase of extrapulmonary TB in HIV positive patients is well known in various regions. For example, in India about 24% to 36% HIV patients have extrapulmonary TB[14,15]. In various countries in Africa, the percentage of HIV positive patients with extrapulmonary TB ranges from 31% to 57%[16]. In the USA, there have been reports of 30% to 50% of seropositive patients having extrapulmonary TB[11,12]. In Brazil, 62%of HIV seropositive people have extrapulmonary TB[17]. The increase in extrapulmonary TB is especially evident as HIV infection progresses and the patient becomes more immunocompromised[18,19].

The mode of infection in extra-pulmonary TB could be either due to swallowing of infected sputum, direct spread from adjacent organs, or due to endogenous reactivation of dormant bacilli in primary infection. It is also feasible that infection occurs via lymphohaemotogenous spread.

2.3 Abdominal tuberculosis

Most of what is to follow has been written about HIV negative adults. Any part of the gastrointestinal tract from the mouth to the anus can be affected by tuberculosis. It can also involve the peritoneum, pancreas and hepatobiliary system. By definition Gastrointestinal Tuberculosis involves the peritoneum, hollow or solid abdominal organs including lymphatic[26]. The common sites affected by tuberculosis are the peritoneum and ileocaecal region.

2.4 Pathogenesis of abdominal tuberculosis

It is believed that the tubercle bacilli reach the gastrointestinal tract through various routes[26]:

(i) Spread haematogenously from the primary lung focus which may have occurred during childhood, then reactivated.

(ii) Swallowed bacilli containing sputum from infected lung focus.

(iii) Spread directly from organs in vicinity, for example infected fallopian tubes in females.

(iv) Lymphatic channels draining infected lymph nodes.

Although it was believed that in most cases the bacilli reached the gastrointestinal tract following reactivation in the lungs, this is being questioned following recent study using DNA finger printing that shows that 40% are due to re-infection[26]. All intestinal tubercular organisms isolated revealed Mycobacterium Tuberculosis and not *Mycobacterium bovis*[20,21].

Possible explanations for the predominant involvement by *Mycobacterium tuberculosis* of the ileocaecal region include[26]:

(i) Increased physiological stasis as water is absorbed from the lumen.

(ii) Fluid and electrolytes are absorbed at a higher rate in this region and minimal digestive activity takes place.

(iii) This region is rich in lymphoid tissue. M- cells of peyers patches have shown to phagocytose bacilli.[22]

Involvement of the peritoneum may be as a result of spread of bacilli from adjacent lymph node or intestinal foci as well as tubercular salpingitis in women.

2.5 Pathology

The gross pathology is seen as transverse lesions with fibrous change and thickening leading to stricture formation in bowel wall. There is also enlarged with matted mesenteric and thickened omentum. The peritoneum is covered with tubercles. Granulomas due to tuberculosis involve the mucosa or the Peyer's Patches. These lesions vary in size and tend to be confluent as opposed to the granulomas found in Crohn's disease. The granulomas are mainly found under the ulcer bed involving the submucosa. However submucosal oedema is not obvious. Ulcers due to tuberculosis are superficial and tend not to involve the muscularis[23]. These ulcers at times are single or multiple. If there are multiple ulcers the mucosa in - between is usually not involved. The ulcers are transverse in orientation as opposed to longitudinal ulcers in Crohn's disease[23]. The circumferential healing pattern of these ulcers leads to stricture formation. Further more the obstruction of arteries will lead to ischaemia and consequently stricture formation[24].

On rare occasions endarteritis may lead to severe bleeding in intestinal tuberculosis. According to Shah *et al*[25], there was some correlation of barium studies and angiography in 20 patients. Angiography studies showed abnormalities in all patients and these angiograms showed stretching and crowding of blood vessels, which also showed hypervascularity. Patients who were found to have intestinal strictures had obstruction of vasa recta. The ulcerated lesions were in fact hypervascularised. If they are longstanding

lesions, this may lead to changes that involve fibrous formation in the bowel wall that may extend from submucosa into muscularis.

Microscopically these portions may show non- specific chronic inflammatory cells without granuloma formation. Involvement of mesenteric lymph nodes, will lead to enlargement of these nodes which may be matted with caseation.

The gross involvement and appearance of the bowel was classified by Hoon *et al*[23] into ulcerative, ulcerohyperplastic and hyperplastic. Ulcerative type is associated with malnourished adult patients while hypertrophic variety is found in well nourished ones. There is thickening of the bowel wall with serosal surface having nodules that vary in size. The ulcerative lesions and strictures are found mainly in the small intestine. Ileocaecal and colonic involvement is hypertrophic which may present as right iliac fossa mass. This mass may constitute ileocaecal region, fat in the mesentery and lymph nodes. This pathology distorts the ileocaecal angle making it obtuse in most cases. The ileocaecal valve, as it is usually involved, becomes incompetent, another helpful distinction from Crohn's disease.

Peritoneal tuberculosis, pathologically involves lesions with multiple yellow-white tubercles covering the peritoneum. The peritoneum becomes thick, hyperaemic and less shiny. Omentum also becomes thick[26].

In tuberculous peritonitis there are three forms[26]:

(i) wet form with ascites

(ii) loculated type with localised abdominal swelling

(iii) fibrotic type which presents with masses in the abdomen comprising mesenteric thickening as well as thickening of omentum together with matted bowel loops that are at times felt as lumps if large enough. Sometimes the three forms may be combined in one patient.

2.6 Clinical features

Generally abdominal tuberculosis affects the young age group. Two-thirds of the patients are aged 21-40 years and males and females are affected equally. In terms of clinical presentation, abdominal tuberculosis can be acute, chronic or acute on chronic. In most cases patients present with constitutional symptoms of fever (40-70%), pain (80-95%), weight loss (40-90%), diarrhoea (11-20%) and constipation[26]. Sometimes diarrhoea and constipation alternate with anorexia and malaise as other features. Abdominal pain is colicky in nature especially if there is luminal compromise or may be dull and persistent if there is involvement of the mesenteric nodes. Other clinical manifestations are dependant on the site and extent of involvement[26].

2.7 Oesophageal tuberculosis

Tuberculosis of the oesophagus is quite rare and accounts for only 0.2 per cent of Gastrointestinal tuberculosis[22]. The oesophagus is involved as a result of disease extending from the surrounding lymph nodes. Oesophageal tuberculosis usually presents with low grade pyrexia, dysphagia and odynophagia. The pain on swallowing (odynophagia) may be due to an ulcer that is localised commonly in the midoesophageal region. As such the disease usually simulates oesophageal carcinoma and there is no evidence of extraoesophageal lesions of tuberculosis.

2.8 Gastroduodenal tuberculosis

Tuberculosis of the stomach and duodenum is rare and each accounts for approximately 1 per cent of abdominal tuberculosis[26]. Gastroduodenal tuberculosis may present like peptic ulcer disease but will not respond to anti acidic drugs[27] and may have a shorter duration in terms of history. It may also mimic gastric carcinoma in terms of presentation. There has been some rare concurrence of gastric carcinoma and tuberculosis in the same patient as reported by Chowdhary *et al*[28].

