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Tuberculosis and HIV Coinfection in Two Districts in Somaliland

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ACADEMIC DISSERTATION
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List of abbreviations

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ARTI	annual risk of TB infection
ARV	antiretroviral
BCG	bacillus Calmette-Guerin
CI	confidence interval
CFR	case fatality ratio
DNA	deoxyribonucleic acid
DOTS	directly observed treatment short course
EuroHIV	European Centre for the Epidemiological Monitoring of AIDS
HIV	human immunodeficiency virus
IPTCS	intervention prevention treatment and care services
MBT	mycobacterium tuberculosis
MCH	maternal and child health
MDR	multi-drug resistance
NRTI	nucleoside analogue reverse transcriptase inhibitors
NNTI	non-nucleoside reverse transcriptase inhibitors
NTM	non-tuberculosis mycobacterium
PAF	population attributable fraction
PI	protease inhibitor
PYR	person-year
RNA	ribonucleic acid
SIV	simian immunodeficiency virus
STD	sexually transmitted disease
TB	tuberculosis
UNAIDS	United Nations Programme on HIV/AIDS
VA	verbal autopsy
VCT	voluntary counselling and testing
WHO	World Health Organization

Summary

The objectives of the study were to assess human immunodeficiency virus (HIV) prevalence among patients with tuberculosis in Somaliland and analyse the differences in disease characteristics, smear conversion and treatment outcome between HIV seropositive and seronegative tuberculosis (TB) patients.

The study was conducted in two main TB centres in Somaliland, Borama and Hargeisa from January 2003 to August 2004. A total of 839 patients treated in these centres were enrolled, 31 patients withdrew from the study and 8 cases were excluded for not fulfilling the study criteria. Data on HIV serological testing and follow up of sputum smear conversions and treatment outcome was obtained for 800 TB patients.

Age groups 15–24 and 25–34 years comprised 66% of the TB patients. Age distribution was similar among men and women. The majority of the patients were residents of Borama and Hargeisa districts.

Of the patients 81.5% (95% 78.4–83.8) had pulmonary and 18.5% (95% CI 16.2–21.6) extrapulmonary tuberculosis. Of the patients with pulmonary disease, 73% (95% CI 69.5–76.3) were smear-positive cases and 27% (95% CI 23.6–30.4) smear-negative. Hargeisa TB centre had a higher proportion of pulmonary smear-negative cases compared to Borama (34% versus 14%).

Among 800 TB patients tested for HIV infection, 10.9% (95% CI 8.9–13.2) were HIV seropositive. In Borama, the HIV seroprevalence was 14.5% (95% 10.9–19.0) and in Hargeisa 8.8% (95% CI 6.6–11.6). Among 536 men and 264 women, HIV prevalence was 11.1% (95% CI 8.8–14.1) versus 10.2% (95% CI 7.1–14.1). Occupation and marital status were also associated with HIV infection.

The disease characteristics among the 713 HIV seronegative TB patients showed that 81.5% (95% CI 78.4–84.1) were pulmonary and 18.5% (95% CI 15.8–21.5) were extrapulmonary, while the corresponding figures among the 87 HIV seropositive patients were 79% (95% CI 69.6–86.4) and 21% (95% CI 13.5–30.3). Among the 581 HIV seronegative pulmonary TB patients, 76% (95% CI 72.9–79.8) were smear-positive and 24% (95% CI 20.1–27.0) smear-negative. Among the 68 HIV seropositive pulmonary TB patients, 44% (95% CI 32.4–55.2) had pulmonary smear positive disease and 56% (95% CI 44.7–67.5) pulmonary smear-negative TB.

Smear results at 5/6 months of TB treatment were obtained from 411 TB patients with smear conversion in 97% (95% CI 94.6–98.2). Treatment outcome was obtained from 800 TB patients and among them 50% (95% CI 46.2–53.2) were cured, 31% (95%

CI 28.0–34.4) completed treatment, 4.5% (95% CI 3.2–6.1) died, 2.4% (95% CI 1.0–2.9) failed, 2.5% (95% CI 1.6–3.8) defaulted, 4.4% (95% CI 3.1–6.0) transferred and 6% (95% CI 4.5–7.8) could not be evaluated.

No smear conversion was reached at 2/3 months of TB treatment for 12% of the HIV seropositive and 6% of the seronegative TB cases (odds ratio, OR 1.9, 95% CI 0.43–7.38). No difference was observed between HIV seropositive and HIV seronegative TB in smear results at 5/6 months of TB treatment, with failure rates of 4% versus 3% (OR 1.3, 95% CI 0.46–9.75). Treatment failure rates among HIV smear-negative and HIV smear-positive TB were 62% versus 27%. HIV smear-negative TB patients had more frequent failures (OR 4.44, 95% CI 1.36–14.96).

HIV seroprevalence among the TB patients in Somaliland has increased. The national prevalence among TB patients was 4.7% in 1999, while the seroprevalence in the current study was 10.9%. The figures of Borama TB centre were 10% in 1999 and 14.5% in 2003. In Hargeisa, seroprevalence increased from 7% to 8.8%. No difference was found between HIV seropositive and seronegative patients in disease characteristics (pulmonary and extrapulmonary). The proportion of smear-negative TB was higher among the HIV seropositive. The treatment outcome was poorer among the HIV seropositive patients. It is recommended to start sentinel sites for HIV surveillance in the TB centres.

1. Introduction

Tuberculosis and HIV co-infection is recognized as a major setback to both tuberculosis and HIV infection control programmes (Godfrey-Faussett et al. 2002). HIV infection is also a strong risk factor for tuberculosis and contributes to the development of active TB from latent and exogenic re-infection (Corbett et al. 2003). Globally incidence of tuberculosis is estimated at 8 million new cases yearly with 3 million deaths (De Cock et al. 1996). An increase of tuberculosis incidence has been observed in the countries with a high prevalence of both tuberculosis and HIV infection (Chum et al. 1996). Tuberculosis and HIV co-infection has a negative impact on TB control programme by increasing case load due to excess incidence attributable to HIV infection (Corbett et al. 2003). Case definition and diagnosis of tuberculosis is altered in TB and HIV co-infection. This can contribute to underdiagnosis or overdiagnosis of smear-negative disease. Delay of diagnosis could increase the case fatality ratio, CFR (De Cock et al. 1996, Mukadi et al. 2001). Multidrug resistance and lower treatment response has been observed among TB/HIV co-infected patients (Weltman and Rose 1994), resulting in increased tuberculosis mortality and CFR (Mukadi et al. 2001). Tuberculosis and HIV co-infected cases have lower treatment compliance and more frequent adverse drug reactions and intolerance to drug ingestion, which further impairs the treatment outcome (Pozniak et al. 1999). The co-infected cases could be a source for HIV transmission to TB patients in health services through inadequate sterilization of instruments for treatment procedures (World Health Organization (WHO) 1989).