A series of 30 cases believed to be the largest series of duodenal tuberculosis was reported in India[29]. The common presentation of these patients was that of duodenal obstruction (73%) which was as a result of extrinsic compression by enlarged lymph nodes in most cases. The remaining cases (27%) had symptomatology of dyspepsia, and infact were thought to have duodenal ulcers. Hematemesis was a rare presentation and only 2 patients had it. Various authors have presented some complications such as pyeloduodenal and duodenocutaneous fistulae[30]. Others have reported perforations and ulcers extending into pancreas[31]. Obstructive jaundice by compression of the common bile duct has been reported[32].

Duodenal tuberculosis has occurred in about more than 80% per cent without pulmonary involvement[30]. Segmental narrowing can occur with duodenal tuberculosis. This occurs usually as short strictures but long segment of the duodenum can be involved. CT scan of the duodenum may show wall thickening and sometimes it can show lymphadenopathy. Endoscopy is non specific for duodenal tuberculosis and even granulomas or acid fast bacilli on endoscopic biopsy material are usually not demonstrated[26].

2.9 Ileocaecal tuberculosis

Patients may complain of abdominal pain which is colic in nature. Vomiting and borborygmi are other presenting complaints. Examination of the abdomen may be normal or may have a doughy feel. On the other hand abdominal examination may reveal a firm mass which is mobile and well defined in the right iliac fossa. One or more lumps occur(s) due to lymphadenopathy especially involving the mesenteric nodes. These lumps are usually mobile but may be fixed if para-aortic iliac nodes are involved[33].

The commonest complication of ileocaecal tuberculosis is obstruction which in most cases is due to narrow lumen as a result of caecal tuberculosis. Adhesions and strictures are other causes of obstruction. Strictures of small intestine are commonly multiple. Bowel loops can become fixed due to involvement of surrounding lymph nodes. These same nodes can lead to narrowing and traction of the bowel loops. Studies in India have shown that about 3 to 20 per cent of intestinal obstruction is due to tuberculosis[33,34,35]. Bhansali and Sethna[34] in a series of 348 cases of intestinal obstruction noted that in 54 (15.5%) cases; 33 involved the small intestine and 21 the large intestine. All these were found to be due to tuberculosis. Tendon *et al*[36] followed up 186 patients over a period of 5 years and observed that there was an increase in patients with a long course and subacute intestinal obstruction in recent years.

In India tuberculosis ranks second to typhoid fever as a cause of intestinal perforation accounting for 5-9 per cent of all intestinal perforations.[37,38] .

In a patient with intestinal perforation as a result of tuberculosis an important clue is evidence of tuberculosis on x-ray or indeed the history of subacute intestinal obstruction. Air in the peritoneum (pneumoperitoneum) may be seen only in half of the case[29]. This may be seen on the radiographs. Perforations due to tuberculosis are in most cases single and proximal to the stricture[40]. Ruptured caseating lymph nodes may lead to acute peritonitis without intestinal perforation.[33,38]

Malabsorption is another common complication of ileocaecal tuberculosis. This ranks second to tropical sprue as a cause of malabsorption syndrome in India[33]. Pimparkar and Donde[41] recruited 40 patients with malabsoption in a study and divided them into those with and without intestinal stricture. Glucose and lactose tolerance tests, D-xylose test, faecal fat and schilling test for B_{12} malabsorption were done and found to be abnormal in 28, 22, 57, 60 and 63 per cent respectively in those with strictures as compared to 0, 0, 8, 25 and 30 per cent respectively without strictures. A number of reasons have been postulated and include; bacterial overgrowth in a stagnant loop, ulceration leading to reduced absorptive surface and lymphatic involvement. Bile salt deconjugation also plays a role.

2.10 Segmental colonic tuberculosis

This involves the colon without affecting the ileocaecal region. Segmental colonic tuberculosis accounts for 9.2 per cent of abdominal tuberculosis. The parts of the colon mostly involved are, sigmoid, ascending and transverse colon[42]. In about a third (28-44%) of patients with tuberculosis of the colon, there is multifocal involvement[43,44]. Most patients present with pain (78-90%) and hematochezia is seen in less than one third[43,44] of the patients. Bleeding is in most cases trivial and massive bleeding is not common. Singh *et al*[45] noted bleeding per rectum in 31 per cent of the patients who had colonic tuberculosis and this was massive in 13 per cent.

Generally about 4 per cent of people with lower gastrointestinal bleeding are as a result of tuberculosis[26]. Fever, anorexia, weight loss and change in bowel habits are the other features of colonic tuberculosis. In terms of diagnosis barium enema or colonoscopy are suggestive.

2.11 Rectal and anal tuberculosis

The clinical features of rectal tuberculosis differs from that affecting the proximal parts of gut. Haematochezia ranks first (88%) in terms of symptomatology followed by constitutional symptoms (75%). Constipation is another feature occurring in about 37 per cent of cases[46]. Rectal bleeding is usually due to mucosal trauma as a result of stools traversing the segments affected by strictures. Digital examination reveals tight and annular strictures and there may be focal areas of ulcerations which are deep[26]. The strictures is usually localised

about 10 cm of the anal verge. It is however rare to find associated perianal disease. There is a lot of inflammation and fibrous formation in rectal disease. It is worth noting that rectal disease is quite rare and may occur without associated pulmonary or small and large intestinal disease[47,48].

Anal tuberculosis presents as a distinct entity usually with multiple fistulae and is less uncommon. According to Dandapat *et al* [49,24] out of 15 multiple fistulae were due to tuberculosis as compared to only 4 out of 61 solitary perianal fistulae. Shukla *et al* [50] noted that in India about 14 per cent of fistula *in ano* were as a result of tuberculosis. All cases presented with anal discharge and only one third had perianal swelling. No patient presented with any constitutional symptoms[50]. Overall rectal tuberculosis is rare and may occur in the absence of other lesions in the chest and small and large bowel[47,48].

2.12 Abdominal tuberculosis in HIV patients

Much less has been written about abdominal tuberculosis in HIV positive patients. There is a particularly high incidence of atypical presentations of tuberculosis in HIV positive patients. The presentation of abdominal TB can resemble other infections as well as malignancies. Fever and weight loss are common presenting features of HIV positive patients presenting with extrapulmonary TB[26]. In a study done in India, extrapulmonary TB was the most common cause of fever of unknown origin (FUO) in HIV positive patients[51]. In an autopsy study done in the Ivory Coast to study the causes of slim disease, 44% of wasted HIV positive patients who died had tuberculosis[2].

This study showed that wasting could no longer be attributed solely to AIDS related enteropathy. These constitutional symptoms can be present in various other systemic diseases, so further definition of symptoms is necessary. More often than not, extrapulmonary TB presents with localized symptoms with pain at the infected site[1]. The most common clinical features of peritoneal and miliary tuberculosis are: fever, weight loss, abdominal pain, diarrhea, ascites, hepatomegaly, and splenomegaly[53,54] . In several studies, characteristics features of gastrointestinal TB included fever, weight loss, abdominal pain, abdominal mass, and ascites[55,56,57]. Due to the indolent course of the disease often these symptoms continue for a prolonged period of time before a diagnosis is reached[58]. A heightened clinical suspicion is important because only 15-20% of patients have concomitant active pulmonary tuberculosis[59].

Abdominal TB is difficult to diagnose due to the lack of efficient and sensitive diagnostic tools as well as its insidious and non-specific symptoms and variable anatomical location. In resource-poor settings, there are very few diagnostic tools from which to choose. Microscopy is the most rapid diagnostic tool, which in ideal settings can produce results the same day, but is highly insensitive especially in severely immunocompromised individuals[10].

Culture systems are sensitive, but often take up to six to eight weeks to obtain conclusive results. Specimens can often be paucibacilliary in nature and therefore result in an even lower sensitivity of acid-fast bacillus (AFB) smear[10].

2.13.0 Radiological studies

These studies have been described mainly in HIV negative adults.

2.13.1 Chest x-ray

This may show evidence of tuberculosis or may be non revealing. Abdominal tuberculosis is supported if the chest x-ray shows some evidence of tuberculosis. There are many instances when a chest x-ray is normal and yet patient has abdominal tuberculosis. Sharma *et al* [60] noted that out of 70 cases of abdominal tuberculosis, 22 (46%) had evidence of healed or active lesions on the chest X-ray. Chest ray findings were more likely to be revealing in patients who had acute complications (80%)[60]. In a series of 300 patients by Prakash none of them had active pulmonary tuberculosis but 39 per cent showed healed lesions of tuberculosis [61]. Tandon *et al* [62] noted that x-rays were positive only in 25 per cent of their patients.

2.13.2 Plain abdominal x-ray

This may show features of intestinal obstruction which are dilated bowel loops with air fluid levels and evidence of ascites. Perforation may also show on plain abdominal X-rays. X-rays may show calcification of the lymph nodes and granulomas[26].

2.13.3 Small bowel barium meal

This may show fast intestinal transit in form of hypersegmentation of barium column which is referred to as ("chicken intestine"), the barium may be flocculated or diluted. There may be folds that are stiffened and thickened[26].

The lumen may be stenosed with smooth but contours that are stiff ("hour glass stenosis"). This barium meal may show bowel loops that are dilated and multiple strictures[26].

2.13.4 Barium enema

This may show the following features[60]:

(i) The iliocaecal region may be involved early enough and may manifest as spasms and oedema of the valve. The lips of the valve may become thick and at times the valve may show wide gaping and narrowing of the terminal ileum ("inverted umbrella sign"). These features are quite characteristics.

(ii) There is fold thickening and contours that are irregular and this is appreciated well with use of double contrast study.

(iii) Barium enema may show shrunken caecum which may be pulled out of the iliac fossa. This is due to fibrosis of the mesocolon and is referred to as conical caecum.

(iv) There is loss of normal ileocaecal angle and terminal ileum is dilated and this looks like "goose neck deformity" on barium enema.

(v) Localised stenosis opposite ileocaecal valve which may also show rounded off and smooth caecum with dilated terminal ileum may show as "purse string stenosis" on enama.

(vi) " Stierlin's sign" this occurs in acute inflammation superimposed on segments that have chronic involvement and is characterized by no retention of barium in the in the inflamed portion of the ileum, caecum and some length of

ascending colon but with normal configuration of barium on the column on either side. It looks narrow in the terminal ileum with rapid emptying into a caecum which may rigid, shortened or obliterated.

(vii) "String sign"- there is stenosis and this shows as a narrow stream of barium.

Stierlin and String signs are not specific to tuberculosis as they can be seen also in chronic inflammatory disease particularly Crohn's disease.

2.14 Ultrasonography

Barium studies are quite accurate for intrinsic intestinal abnormalities but do not detect peritoneal lesions. Ultrasound has shown to be useful for detecting peritoneal tuberculosis and the following may be detected by ultrasound imaging[63]:

(i) loculated or free abdominal fluids which may be clear or contain septae and debri. Pelvic cavity may also collect some fluids and it may have thick septa simulating ovarian cyst.

(ii) In a patient with inter bowel loop ascites, a "sliced bread sign" may be seen on ultrasound and is due to fluid that is localised in between radially oriented bowel loops. This fluid is as a result of local inflammation of the bowel loops involved.

(iii) Intra-abdominal lymphadenopathy is seen on ultrasound. These enlarged nodes may be matted or sometimes discrete and may be seen to have heterogenous echogenicity as opposed to homogenous hypoechoic nodes of lymphoma.

Sometimes discrete anechoic portions of the lymph nodes representing zones of caseation are visible on ultrasound. Healing nodes may become calcified and are seen as reflective lines. Appearance of calcification and caseation is very suggestive of tuberculosis and both are not common in lymphadenopathy due to malignancy.

(iv) Ultrasound can also reveal bowel wall thickening especially in iliocaecal tuberculosis. The thickening is concentric and quite uniform compared with the thickening in Crohn's disease which is eccentric at the mesenteric border.

(v) The ileocaecal portion may be pulled up to sub hepatic position and will give a pseudokidney appearance on ultrasound.

2.15 Computed tomography (CT) scan

CT scan evaluates ileocaecal tuberculosis quite well as this area is hyperplastic. In initial stages of the disease, the caecum and terminal ileum may show symmetrical and circumferential thickening. As the diseases progresses the ileocaecal valve and the medial wall of the caecum become asymmetrically thick. In more advanced disease CT scan will reveal a soft mass around the ileocaecal junction [64] which is composed of the adherent loops, wall thickening and large adjacent lymph nodes. CT can also reveal ulcers or nodules within the terminal ileum and will also pick up narrowing and proximal dilatation. In the colon, the hepatic flexure involvement is seen commonly. Complications such as perforation abscess and obstruction can be seen on the CT scan.

Ascites due to tuberculosis is of high attenuation value (25-45 Housnfied Units) as it contains a lot of protein. Debris and strands are characteristic of tubercular ascites but better appreciated on ultrasonography[64] than CT scan. CT scan may pick peritoneal thickening as well as peritoneal nodules.

Mesenteric disease on CT scan appears as a patchy or diffuse and increased in density. Enlarged lymph nodes may appear interspersed and thickening of the omentum is seen.

Caseating nodes appear as having hypodense centers with enhancement of peripheral rims. Calcification may be seen in the nodes and together with features of the nodes described above is quite suggestive of tuberculosis[26].

In tuberculosis the lymph nodes that are usually involved include mesenteric, celiac, portal hepatis and parapancreatic nodes. Retroperitoneal nodes are usually not involved and are almost never seen in isolation , unlike lymphoma[64].