In addition to the burden of HIV and tuberculosis, malaria is another major infectious disease, which is an important cause of deaths in the developing countries (Adjuik et al. 2006). It is estimated that over 5.6 million people are killed by HIV/AIDS, tuberculosis and malaria yearly (Tan et al. 2003). Malaria causes more deaths among children and pregnant women than HIV and tuberculosis, which more commonly affect young adults and adults (Adjuik et al. 2006). The three diseases constitute the most serious health challenges in sub Sub-Saharan Africa. Malaria and tuberculosis have some features in common as both diseases originated in the prehistoric era, but nevertheless their control and eradication is difficult (Breman 2001, Carter and Mendis 2002). The malaria parasite has developed resistance to antimalarial drugs and the mosquito vector has also developed resistance to spraying agents (Carter and Mendis 2002). In tuberculosis, the appearance of MDR is a serious challenge to control (Trivedi 1988, Weltman and Rose 1994). After the failure of measures against

malaria and the new global pandemic of HIV/AIDS and combined HIV/TB infections, the international community has launched the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) in Okinawa (Tan et al. 2003).

Somaliland has a high prevalence of tuberculosis and an estimated incidence of 200/100,000 persons yearly. The annual risk of tuberculosis infection (ARTI) was estimated as 4% (Peltola et al. 1994). The prevalence of HIV infection among the population was estimated as 0.9% and among the blood donor and antenatal centres as 0.8% (WHO 1999). The first HIV-infected cases were reported among Somali refugees Ethiopia in the early 1990s (Salama and Dondero 2001). Information from antenatal sentinel sites, population surveys, surveys on risk groups and TB patients are considered to contribute to the surveillance and are informative on the trend of HIV infection (WHO 2002). The age groups most affected with HIV among the TB patients are those with the highest seroprevalence in the population, 15–24 and 25–34 years. Women have higher HIV prevalence than men in the age groups 15–24 years, as they have earlier sexual contact than men and their partners are frequently older (Elliott et al. 1990, Chum et al. 1996, Pettifor et al. 2004).

In Somaliland, few studies on HIV prevalence among TB patients have been conducted and no earlier data are available on the effect of HIV on clinical manifestations, smear conversion, treatment outcome and disease pattern. HIV and TB control programmes could benefit from surveys on prevalence and data from sentinel site. Information on the trend of HIV prevalence in the population and TB patients will be important for planning adequate interventions in both tuberculosis and HIV control.

In this study, HIV prevalence among TB patients was assessed and the difference in disease presentation (pulmonary/extrapulmonary and sputum smear-positive and negative disease) was examined for HIV-seropositive and seronegative TB patients. The smear conversion rates after 2/3 and 5/6 months of treatment were evaluated and treatment results after 6/8 months treatments were reported.

2. Literature review

2.1 Approach to the literature review

The reports included in the literature review were selected from the published studies on the occurrence, disease pattern and treatment outcome of combined tuberculosis and HIV infection. Recent results were a priority and older studies were used when no newer data were available. The articles selected were published in English either in electronic or printed form by medical journals. The main electronic collections were Medline, WHO Internet sites and the UNAIDS virtual database. Studies on the impact of HIV infection on tuberculosis disease presentation, such as pulmonary smear-positive and smear-negative tuberculosis were emphasized. Literature on the treatment outcome in HIV seropositive and seronegative tuberculosis was reviewed. The global and specifically Sub-Saharan African prevalence of tuberculosis and HIV co-infection was sought for making comparison with the study in relation to international and regional burden. The published literature on the global trends of tuberculosis in the era of HIV/AIDS pandemic was reviewed. Studies on TB co-infection and on TB/HIV prevalence in Somaliland were covered to identify gaps in the literature concerning the Somali situation. Results from the neighbouring countries were cited to assess consistency and differences. Literature on the influence of co-infection and on drug susceptibility and survival after TB treatment was appraised from the selected articles. References were made to available data on the different interventions on the prevention and care of tuberculosis and HIV co-infection to complement the care that can be planned beside TB treatment of the co-infected. The items for the literature review were selected according to the pertinence to the aims of the study and in accordance with the gaps in knowledge in the existing literature. The main limitation observed was lack of studies on the effect of co-infection on treatment outcome and smear conversion. There were few studies on co-infection in Somalia and no prior study on the impact of HIV on tuberculosis disease manifestations. At the international level there were some studies on the treatment and smear conversion results of the HIV seropositive and seronegative TB.

2.2 Aetiological agents and pathogenesis of tuberculosis and HIV infections

The aetiological agents of HIV and TB share some characteristics; immunity to both diseases is cell-mediated and both have long latent periods so that disease may manifest only after several years since acquiring the infection. The aetiological agent of tuberculosis is mycobacterium tuberculosis and the causative agent of HIV is a retrovirus (Barre-Sinoussi et al. 1983, Drobniewski et al. 2003).

2.2.1 Tuberculosis aetiology

Robert Koch discovered the Tuberculosis bacilli in 1895 and presented his finding on the aetiology of tuberculosis in a famous paper to the Physiological Society of Berlin. His description of the method of staining specimen slides, the method of culturing and inoculating of the bacilli into animals was a major advance in the understanding of TB bacteriology. The discovery enhanced further the development in finding a remedy for tuberculosis (Sakula 1982).

Mycobacterium tuberculosis belongs to the genus Mycobacterium. The genus is classified into the Mycobacterium tuberculosis complex, which produces tuberculosis diseases in humans and other non-tuberculosis-Mycobacteria species or opportunistic Mycobacteria which can produce disease in immunocompromised individuals (Wayne 1982, Drobniewski et al. 2003). The Mycobacterium complex includes mycobacterium tuberculosis, M. bovis, M. microti and M. canetti and M. africanum (Wayne 1982, Drobniewski et al. 2003).

Mycobacterium tuberculosis is epidemiologically the most important species because it causes tuberculosis in humans and is responsible for tuberculosis infection worldwide. M. bovis can also infect man, but is mainly responsible for TB disease in cattle and goats. M. microti is infectious to some rodents, but occurrence of human infection is unclear. The recently discovered M. canetti can also infect humans (Niemann et al. 2000a).

Non-tuberculosis or opportunistic Mycobacteria includes M. aviam and M. intracellulare. Non-tuberculosis Mycobacterium (NTM) is responsible for some infections among immunocompromised patients.

Mycobacterium tuberculosis can be distinguished from other species with classification tests, which are based on oxygen preference, temperature, and Tween hydrolysis and also in modern settings spolligotyping analysis. Other characteristics of M. tuberculosis are growth in culture media after two weeks with eugonic growth, and optimum temperature is 37ºC. It is aerobic and sensitive to antituberculosis

drugs. It grows in semi-solid medium and no pigmentation is produced (Marks 1972, 1976, Niemann et al. 2000b).