2.16 Colonoscopy

Although not used so much, colonoscopy is an excellent investigating tool for tuberculosis especially that of the colon and terminal ileum. Nodules of variable size (2-6mm) in the mucosa and ulcers in the colon (4-8cm long) are pathognomic of tuberculosis. These nodules have a surface that is pink and is not friable. The nodes are mostly found in the caecum and especially in the ileocaecal valve. Some ulcers located between the nodes. Portions of strictures with nodules and ulcers may be seen in the mucosa. The ileocaecal valve may be deformed and edematous. Rarely (4%) is the entire colon involved but may

look very similar to ulcerative colitis on endoscopy. Lesions that look like carcinoma have been described [65].

Most clinicians take about 8-10 biopsies on colonoscopy for histopathology and culture. Aim to take biopsy from the edge of the ulcers. Histopathology yield is quite low as the submucosa is mainly involved. Granulomas have been noted in 8-48 per cent of cases and caseation in one third which accounts for 33-48 per cent of positive cases[66]. There are variable results on the yield of acid fast bacilli stains in different studies. Bhargava *et al* [65] showed positive cultures in 40 per cent of patients and made a conclusion that routine culture of biopsy increases diagnostic yield.

2.17 Laparascopy

Bhagava *et al* [65] studied 87 patients with ascites comprising a lot of protein of which 38 had a diagnosis of tuberculosis. Visual appearance was found to be more helpful (95% accurate) as compared to histology, culture or guinea pig inoculation (82, 3 and 37.5 per cent sensitivity respectively). About 85-90 per cent of biopsies may show caseating granulomas. The findings on laparoscopy in tuberculosis of the peritoneum can be grouped in three categories[26]:

(i) multiple tubercles on the thick peritoneum which may be uniform measuring about 4-5 mm. The peritoneum is hyperaemic and shines less. Omentum, liver and spleen may also contain studs of tubercles.

(ii) Peritoneum may be thick but without tubercles.

(iii) Fibrous formation with a thick peritoneum and many adhesions which tends to fix the viscera.

2.18 Ascitic fluid examination

The fluid in tuberculosis is straw coloured with protein level of more than 3 g/dl and total cell count of 150-4000/µl comprising mainly lymphocytes (>70%). Ascites to glucose level is less than 0.96[66] while serum ascites albumin gradient is less than 1.1 g/dl.

There is a very low yield of organism on smear and culture. Staining for acid fast bacilli is not that helpful as this is positive in less than 3 per cent of cases. Culture is positive in less than 20% it may take 6-8 weeks for growth to take place. However when Singh *et al* [64] centrifuged a litre of ascitic fluid and cultured it, they got 83 per cent culture positivity.

Adenosine deaminase (ADA) increases in ascitic fluid caused by tuberculosis as a result of stimulation of T-cells by mycobacterial antigens. ADA is an aminohydrolase and converts adenosine to inosine. It is involved in the catabolism of purine bases. The activity of this enzyme is seen more in T than in B lymphocytes hence its association with tuberculosis. Dwivedi *et al* [67] noted that ADA levels were significantly higher in tubercular ascites than in ascites due to cirrhosis or malignancy in 49 patients studied. How ever in the co- infection with HIV, ADA levels are normal or reduced and levels may be falsely high in ascites due to malignancy[26]. Ascites due to tuberculosis has been noted to have higher interferon-γ levels which is of value in making diagnosis[68]. Combining the two would increase sensitivity and specificity.

Chapter 3

3.0 Methods and cases

The University Teaching Hospital, Lusaka, Zambia functions as secondary and tertiary care hospital with 1,200 beds, which serves as the major referral center for all of Zambia. This hospital diagnoses and treats large numbers of TB and HIV patients and allows for the necessary conditions for the study of co-infected patients.

All patients were drawn from in-patients of the medical wards at the University Teaching Hospital (UTH), Lusaka, Zambia.

A total of 5,609 patients were screened over a period of 27 weeks from September 2005 until May 2006. The inclusion criteria were fever and weight loss, with one or more of the following: diarrhoea persisting for >1 month, ascites, abdominal lymphadenopathy based on ultrasound, mesenteric masses based on ultrasound, hepatomegaly or splenomegaly, pancreatic enlargement, or unexplained focal or generalized abdominal tenderness persisting over 7 days.

A detailed clinical history, physical examination, laboratory investigations, and an abdominal ultrasound were then conducted. The following were used as exclusion criteria: HIV negative, solely pelvic and renal abnormalities, on anti-tuberculosis treatment (ATT) for greater than 1 week or too sick to undergo laparoscopy or colonoscopy. The decision whether to perform laparoscopy or colonoscopy was based on clinical findings, ultrasound findings, and HIV test (Figure 1).

3.1 Controls

In order to determine if abdominal lymphadenopathy was attributable to HIV, an equivalent number to those who met the criteria was recruited as controls and under went abdominal ultrasound scanning to see if at all had any appreciable abdominal lymphadenopathy or indeed any organomegally. These subjects had no features of pulmonary or abdominal tuberculosis and were HIV positive.

3.2 Autopsy

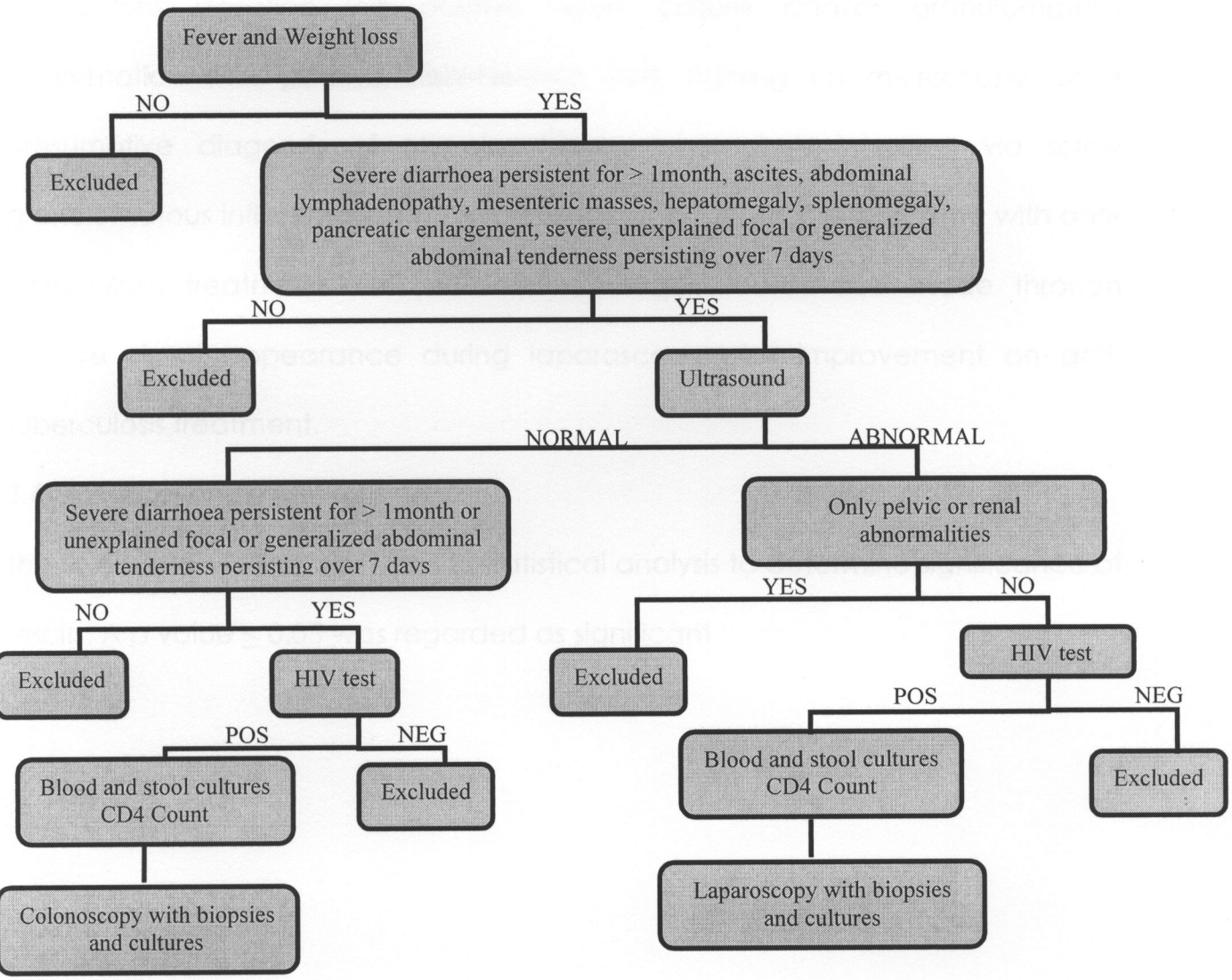
Twenty autopsies were conducted parallel to laparoscopy and colonoscopy. The subjects chosen were HIV positive. These subjects had symptoms suggestive of pulmonary tuberculosis and or abdominal tuberculosis on reveal of records in their files. Permission to do autopsy was taken from the relatives. The probable causes of death were communicated to the relatives or the next of kin.

3.3 Ethics

Ethical approval for the study was given by the University of Zambia Research and Ethics Committee. Informed consent was obtained from all subjects. An information sheet was given to each participant in both English and the predominant local language, Nyanja. Participants were able to withdraw at anytime. All patients with definite or probable TB were treated accordingly.

3.4 Selection of subjects

Figure 1. Algorithm for evaluation of subjects with high suspicion of abdominal tuberculosis.



3.5 Study Design

In this study, abdominal tuberculosis was defined as tuberculosis affecting the peritoneum, abdominal lymph nodes, omentum, liver, spleen, pancreas and/or gastrointestinal tract. The following diagnostic criteria were used to determine which study patients had abdominal TB: definitive diagnosis of *Mycobacterium tuberculosis* infection via positive MGIT culture and/or granulomatous inflammation with positive Ziehl-Neelsen (ZN) staining on microscopy; or a presumptive diagnosis of Mycobacterium tuberculosis infection via solely granulomatous inflammation on microscopy and favourable outcome with anti-tuberculosis treatment. A presumptive diagnosis was also made through positive visual appearance during laparoscopy plus improvement on anti-tuberculosis treatment.

3.6 Statistical analysis

The Kruskal- Wallis test was used in statistical analysis to determine significance of results. A p value ≤ 0.05 was regarded as significant.

Chapter 4

4.0 Laboratory methods and measurements

4.1 Blood

Blood was submitted for an HIV test (if the status was not already known), CD4 count (FACScount, Beckton Dickinson), full blood count, and liver function tests. It was also placed in a blood culture bottle and submitted for Mycobacterium Growth Indicator Tube (MGIT) culture (Bekton Dickinson). Specimens were centrifuged at 4,000 X *g* and the sediments were washed with sodium hydroxide to a final concentration of 2% for 15 minutes. After neutralization with phosphate buffer (pH 6.8), 0.5 ml of the centrifuged sediment was pipetted into a Bactec MGIT 960 system tube containing Enrichment supplement (0.8 ml; MGIT system oleic acid-albumin-dextrose-citric acid) and an antimicrobial supplement (MGIT system PANTA [polymyxin B, nalidixic acid, trimethoprim, and azlocillin]) and incubated. The MGIT system was programmed for 7 weeks incubation at 37°C. Positive samples were remove from the machine and subjected to ZN staining for confirmation.

4.2 Ascites

Fluid was tapped from those with ultrasound proven ascites and the specimen was centrifuged at 4,000X *g*. Sediments were washed and prepared as above.

4.3 Biopsies

Laparoscopies were done under general anaesthesia. Two or three 10mm and 5mm ports were used to insert biopsy forceps through which biopsies were taken. Colonoscopy was performed under sedation with an Olympic FG-10 scope and biopsies were taken from the ileocaecal region or any abnormal site. Two biopsies were fixed in 10% formalin, embedded in paraffin wax, and subjected to histopathological examination, PAS, and ZN staining. The other part was placed in saline and submitted for MGIT culture. These specimens were teased with sterile surgical blades and homogenized in a sterile homogenizer for 15minutes. The vial was centrifuged at 4,000 X *g*. The sediment obtained was washed and prepared as the above.

4.4 Quality control

A known ZN positive control slide was stained simultaneously with the test slide and the same was done for PAS staining. Each batch of MGIT system tubes was controlled for support of growth by using *M. tuberculosis* ATCC 27294, *M. kansasii* ATCC 12478, and *M. fortuitum* ATCC 6841 and quality controlled for L-J media was carried out using *M. tuberculosis* H37Rv standard strain.

Chapter 5

5.0 RESULTS

5.1 General description of results

Over the period from September 2005 to May 2006, 5609 subjects that were admitted to the medical wards at University Teaching Hospital (UTH) were evaluated. Of these 162, fit the inclusion criteria, but 129 did not complete the algorithm (35 had been on ATT for more than a month, 30 were too sick, 25 were discharged, 22 were HIV negative, 8 died without autopsy, 7 refused, and 4 did not return for surgery).

The study population consisted of 31 patients (23 females and 8 males). The age range was 18-54 years and the mean was 33.1 years. All patients were black Zambians. Their CD4+ count range was 7-490 cells/uL and the mean was 125 cells/uL (Figure 2).

Of the 31 patients studied, 22 patients (70.97%) (15 females and 7 males) had evidence of abdominal TB. 9 had no evidence of tuberculosis and the ratio of female to male in this group was 8:1. Laparoscopy was performed on 23 of the study subjects, colonoscopy on 5, and final diagnosis was made at autopsy for 3 patients who died before laparoscopy could be carried out. A diagnosis of HIV was made during this process of evaluation for 14 (42%) of the study subjects. Three (13%) of TB subjects admitted recent contact with another TB person. Eight (36.36%) of abdominal TB patients had night sweats. For the TB patients

that had a full blood count available, the mean haemoglobin was 9.8 (2.7)g/dl. The mean leucocyte count was 5.1(2.2) x 10^9 / litre. The mean lymphocyte and neutrophil count were 22.5 (15.8)% and 72.0 (15.9)% respectively. The mean CD4 count was 92 (114.7) cell/ µl.