2.2.2 Pathogenesis of tuberculosis

Mycobacterium tuberculosis is transmitted by airborne nuclei droplets. The droplet is passed into the air, when a person infected with pulmonary tuberculosis coughs, sneezes or speaks (Bass et al. 1990). When a healthy individual inhales the bacilli, the first implant is in the lungs at bronchiole or alveolar level. The bacilli multiply and produce the primary lesion there. Some bacilli pass into the hilar lymph nodes causing lymph node enlargement. The bacilli from the alveolar lesion, the Ghon focus and from the enlarged hilar lymph nodes can be more widely disseminated via the lymphatic system or bloodstream, leading to serious complications such as meningitis, bone, joint and renal tuberculosis (Festenstein and Grange 1991). The host response to tuberculosis is through cell-mediated immunity, and the cells involved include macrophages and T-lymphocytes. The lymphocytes recognise TB antigens and release cytokines such as gamma interferon, which activates macrophages at the site of the lesion (Riley 1982).

Hypersensitivity to the organism appears at 8–10 weeks and the infected individual becomes tuberculin-test positive. It is estimated that 10% of infected individuals develop clinical tuberculosis during their lifetime. Around 50% of them will develop TB during the first years of infection and the rest many years later (Bass et al. 1990).

2.2.3 Aetiology of HIV infection

The causal agent of HIV infection and AIDS is a lentivirus of the retrovirus family. There are two human HIV viruses, HIV-1 and HIV-2. HIV-1 is the aetiological agent of most cases of HIV infection worldwide and HIV-2 is mainly confined to West Africa (Peeters and Sharp 2000).

The first description of the acquired immunodeficiency syndrome was made in 1981. The HIV virus was discovered and isolated in Paris at the Pasteur Institute. The virus was obtained from cultured T lymphocytes of patients with lymphadenopathy (Gallo and Montagnier 2003). The Besthand Myrland Centre developed a specific factor for culturing T lymphocytes, which was essential for isolating retroviruses. Gallo and colleagues further proved the HIV virus as the cause of HIV and contributed to the development of HIV testing (Gallo 2002). Recent

studies have demonstrated that the diversification of HIV-1 in West and Central Africa occurred long before the current AIDs pandemic. Phylogenetic analysis of viral sequences, DRC60 and ZR59 date them to near the earliest days of the twentieth century (Worobey et al. 2008).

With phylogenetic analysis, HIV is subdivided into groups, types, subtypes and still further into sub-subtypes. HIV-1 is classified at the group level into the categories (M, N; and O). Group M is the most widely distributed and is considered to be responsible for most of the international burden of HIV/AIDS. The M subgroup is further divided in A-D, F-H, and K subgroups (Peeters and Sharp 2000, Lal et al. 2005). HIV-2 is endemic in West Africa, and its transmission and pathogenesis are less severe than those of HIV-1.

In HIV-2, there are seven subtypes (A-G). The subtype A is prevalent in Senegal, Guinea-Bissau and subtype B is mainly found in the Ivory Coast (Peeters et al. 2000). Both HIV-1 and HIV-2 viruses are recognized to have zoonotic origin. HIV-1 is accepted to have originated from simian immunodeficiency virus (SIV) from chimpanzees, while the HIV-2 is related to SIV from sooty mangabeys (Peeters and Sharp 2002).

2.2.4 Pathogenesis of HIV infection

The HIV virus is formed of a core protein enclosed in gag protein, p24 and a two RNA structure. The viral structure also contains enzymes important for its replication, RNA reverse transcriptase and HIV-specific protease. The viral envelope carries the gp120 antigen, which is important for interaction with CD4 protein in the T-cells (Volberding et al. 2003). The HIV infects the CD4 T-cell and inflicts a decline of CD4 count. The CD4 contains receptors for HIV antigen, the chemokine receptors of CCR5 and CXCR4. HIV-infected macrophages attract T-cells and bring them in contact with the HIV virus (Weber 2001).

2.3 International burden of tuberculosis and HIV infections

2.3.1 Tuberculosis

Tuberculosis is the second most frequent cause of deaths among communicable diseases. The international prevalence of the TB infections is estimated at 1.8 billion and the number of new cases was 8.8 million in 2002 (Frieden et al. 2003, WHO

2004b). The estimated number of new cases in 2005 was 8.8 million and 9.2 million in 2006 (WHO 2007 and 2008). The number of deaths from TB in 2005 was estimated at 1.6 million (WHO 2007). There has been a major declining trend in tuberculosis in the developed countries of Western Europe and the United States during the 20th century already before potent chemotherapy was introduced mainly due to improved socioeconomic situation. In the United States, the incidence declined from 194 per 100,000 persons in 1900 to 40 per 100,000 persons in 1945 (Snider 1997). There was still a further decline in the United States and by the end of 1984, mortality dropped to 0.7 per 100,000 person-years and incidence decreased to 9.4 per 100000 (Snider 1997). In Britain, mortality declined from 313 per 100,000 persons in 1882 to 5 per 100,000 in 1972 (Miller and Thompson 1992).

The tuberculosis situation in the developing countries has not improved over the last century and the WHO declared tuberculosis an international emergency in 1991, and launched a new strategy to cope with the tuberculosis epidemic (Kochi 1991). There are marked differences between WHO regions in the current tuberculosis situation. The highest numbers of case notifications come from Africa and South East Asia. WHO ranks countries by number of cases and 22 developing countries account for 80% of TB cases. When countries were ranked according to incidence per capita, 13 African countries belong to the 15 countries with the highest incidence in the world (WHO 2003).

The annual risk of infection is high in the African countries and has not shown any downward trend similar to that in the industrialized countries. The age groups mostly affected by tuberculosis in the developing countries are 15–59 years, while in the industrialised countries the age groups most affected are 50 years and over (Christopher et al. 1999). The annual risk of infection has fallen in the developed countries to 0.1% or less, while in sub-Saharan Africa the estimate is 1.0–2.5%, indicating high rates of TB transmission.

The studies regarding the global trend during the period 1982 to 1992 showed an increase of tuberculosis cases estimated at 8 million new cases in 1990 (Figure 1). In the United States, the yearly incidence of TB cases increased slightly from 9.4 per 100,000 in 1985 to 10.3 in 1990. During the period 1985–90, the annual number of cases was increased by 51,500 compared with 1984 and earlier (Snider 1997). The HIV epidemic and emigration from high-prevalence countries could be the reasons for the increase.

During the same period an increase of TB notifications in other WHO regions of the world was observed. The notification rate increased by 20% to 30% worldwide from 1984–1986 to 1989–1991. The increase occurred in four WHO regions: Africa, Eastern Mediterranean, South East Asia and the Western Pacific region (Raviglione

et al. 1995). The increase in Eastern Europe was 5% per year in the same period (WHO 2004c). In African countries with a high HIV prevalence, the notification rate increased by 7% per year during period 1997–2002. The notification rate for tuberculosis increased in Kampala City, Uganda from 1980; which was associated with an annual increase of AIDS incidence from 10–20% (Festenstein and Grange 1991, Eriki et al. 1991). In Tanzania, there was an increase of registered TB cases during 1983–1993 by 160%. The extra cases were attributed to the HIV epidemic (Chum et al. 1996).

The burden of tuberculosis mortality is high globally with 1.6 million deaths from tuberculosis in 2005 (WHO 2007). Of the deaths from tuberculosis, 12% were attributable to HIV. Tuberculosis was the cause of 11% of all adult AIDS deaths worldwide. The majority of the deaths were in Africa with annual death rates of 75 per 100,000 person-years (Corbett et al. 2003).

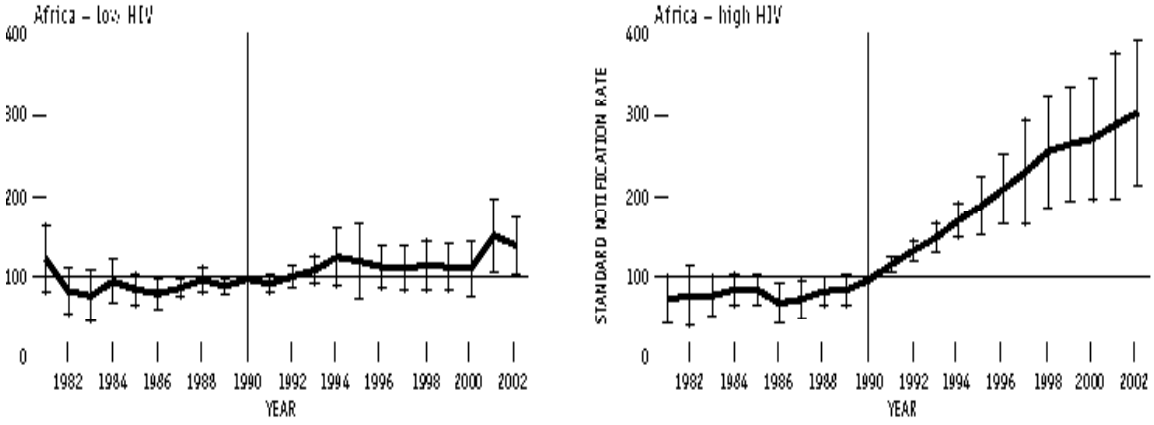

Figure 1. Trends in tuberculosis case notification rates in Africa showing high HIV countries (Southern, Eastern and Central African countries) and low HIV countries (Western and Northern African countries) between 1982 and 2002 (source: WHO Report 2004. WHO/HTM/TB2004.33.1).

2.3.2 HIV/AIDS

Data for HIV surveillance are mainly based on women attending antenatal care. Countries report the data to the regional WHO office. Data are also obtained from national surveys and from surveys in high-risk groups including sex workers, blood donors as well as STD and tuberculosis patients (WHO 2002). Data obtained through antenatal care information are regarded to represent HIV in the general population aged 15–49 years (Zaba and Gregson 1998).

The global estimate of people living with HIV/AIDS was 40 million in 2003 and the number of deaths totalled 3 million (UNAIDS 2003). There has been a global

downward trend in recent years and the number of people living with HIV or AIDS in 2007 was estimated at 33.2 million and the number of deaths at 2.1 million (UNAIDS 2007). The peak of the HIV pandemic was in the mid-1990s and worst stricken was Africa. The regions where the epidemic is also spreading are Sub-Saharan Africa, Asia and the Pacific, Eastern Europe and Central Asia, as well as Latin America and the Caribbean (WHO 2004c).

2.3.3 Sub-Saharan Africa

The number of people living with HIV in 2003 was 26 million and the number of deaths was 2.3 million (UNAIDS 2003). Sub-Saharan Africa still has the highest burden of disease and death from HIV with an estimated number of people living with HIV or AIDS was 22.5 million and deaths 1.6 million (UNAIDS 2007). Wide variation was observed between the sub-regions of Sub-Saharan Africa (UNAIDS 2003). The mostly heavily affected countries were in Southern Africa, where prevalence among pregnant women was >25%. The adult HIV prevalence was 39% in Botswana, 33% in Lesotho, 33% in Swaziland and 34% in Zambia (UNAIDS 2002). The prevalence among pregnant women has shown some improvement in some southern African countries in recent years. In South Africa, the seroprevalence has decreased from 30% to 29%, in Zimbabwe from 26% to 18% and highest prevalence of 38% in Lesotho (UNAIDS 2007). The HIV seroprevalence of pregnant women in Namibia increased from 4% in 1992 to 22% in 2002 and from recent data the prevalence appears stabilized (UNAIDS 2007). The HIV seroprevalence of pregnant women in Namibia increased from 4% in 1992 to 22% in 2002. The seroprevalence among women aged 18–35 years in Zimbabwe between 1999 and 2002 was 40% (Pettifor et al. 2004). The adult prevalence in Malawi was estimated to 16% in 2000–2001 (WHO 2002). South Africa is believed to face the most rapidly growing epidemic and seroprevalence among attendees of antenatal clinics increased from 0.8% in 1990 to 24.5% in 2000 (Hosegood et al. 2004).

East Africa was the first area to experience the spread of the HIV epidemic in the 1990s with seroprevalence among pregnant women reaching 10–15%. Studies in rural Uganda showed 16% HIV seroprevalence among adults aged 15–59 years (Sewankambo et al. 2000). In Tanzania, surveys from sentinel sites on pregnant women showed an increase of prevalence from 7% to 20% during the period 1994 to 1999 and then a decrease to 15% in 2000 (Jordan-Harder et al. 2004). In Ethiopia, the national HIV prevalence among pregnant women was 11% (WHO 2002).

In West Africa, the situation in Senegal was stable with 1% prevalence among pregnant women. Investment in the control of the epidemic has shown success in keeping the prevalence low. Other countries with a low prevalence (around 1%) included Gambia, Mauritania and Niger (UNAIDS 2003). The Ivory Coast was an exception, with the highest prevalence in West Africa and median prevalence 6–8% among pregnant women. In Nigeria, the prevalence among pregnant women increased from 3.4% in 1994–1995 to 4.7% in 1999 (WHO 2002).

2.3.4 Asia and the Pacific Region

In the Asian and Pacific region, the seroprevalence was low in 2001, but the epidemic was progressing with a prevalence of 0.6% of the population (UNAIDS 2001). Surveillance data for 2007 in East and South-East Asia indicated prevalences from 0.1% to 0.3%. In South and South-East Asia, the number of people living with HIV/AIDS was estimated to be 4.0 million in 2007 (UNAIDS 2007). In China, the number of people living with HIV was estimated at 840,000 in the year 2003 and prevalence among the general population was estimated at 1% in 2002, but the epidemic was spreading in certain provinces (WHO 2004d, UNAIDS 2003). In Korea, from the first HIV cases in 1985, the number of HIV cases increased to 1,280 in 2000 (Kim et al. 2003). The first case of HIV was detected in Vietnam in 1990 and the prevalence among drug users increased from 1% to 42% in 1995. A decline was observed in 1996 with a prevalence of 37% (Lindan et al. 1997). Thailand was successful in controlling the epidemic with a 100% condom use programme and the prevalence was 2% in 2002. The prevalence among military conscripts decreased from 4% in 1990 to 1% in 2002 (UNAIDS 2003).