The 9 remaining study patients had the following diagnosis: 2 had diarrhoea of unknown cause, 1 had lymphoma, and 6 had no conclusive diagnosis following laparoscopy and histopathology of samples taken. The 2 patients that had diarrhoea presented with fever and weight loss, each had been having loose stools everyday for more than 4 weeks and had abdominal tenderness. Both patients submitted 3 stool samples which showed no organisms and had no positive findings on abdominal ultrasound. Both had colonoscopies that revealed normal bowel and biopsies that showed normal mucosa. The patient with lymphoma presented with fever, weight loss, diarrhoea for 2 weeks, 3L of chylous ascites, hepatomegaly, mesenteric masses, fibrous stranding throughout the abdomen, and abdominal lymphadenopathy. The final histology result was T cell type lymphoma. One of the patients with no diagnosis presented with fever, weight loss, abdominal tenderness, abdominal lymphadenopathy and a mesenteric mass. Biopsies of mesenteric mass showed non-granulomatous inflammation. The patient subsequently died and the family refused an autopsy.

Figure 2

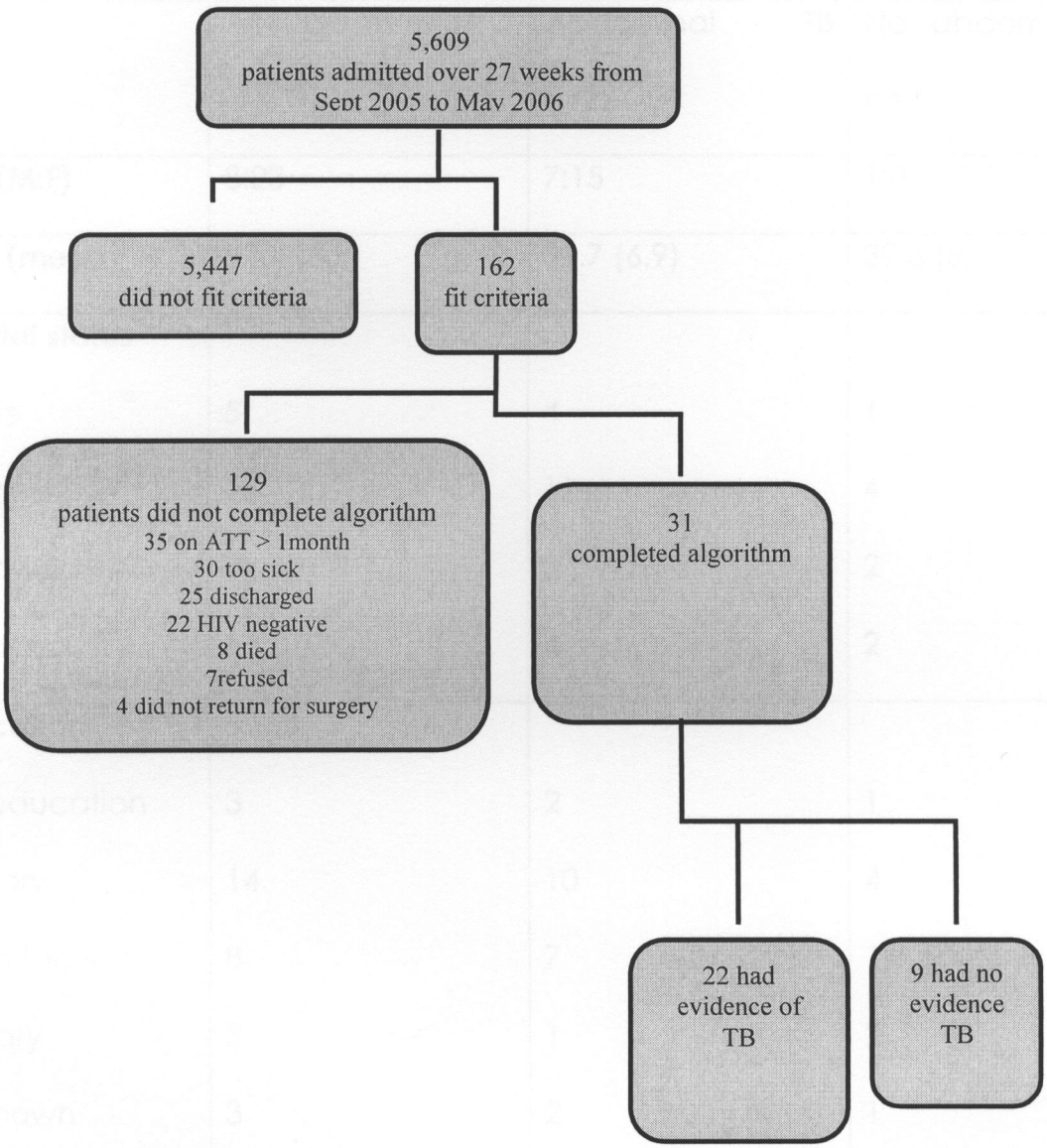

5,609
patients admitted over 27 weeks from
Sept 2005 to May 2006
5,447
did not fit criteria
162
fit criteria
129
patients did not complete algorithm
35 on ATT > 1month
30 too sick
25 discharged
22 HIV negative
8 died
7refused
4 did not return for surgery
31
completed algorithm
22 had
evidence of
TB
9 had no
evidence
TB

Table 1. demographic data

	All subjects n=31	Abdominal TB n=22	No abdominal TB n=9
Sex (M:F)	8:23	7:15	1:8
Age (mean)	33.4 (8.3)	30.7 (6.9)	39.8 (8)
Marital status			
Single	5	4	1
Married	15	11	4
Widowed	5	3	2
Divorced	6	4	2
Education			
No education	3	2	1
Primary	14	10	4
Secondary	8	7	1
Tertiary	3	1	2
Unknown	3	2	1

Table 2. Haematological profile

	All subjects	Evidence of TB	No evidence of TB	P value
CD4 count (mean) cell/µl	125 (127.8)	92(114.7)	194 (133.9)	0.05
Percentage of CD4 count ≤ 100	60	76	25	
Haemoglobin (mean) g/dl	9.0 (2.4)	9.8 (2.7)	8.5 (1.7)	0.24
Lymphocytes (mean) %	26.5 (21.9)	22.5 (15.8)	34.6 (31.0)	0.35
Platelets (mean) 10^9 /litre	224.3 (122.6)	232.4 (128.9)	204.6 (112.4)	0.82
Leucocytes(mean)10^9 /litre	6.3 (5)	5.1 (2.2)	8.9 (8.1)	0.24
Neutrophils (mean) %	66.3 (21.3)	72.o (15.9)	51.5 (29.8)	0.09

5.2 Clinical features

All patients were fully assessed according to the history and examination. The results in table 3 showed that the majority (86%) of those that had abdominal tuberculosis presented with abdominal pains and had tenderness. 8 (36) patients with abdominal TB complained of diarrhoea lasting for one or more months while 9 (41%) had generalised lymphadenopathy. 8 (36%) had night sweats, 5 (23%) had clinical pallor and 3 (14%) were jaundiced on presentation.

Table 3. clinical features of study patients (n=31)

Clinical feature	TB pos (N=22)	TB neg (n=9)
Abdominal tenderness	19 (86%)	9
Generalised lymphadenopathy	9 (41%)	3
Diarrhoea	8 (36%)	3
Night sweats	8 (36%)	3
Pallor	5 (23%)	5
Jaundice	3 (14%)	3

5.3 Culture of Blood and Ascitic Fluid

Although blood culture has been found to be a useful diagnostic tool, in this study none of the 22 TB patients had positive MGIT blood cultures. Of the 16 (52.7%) TB patients that had ascites, 3 patients (19%) had a positive ascites MGIT culture.

5.4 Ultrasound findings

A great majority of the abdominal TB patients had ascites and/or fibrous stranding. Table 4 shows the ultrasound findings in the TB positive subjects. Lymph nodes varied in size from 1.1cm X 1.8cm to 2cm X 3cm and were found in the para-aortic or portal hepatic region.

Table 4 Ultrasound findings of study patients (N=31)

	TB pos (N=22)	TB neg(N=9)
Finding	No. (%)	No.
Ascites	16 (72.7%)	6
Ab Lymphadenopathy	9 (40.9%)	4
Hepatomegaly	8 (36.36%)	2
Splenomegaly	1 (4.54%)	1
Mesenteric Mass	6 (27.27%)	1
Pancreatic Mass	0	0
Fibrous Strands	12 (54.54%)	2

5.5 Controls

None of the controls (all HIV positive) had abdominal lymhadenopathy, ascites, organomegaly or any abdominal mass on ultrasound. The average age (years) was 37 for the controls against 33 for the active subjects and average CD4 count (cell/μl) was 276 and 125, respectively. The Male:Female (M:F) SEX ratio was 8:20 and 8:23, respectively.

Table 5. Controls

	Active subjects (n=31)	Controls (n=28)
Sex (M:F)	8:23	8:20
Age (mean)	33. (8.3)	37 (9.3)
CD4 count (cell/μl)-mean	125 (127.9)	276 (192.6)
Percentage of CD4 count ≤ 100 cell/μl	60	21

5.6 Laparoscopic Findings

The laparoscopic findings varied widely in the subjects that underwent the procedure. Of these patients, 2 had to have a conversion to a mini-laparotomy because of too many adhesions. Descriptions of laparoscopic finding are shown in Table 6. The quantity of ascites varied from 1.6L to 5L. Of the 17

patients with ascites, 88% had straw coloured ascites and 12% had yellowish-green coloured ascites.

Table 6. Laparoscopic Findings in TB patients

Finding	No.	(%)	CD4+cour
Ascites with tubercles covering the parietal peritoneum	1		-
Ascites with tubercles covering omentum and liver	1		139
Ascites, a retroperitoneal mass, and tubercules covering the bowel	2		49
Ascites, peritoneum covered with pus and caseating mesenteric lymph nodes	1		-
Fibrous stranding in the ileal-cecal region and granulation and ulceration covering spleen	1		41
Fibrous stranding around pale liver with small yellow ulcerations	1		214
Fibrous stranding around liver covered with a few tubercles	1		92
Fibroadhesive peritonitis with ascites	1		128
Fibroadhesive peritonitis with tubercles covering bowel, omentum, and peritoneum	3		48, 14
Ascites, fibroadhesive peritonitis with a mass in ileal cecal region and tubercles covering liver and peritoneum	1		47
Fibroadhesive peritonitis with irregular peritoneum and matted bowel in ileal cecal region	1		35
Ascites, fibroadhesive peritonitis, mesenteric lymph nodes, and tubercles covering small bowel and omentum	1		20
Ascites, thick fibrous sheet covering lever, irregular peritoneum and tubercles covering bowel	1		7
Ascites and white liver ulcerations	1		35
Ascites, discolored liver and caseating mesenteric lymph nodes	1		490
Fibroadhesive peritonitis and mesenteric lymph nodes	1		49
Ascites, fibroadhesive peritonitis and tubercles on bowel	1		103

- indicating missing CD4 count

5.7 Colonoscopy Findings

Of the three TB patients that had colonoscopies, one had a classical appearance of TB with nodular ulceration around the ileal-cecal valve. The second had non-specific inflammation in the caecum. The third had a normal appearing bowel.

5.8 Diagnosis of TB

TB was diagnosed by both MGIT culture and microscopy in 6 patients (27.27 %). MGIT culture alone was used to make a diagnosis in 8 patients (36.36%). Of the 14 that had positive MGIT culture results, 8 also had positive L-J culture results. Microscopy was the method of diagnosis in 2 patients (9%). Visual appearance plus improvement on ATT was used to diagnose 6 patients (27.27%) (Table 7). Of the 22 patients, visual appearance either via laparoscopy or colonoscopy was accurate in 18 (81%) of patients. The length of time for diagnosis via MGIT culture ranged between 3 days and 42 days. The length of time for diagnosis via microscopy ranged from 21 days to 48 days.

Table 7. Method of Diagnosis for TB Patients

Method	No. (n=22)
Culture alone	8
Culture and microscopy	6
Microscopy alone	2
Visual appearance plus improvement on ATT	6

5.9 Autopsy results

Twenty post-mortems were conducted on subjects who were suspected to have died from pulmonary TB, abdominal TB or disseminated TB. Sex ratio of male /female was 9:11 and mean age was 34.8 (6.4) years.

These results show that there were more disseminated tuberculosis cases than just pulmonary or abdominal tuberculosis. The clinical features do not quite correlate with autopsy findings.

Table 8 **Autopsy results**

Clinical suspicion of TB	n=20	Pulmonary TB	Abdominal TB	Disseminated TB	No Tuberculosis
Pulmonary TB	10	1	1	2	6
Abdominal TB	7	1	1	5	0
Disseminated TB	3	0	0	3	0

Chapter 6

6.0 Discussion

The dual epidemic of HIV and tuberculosis is probably the biggest single challenge facing health workers in sub-Saharan Africa. It has been known for many years that increasing immunodeficiency changes the clinical presentation so that extrapulmonary TB comes to dominate the clinical picture, and abdominal TB is an important manifestation of extrapulmonary TB [14,17,19] . Current HIV seroprevalence in Lusaka province is probably close to the 2002 estimate of 22%[69]. Defining the incidence or prevalence of abdominal TB is fraught with difficulties. Abdominal TB at a population level can not be estimated but this data suggest a large and under-diagnosed disease burden amongst HIV positive adults.