2.3.5 High-income countries

The number of people living with HIV is increasing mainly because of wide provision of antiretroviral drugs. The number of people living with HIV was estimated at 1.6 million in 2003. The number of deaths declined also because of treatment with antiretrovirals. The estimated number of people living with HIV/AIDS in the United States was slightly above 1 million in 2003 (CDC 2006a). The proportion of the HIV infections among the ethnic minorities increased during 2001–2004 and blacks accounted for 50% of the new cases and the Hispanic for 20% (CDC 2006b). The proportion of women infected was also rising and one third of

new infections were through heterosexual transmission (UNAIDS 2003). The HIV seroprevalence in London increased from 0.003% in 1988 to 0.19% in 1996. Results from other cities in the UK were low, with exceptions in Edinburgh and Dundee, where initially the prevalence was high and then declined from 0.22% in 1990 to 0.088% in 1996 (Nicoll et al. 1998). In Western Europe, the number of new cases increased by 46% from 8021 cases in 1997 to 11,683 cases in 2002. Trends increased in Ireland by 234%, United Kingdom 111%, Finland 83% and Norway 74% (EuroHIV 2003). In Western and Central Europe, the prevalence reported in 2007 was 0.3%, with 760,000 people living with HIV/AIDS (UNAIDS 2007).

2.4 Impact of mortality on demographic and socio-economic indicators

The devastating impact of the HIV epidemic on adult and child mortality is seen in Sub-Saharan Africa, and particularly in Southern Africa and East Africa (WHO 2002, 2004). In a Ugandan study, mortality was 132.6 per 1000 person-years among HIV seropositive individuals and 6.7 per 1000 person-years among the seronegative. Infant mortality of babies of HIV-infected mothers and non-infected mothers was 209.4 and 97.7 per 1000, respectively (Sewankambo et al. 2000). Mortality studies in Namibia reported an annual increase of post-neonatal mortality in 1991 to 2000, from 13 to 77 per 1000. Adult mortality was high at ages 30–54 years among men and 25–49 years among women. The increased in mortality is believed to be attributable to AIDS (Doctor and Weinreb 2003, Notkola et al. 2004).

In South African, a rise in adult mortality was observed in the late 1990s. Mortality increased with age among young adults, with a five-fold increase in women and four-fold among men. The deaths were highest in the ages 15–19 years in women and 20–24 years among men. AIDS was the dominant cause of death, at 48% of all adult deaths (Hosegood et al. 2004). Verbal autopsy in Malawi revealed that 75.5% of VA deaths were attributable to AIDS, with 75% for women and 76% for men.

2.4.1 Child mortality

Reducing child mortality by two thirds by 2015 is one of the Millennium Development Goals of the World Assembly. This target will not be achieved with the current child mortality situation in Africa. The number of deaths from HIV infection

in children under 5 years in Africa was 330,000 in 1999. Mortality attributable to HIV was less than 5% and mortality rate was 30 per 1000 in five countries, Botswana, Namibia, Swaziland, Zambia and Zimbabwe. In another 16 countries, the under five mortality rate was 10–25 per 1000 and in 18 other countries the rate was under 10 per 1000 (Walker et al. 2002).

Gender difference in mortality was found in all studies. In a Ugandan study, women had higher population attributable fraction associated with the HIV in all age groups. In Namibia, the death rate of women was higher than that of men at ages of 25–49 years. In South Africa, the proportion of deaths from AIDS was higher among women than men, 52% among women and 44% among men (Sewankambo et al. 2000, Hosegood et al. 2004, Notkola et al. 2004).

The probability of dying between the first and the fifth year of life increased from 6 to 18 per 1000 children and the probability of dying between ages 15 and 60 increased from 220 to 550 per 1000 for men and from 95 to 335 per 1000 for women in 1993–2000 in Namibia (Notkola et al. 2004).

2.4.2 Socio-demographic impact

Mortality has been higher in the educated compared to uneducated population. According to employment, the most affected were military/police and students. In addition, a high attributable fraction was found among government technical employees and military/police with a PAF of 87.7% (Sewankambo et al. 2000). The attributable fraction due to HIV among HIV-positive widows was 89.6%.

Studies in Africa have shown the drastic economic impact of the HIV/AIDS epidemic. Mortality from HIV/AIDS has reduced labour supply. In South Africa, 60% of the mining manpower is between ages 30 and 44 years, and a 10% fall in manpower is predicted within 15 years. In the South African health sector, 20% of student nurses are HIV-infected (Dixon et al. 2002, Rosen et al. 2004). Labour productivity is also a major problem in Africa and annual cost due to sickness and loss of productivity was estimated at $17 per employee in Kenya and $300 in Uganda. Reduction of exports and increase of imports are predicted due to collapse of sectors of export production. The pandemic had a negative impact on general per capita production (GPP) and average economic growth rate was falling by 2–4% (Dixon et al. 2002).

In South Africa, the cost of labour is increasing and has weakened the competitiveness South African business on the international market. HIV prevalence in the labour force ranges from 7.9% to 25%. The extra cost on annual wages and

salaries due to AIDS was estimated to 0.4–5.9%. The cost per incident HIV infection ranged from 0.5 to 3.6 times the median salary of an affected worker (Rosen et al. 2004).

In Zambia, the education sector had an economic setback from the HIV/AIDS epidemic. The extra costs paid in the HIV/AIDS burden on primary school education was estimated at $1.3–3.1 million in 1999 and the projected cost over the period 1999-2010 was estimated at $10.6–41.3 million. The nature of the costs was excess salaries due to teacher absenteeism due to HIV, which was estimated at 70%, and the cost of additional training on teachers was 22%. Funeral costs comprised 7% (Grassly et al. 2003).

2.5 International situation in tuberculosis and HIV co-infection

The combination of HIV and tuberculosis infection has a major impact on the global tuberculosis situation and contributed to the increase of tuberculosis in countries with high a prevalence of both infections (Styblo 1990, Figure 2). TB is considered the most important opportunistic infection among the HIV-infected and is a major cause of death among HIV-infected adults. HIV is a major risk factor of tuberculosis and enhances reactivation of latent tuberculosis and rapid progression of exogenous re-infections to active tuberculosis (Corbett et al. 2003). In the United States, follow-up of newly infected HIV infected persons revealed that progression to active tuberculosis could develop within 60 days (Daley et al. 1992). In Nairobi, Kenya, the incidence of tuberculosis in a cohort of HIV-1-infected sex workers was 34.5 per 1000 person-years, while no TB was found among HIV-negative sex workers. Tracing the sources of transmissions through DNA fingerprinting showed that 53% of cases were due to recent transmissions (Gilks et al. 1997).