In this study the subjects affected ranged in age from 18 to 46 years and there was a predominance of women over men (23:8). The mean age was 33.3 and 48% were married , 16% single, 5% widowed and 19% divorced.

While fever and weight loss are important features of abdominal tuberculosis, this study revealed that abdominal pain/tenderness 19 (86%) is quite a good predictor of abdominal tuberculosis in the presence of fever and weight loss. This study shows that abdominal TB can affect single organs as well as multiple organs and can manifest itself in various ways. In contrast to a previous study[70] ascites was the second most common (72.7%) manifestation in these HIV positive patients. The commonest clinical feature was abdominal tenderness

(86.36%) which is in conformity with literature review[26]. Fibrin strands with ascites were also a common feature in subjects with abdominal TB accounting for 54.54%. In contrast to the expectation quite a low number (40.9%) of abdominal TB subjects had abdominal lymphadenopathy. This could be attributed to technical error as a result of massive ascites and excess bowel gas in some subjects. Of all the abdominal TB cases none had pancreatic mass on abdominal ultrasound and so was on laparoscopy although it has been described[71]. Abdominal ultrasound also revealed a small number of mesenteric masses (27.27%) and this could also be attributed to technical error due to excess gas or ascites.

Although at laparoscopy a miliary picture was frequently observed, no mycobacteria were cultured from any of the blood samples. It is suspected that this may have been a technical issue, although one cannot be sure. In this study positive culture of the ascitic fluid for tuberculosis was quite low (13.6%) which is in conformity with general knowledge about low yield of bacilli in ascitic fluid, although this low yield could also be attributed to the to the low quantity of ascitic fluid (10mls) examined from each subject, Singh *et al*[45]. Literature available indicates that about 11-20 per cent of patients with abdominal tuberculosis present with diarrhoea, but this study revealed 36.36 per cent. No conclusion can be made since the trend is more less the same especially that the number of subjects in this study was small.

Straw coloured ascites is associated with abdominal tuberculosis as most of the subjects with abdominal TB with ascites had straw coloured fluid. The range of the amount of ascites was 1.6-5 litres on laparoscopy. This wide range could be attributed to late presentation to the hospital as well as disease activity in different subjects. Although literature says ileocaecal TB is the commonest presentation of gastrointestinal TB, this study revealed few cases of it and many cases had peritoneal TB. Not all subjects under went colonoscopy, only if diarrhoea was prominent and this could account for few cases of ileocaecal tuberculosis detected in this study. CT scan and barium studies were not employed in this study as these may help in the diagnosis of ileocaecal Tuberculosis.

6.1 Level of immunodeficiency

These data suggest that abdominal TB occurs most frequently in subjects with CD4 count of less than 100cell/μl. The mean CD4 count for all study subjects was 125(128). The mean CD4 count for those with abdominal tuberculosis was 92 (114) and those without TB was 194(134). This translates into borderline significance (P=0.05) by Kruskal-Walis calculation. In a study from Brazil the mean CD4+ count of patients with extrapulmonary TB was 184[19], this could be a genuine biological difference or could be attributable to my patients having more advanced disease at presentation.

6.2 Diagnostic markers

It is important in a setting such as ours, with limited resources and high HIV and TB co-infections rates, for physicians to have a high clinical suspicion of abdominal TB. Due to the difficulties in differentiating its non-specific presenting features and difficulty of diagnosis, the algorithm used could be of a lot of help. This study showed that [71%] of patients that fit our algorithm had abdominal TB, which indicates that it is an effective tool to use.

In patients with fever and weight loss, the most predictive diagnostic markers were ultrasound findings of ascites (73%) and fibrous stranding (55%).

Although abdominal lymphadenopathy was not the commonest (41%), it is important to note that no controls had abdominal lymphadenopathy, so this finding may lead to the conclusion that HIV on its own may not explain abdominal lymphadenopathy hence other causes including TB should be looked for.

Ascites culture was only positive in 13.6% of patients with this clinical feature. This result was lower than that found in other studies[53], but it should be noted that these studies did not separate findings among HIV positive and HIV negative patients.

In this study blood culture was not a useful diagnostic tool. It may be that the MGIT system is less effective for blood than for sputum or tissue.

Table 6 shows the diverse range of diagnostic appearances with laparoscopy of abdominal TB, including TB solely affecting the liver, spleen, peritoneum, bowel, as well as a combination of these organs. In other laparoscopic studies, abdominal TB is categorized in discrete presentations. Bhargava *et al.* defines peritoneal TB into three types, but this study does not fit such a clean pattern[44]. It is not clear whether this is due to findings being subjective or whether it is because all the patients were HIV positive. For patients that underwent colonoscopy, it was noted that it is possible for normal looking mucosa to be colonized by *M. tuberculosis*, occurring in 1 out of 5 patients. In the patient with positive visual findings it was noted that the appearance was similar to other descriptions[10], including nodular ulceration in the ileal-cecal region.

6.3 Autopsy

Autopsy results showed that the number of patients dying from disseminated tuberculosis was higher than those dying from either pulmonary or just abdominal tuberculosis. This could be due to the over whelming HIV infection in the subjects considered or due to the fact that the subjects presented to the hospital late. It was not possible to ascertain if the same species of Mycobacteria Tuberculosis was responsible for both pulmonary and abdominal tuberculosis in the same subject as polymerase chain reaction (PCR) was not used.

The clinical features did not correlate so much with autopsy findings (table 8), this could be due to co-infection with HIV.

Chapter 7

7.1 Conclusions

Abdominal tuberculosis is a common manifestation of extra pulmonary tuberculosis in HIV/ AIDS patients. The frequency of abdominal tuberculosis in this study was 71%. It leads to acceralated wasting and death if not diagnosed early and treated. In a poor resource set up like here, high index of suspicion is very important. This emphasises good history and physical examination. Hence an algorithm as in figure 1 is a good tool for making a diagnosis of abdominal tuberculosis especially for a poor resource set up.

In this set up where patients can not afford expensive diagnostic tools like CT or MRI scanning, abdominal ultrasound is a good tool to use (table 4). Laparoscopy with biopsy is a confirmatory tool that can be used in abdominal tuberculosis (table 6).

Abdominal tuberculosis is associated with severe immunodeficiency. The average CD4 count in subjects with abdominal tuberculosis was 92 cell/ μ litre in this study.

Abdominal lymphadenopathy in HIV positive patients should be investigated for the cause as may not necessarily be due to HIV as none of the controls in this study had abdominal lymphadenopathy on ultrasound.

7.2 Recommendations

1. An algorithm (figure 1) is necessary to make it easy for diagnosis of abdominal tuberculosis especially for poor resource set up areas that are affected with HIV/AIDS.
2. Governments to make ultrasound machines readily available especially in African set up where tuberculosis is on the increase due to HIV/ AIDS pandemic.
3. Trainings in ultrasonography need to be enhanced.

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