The global yearly increase of tuberculosis cases was 1.8% in 1997–2000. Some improvement has occurred in the new millennium with yearly increase estimated at 0.6% in 2005–2006 (WHO 2008). The increase was highest, approximately 6%, in the African region and in the former Soviet Union. The prevalence of HIV infection

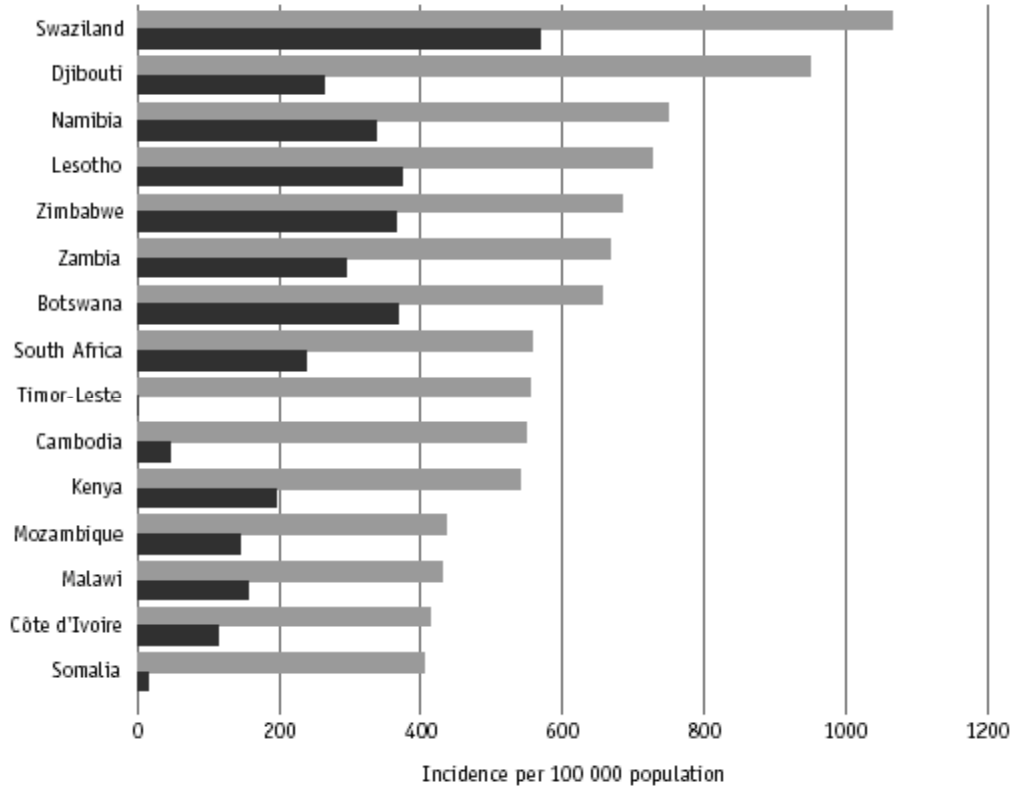

Figure 2. Fifteen countries with the highest estimated TB incidence rates per capita (all ages, all forms; grey bars) and incidence of TB/HIV coinfection (dark bars; source WHO Report 2004. WHO/HTM/TB2004.33.1).

among new TB cases was estimated at 1% in WHO West Pacific region, 14% in the industrialised countries and 38% in the WHO African region (WHO 2003, Corbett et al. 2003, WHO 2004b). In Tanzania, HIV prevalence among smear-positive tuberculosis patients increased from 28 to 40% during the periods 1991–1994 and 1994–1998. There was a parallel increase in notification of new smear-positive cases from 54 to 74/100,000 person-years and it was estimated that 60% of the cases were attributable to HIV. The age group most affected was 25–44 years (Chum et al. 1996). The HIV seroprevalence reported in Zambia was 60%. The prevalence was highest at ages below 25 years in women and then decreased with age. Prevalence among women was higher than that of men, 64% versus 56% (Elliot et al. 1990). In Zambia, annual tuberculosis incidence has increased from 100 per 100,000 in 1986 to 400 per 100,000 in 1994. TB notification rates have increased six-fold (Foster et al. 1997).

In Abidjan, Ivory Coast, 35% of HIV/TB coinfection cases were attributable to HIV-1 and 4% to HIV-2 (De Cock et al. 1991). In Malawi, both smear-positive tuberculosis and other forms of tuberculosis reached a peak during the 1990s. The age groups most affected were 30–44 years and there was a decrease of female to

male ratio from 1.3 to 0.8. The proportion of TB cases attributable to HIV increased from 17% in 1988 to 57% in 2000–2001 (Glynn et al. 2004). In Kenya, tuberculin surveys have shown an increase of annual risk of TB infection among children aged 6–14 years during 1994–1996. The increase was observed in districts, where an increase of TB notification was seen in before 1994 (Odhiambo et al. 1999). HIV prevalence among the TB patients was 50% in the Western Kenyan District, where the notification rates increased and in other district HIV prevalence among TB was 29–27% and notification rates increased either moderately or not at all.

2.5.1 Impact of HIV on the development of active tuberculosis

HIV infection is a major risk factor for tuberculosis and there is an increased risk of reactivation of latent tuberculosis among HIV-infected individuals. The HIV-infected are also at higher risk of rapid progression to active tuberculosis from latent TB or exogenous transmission (Styblo 1990, Daley et al. 1992). The annual risk of developing active tuberculosis among HIV-infected persons exceeds 10%. It was estimated that 10% of TB-infected persons will develop active TB in the absence of HIV and 40% in the presence of HIV-infection (Styblo 1990, Godfrey-Faussett et al. 2002).

HIV infection contributed to the increase of tuberculosis in the developing countries. Studies from Sub-Saharan Africa showed that 31% of adult TB cases were attributable to HIV infection (Corbett et al. 2003)

Several studies have shown that HIV and TB coinfected cases were less infectious in transmission of Mycobacterium tuberculosis (MBT) than non-coinfected patients. In the Dominican Republic, 61% household contacts of HIV-positive TB patients were tuberculin tests-positive compared to 76% among the household contacts of the HIV-negative cases (Espinal et al. 2000). In Zambia, 52% of household contacts of the HIV-positive cases were tuberculin test-positive compared to 71% of HIV- negative TB cases contacts (Elliot et al. 1993).

2.5.2 Impact of HIV on mortality and case fatality

TB deaths attributable to HIV among global TB deaths were estimated at 12% in 2000 and the overall case fatality ratio (CFR) for HIV and TB coinfection in the developing countries was estimated at 50%, when undiagnosed cases are included (Corbett et al. 2003). In studies from Sub-Saharan Africa, CFR was related to high prevalence of HIV and the CFR of all forms of tuberculosis was estimated at 31% in

Zambia, Malawi and 21% in Uganda (Mukadi et al. 2001). The increase in CFR corresponded to the period of increase in HIV prevalence in the general population. For instance in Malawi CFR increased from 6% in 1987 to 21% in 1996.

Mortality among HIV-infected TB patients is higher than among HIV-negative TB patients. In South Africa, mortality was four-fold higher among HIV-infected cases, 17.8 per 100 PYRs compared 4.4 per 100 PYRs (Connolly et al. 1999). In an autopsy study of HIV deaths in the Ivory Coast, TB was found in 54% of pathologically confirmed AIDS cadavers and pneumocystis pneumonia was seen in 4% (Lucas et al. 1993).

Variation of CFR was seen according to the sputum smear status and higher CFR was reported among sputum-smear negative than among sputum smear-positive. In Malawi, the CFR among sputum smear negative patients was 46% compared to 19% among the sputum smear positive cases (Mukadi et al 2001).

Survival difference has been reported between HIV-infected TB cases and the HIV-negative TB patients. In South Africa, the probability of survival at 18 months was 76% among HIV-positive patients and 96% among HIV-negatives cases (Connolly et al. 1999). Other studies reported survival difference during treatment among HIV positive and negative cases in Kenya and Tanzania. The probability of death among HIV-negative TB patients was stable, while mortality increased among HIV-positive cases during and after treatment. In Tanzania, it was estimated that 35% of deaths among HIV positive tuberculosis occurred within 4 years after diagnosis compared to 13% of deaths among HIV-negative cases (Mukadi et al. 2001).

Factors found to contribute to short survival were having both pulmonary and extra-pulmonary disease, previous opportunistic infection and CD4 count under $200x10^6$ (Whalen et al. 1997). Studies in the United States have shown that reduced survival was associated with disseminated tuberculosis, intra-thoracic lymphadenopathy, oral candidiasis and CD4+ count below $300x10^6$ (Shafer et al. 1996).

2.5.3 Impact of HIV on TB manifestation and sputum smear

A change in the proportion of extrapulmonary and pulmonary tuberculosis was observed in the countries with high prevalence of HIV-infection. An increase on the proportion of sputum smear negative TB was also seen among HIV and TB co-infected cases (De Cock et al. 1996, Harries et al. 1998).

In Tanzania, 45% of HIV-positive TB patients were sputum smear negative compared to 29% of the HIV-negative TB cases (Chum et al. 1996). Another study from Zambia showed 39% of sputum smear-positive disease among HIV-positive TB patients compared to 82% among the HIV-negative patients. The smear-negative cases were increasing in TB notifications from Tanzania and in Malawi (Chum et al. 1996, Glynn et al. 2004). In Tanzania, the proportion of smear-negative cases increased from 42% in 1986 to 53% in 1995.

The clinical picture of co-infected pulmonary tuberculosis depends on the onset of immunosuppression and stage of HIV-infection. In the early stage of HIV-infection with modest immunosuppression, the clinical pattern of TB of an HIV-positive patient resembles that of post-primary tuberculosis. In late stage of HIV, the smear results are often negative with typical radiographic features including with diffuse infiltration in lower lobes of the lungs and lack of cavitations (Festenstein and Grange 1991, Harries et al. 1998). In Zambia, 92% of the HIV-negative patients presented with chest radiographic changes of the upper zones of the lungs compared to 69% of the HIV-positive patients (Elliot et al. 1990).

Extrapulmonary tuberculosis occurs more frequently among HIV seropositive individuals than among seronegative. In Nairobi, Kenya, 82% of HIV seronegative cases had pulmonary tuberculosis compared to 42% among the HIV seropositive patients (Gilks et al. 1990). Other surveys in Kenya and Tanzania have shown that the proportion of extrapulmonary/pulmonary was low during 1964–1984 with 90% cases being pulmonary and 85% of the reported extrapulmonary had cervical lymphadenopathy. Disseminated spread was rare with pericardial involvement and peritonitis found in less than 5% of the extrapulmonary patients. The proportion of TB cases with extrapulmonary disease has increased with HIV prevalence in Africa (Harries et al. 1998). In Malawi, the extrapulmonary cases were less than 10% before 1997 and 11% thereafter (Glynn et al. 2004). In Ethiopia, extrapulmonary disease accounted for 40% of TB cases and reports from Tanzanian showed that 27% of total cases were extrapulmonary (Chum et al. 1996, Yassin et al. 2003).

HIV prevalence was higher among patients with extrapulmonary and sputum smear-negative tuberculosis compared to pulmonary sputum smear positive tuberculosis in a Tanzanian survey (30%, 40% and 28% respectively) (Chum et al. 1996). In Malawi, 83% of the non-pulmonary cases were HIV seropositive compared to 50% among the pulmonary tuberculosis (Glynn et al. 2004). In another study, HIV prevalence has been higher among patient with pleural and pericardial tuberculosis than those with pulmonary disease (HIV prevalence 84%, 81% and 49% respectively) (Elliot et al. 1990).

Mortality and survival studies have shown that HIV seropositive patients with extrapulmonary and pulmonary smear-negative TB have higher mortality than HIV seropositive smear-positive pulmonary cases. In the United States, relative risk of death was four-fold among patients with both pulmonary and extrapulmonary manifestations, and two-fold among patients with extrapulmonary TB relative to patients with pulmonary disease. The CFR was lower for patients with pulmonary disease compared to cases with meningitis or lymphadenopathy, (27%, 44% and 56% respectively) (Mukadi et al. 2001).

2.5.4 Impact of HIV on smear conversion

The literature on smear conversion rate according to of HIV serostatus was limited. In Kinshasa, Zaire, no difference in sputum smear conversion rate was observed between HIV seropositive patients and HIV seronegative patients (87.6% versus 88.5% after two months and 99.2% versus 98.9% after 6 month treatment, respectively) (Perriens et al. 1995). In another study, the conversion rate was 96.7% among HIV-infected patients and being smear positive at 2 months did not increase mortality and relapses (Connolly et al. 1999).

2.5.5 Impact of HIV on TB treatment results

The occurrence of adverse drug reactions to antituberculosis treatment among HIV seropositive patients is well established. In one study, the proportions of patients with adverse drug reactions were 11% in HIV seropositive cases and 2% among HIV seronegative cases (Perriens et al. 1995). Other studies have shown 18% to 27% among HIV seropositive patients (Perriens et al. 1991, Small et al. 1991)

The difference in treatment outcome between HIV seropositive and HIV seronegative patients has not been large. In Kinshasa, treatment failure and relapse were 3% and 5% among HIV seropositive TB patients respectively, while the corresponding figures of HIV seronegative were 4% and 9% (Perriens et al. 1995). Other studies have not reported a clear difference in relapse rate between the HIV seropositive and seronegative cases. Estimated relapse rates were 3.9 and 3.6 per 100 PYRs respectively (Shafer et al. 1996, Connolly et al. 1999).

Post-treatment mortality is higher among HIV-positive than HIV-negative TB patients, with a mortality rate of 17.8 and 4.4 per 100 PYRs, respectively i.e. four-fold higher mortality among the HIV-infected (Connolly et al. 1999). Mortality was

reduced with short course treatment regimens which contain rifampicin and no deaths were reported among HIV-positive cases treated with short course compared to 21 deaths among 88 treated with standard TB drugs (streptomycin, thiacetazone, and isoniazid). Other studies have shown increased CFR among HIV patients treatment with standard regimens (Perriens et al. 1991, Mukadi et al. 2001)

2.5.6 Impact of HIV on drug resistance to anti-tuberculosis chemotherapy

The association between HIV/AIDS infection and resistance to anti-tuberculosis drugs has been discussed in several studies. A multidrug resistance study in New York City showed an odds ratio of 2.34 MDR among HIV seropositive cases and 3.42 among AIDS patients (Weltman and Rosen 1994). In other studies, no difference was found between HIV-infected and non-infected. In Zaire, resistance to isoniazid among HIV-positive was 18.35% and 19.1% in seronegative cases (Perriens et al. 1995). In Tanzania, drug resistance among the HIV-positive new cases was 4% compared to 5.8% among HIV-negative cases (Chum et al. 1996). The prevalence of drug resistance among relapses was 9.5% among the HIV-positive cases and 19% among HIV-negative cases. In Brazil, the difference in drug resistance between HIV-positive and HIV-negative was not statistically significant, resistance to one or more drugs observed in 31% and 25% respectively (Liberato et al. 2004).

2.6 Control measures of TB and HIV/AIDS

2.6.1 Tuberculosis

The WHO adopted in 2006 a new strategy called ‘Stop TB’ to reach by 2015 the targets defined in the Millennium Development Goals including access to high-quality TB diagnosis and treatment for all, reduction in TB burden, protection of vulnerable populations from TB, as well as TB-HIV co-infection and treatment-resistant TB. The overall goal is to reduce TB prevalence and deaths by 50% by 2015 (compared with 1990).

In tuberculosis control, the internationally accepted measure is the directly observed short course treatment (DOTS) strategy, which combines five elements: 1) Political commitment from governments and local authorities, 2) Case detection by microscopy and through mainly passive case finding, 3) Establishment of DOTS. 4)

Regular logistic supplies of essential anti-TB drugs (isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutole), 5) Strong and sustainable reporting and recoding system and follow up and monitoring of individual treatment (Pio and Chaulet 1998, Harries et al 2002). The target of TB control is detection rate of 70% of the expected yearly incidence of sputum smear positive cases and a cure rate of 85%. These global TB programme targets were adopted by The World Health Assembly in May 1991 (Pio and Chaulet 1998). A control programme that reaches WHO target in detection and cure rate is expected to reduce incidence and death rate by 11% and 12% per year (Dye et al. 1998, Borgdorff et al. 2002). The globally reported number of notified TB cases was below the WHO target in 2001 with 3.8 million cases of tuberculosis were notified, corresponding to 45% of the 8,3 million estimated incident cases of all forms of tuberculosis. Notification of sputum smear positive cases was 32% which falls short of the target of 70% of detection of smear positive cases.

The level of success in achieving the targets of detection rate and cure rate of treatment showed a wide difference between developing countries. Detection rate in Tanzania and Zimbabwe is estimated to 47%, while in South Africa the target was achieved in year 2000. The treatment success rate in Africa was estimated to 63% (Harries et al. 2002, WHO 2003).

2.6.2 Anti-TB drugs versus antiretroviral drugs

In treatment of cases with TB/HIV co-infection, Priority is given to anti-TB treatment in the cases of smear-positive TB. In some cases combined treatment of anti-TB and antiretroviral therapy may be feasible. However, precaution should be taken to control adverse reactions and drug interaction. The interaction of antiretroviral drugs with rifampicin and rifabutin could influence the plasma levels of antiretroviral and anti-TB drugs.

The interaction of rifampicin and rifabutin with protease inhibitors reduces the plasma level of protease inhibitors (PI). Saquinavir plasma level is reduced by 80% with rifampicin and 40% with rifabutin. Retonavir is a potent inhibitor of enzymatic metabolism of rifampicin and rifabutin therapy and increases their plasma concentration. The dosage can be altered in both antiretroviral therapy and anti-TB drugs to adjust plasma levels, where the combinations are not contraindicated (Ponziak et al. 1999). The interaction of rifampicin and rifabutin with other antiretroviral drugs is mainly reduction of plasma concentration of the nucleoside

analogue reverse transcriptase inhibitors (NsRTIs) and also of the non-nucleoside reverse transcriptase inhibitors (NNRTIs).

2.7 Interventions in TB control

2.7.1 BCG vaccination

BCG is considered to have some benefit in TB control though some doubt is connected with its efficacy beyond miliary tuberculosis in childhood (Ten Dam and Hitze 1980, WHO 1995). BCG vaccinations have been useful in preventing sever form of tuberculosis, like miliary TB and TB meningitis in children. BCG vaccinations are not recommended for children infected with HIV/AIDS for the risk of developing vaccine-induced disseminations (De Cock et al. 1996).

2.7.2 Isoniazid chemoprophylaxis

Isoniazid chemoprophylaxis is beneficial for HIV patients with positive tuberculin test. Some studies have cast doubt on the efficacy of 6 months isoniazid preventive therapy. However, some benefit was seen in protecting people infected with HIV and in reducing mortality of HIV and TB co-infected patients (Hawken et al. 1997). Other studies have shown the cost and benefits of preventive therapy. The benefits exceeded the costs when prophylactic treatment prevented occurrence of five further cases. This was likely for target groups such us teachers, military, students, police and prisoners (Foster et al. 1997).

Compliance with preventive therapy has been low in the developing countries. In Uganda, the treatment completion was 3.3% out of 9,862 patients. Other necessary decisions in starting preventive therapy are duration of therapy, case definitions by voluntary testing and excluding active tuberculosis. Other considerations would be the possible rise of MDR and whether to give secondary preventive therapy for co-infected cases that complete anti-tuberculosis chemotherapy (De Cock et al. 1996).

2.7.3 HIV/AIDS Prevention in TB patients

In TB/ HIV collaboration the goal is to reduce the burden of HIV on the TB patients. The introduction of HIV/AIDS intervention prevention treatment and care services

(IPTCS) within TB programme is recommended (WHO 2004a). The target is to reduce the transmission of HIV. The use of condoms and the care of sexually transmitted infection (STI) reduces HIV incidence (Laga et al. 1994). Preventive measures with voluntary counselling and testing increase behaviour changes in unsafe sex and increased condom use (Kamenga et al. 1991, Jordan-Harder et al. 2004).

Trimethoprim-sulphametazole prophylaxis was beneficial for HIV-infected patients in reducing mortality and severe adverse reactions (Wiktor et al. 1999, Anglaret et al.1999).

Antiretroviral therapy was reported to reduce the incidence of HIV-associated tuberculosis. The risk of tuberculosis was reduced with combination antiretroviral therapy by more than 80% with combination treatment and more than 90% with triple treatment (Girardi et al. 2000). Antiretroviral medication reduces mortality and development of AIDS among HIV-infected individuals (Phillips et al. 2003, Borgdorff et al. 2002).

2.8 Justification of the study

Tuberculosis is one of the most frequent opportunistic infections in HIV-infected individuals. The HIV epidemic has been recognized as a major factor contributing to the increase of tuberculosis in both the developing and developed countries. There are gaps in understanding the TB control measures in the era of both tuberculosis and HIV epidemics. There are few studies on the situation regarding TB and HIV co-infection in Somalia and earlier data were from all cases of tuberculosis under treatment while this study is the first on newly diagnosed cases. There were no earlier studies on the pattern of the tuberculosis and HIV infection. There is a lack of data on the impact of TB and HIV co-infection on the TB treatment outcome and on sputum smear results.

Surveillance data on TB and HIV co-infection is recommended by the WHO in setting up a national surveillance system of the trend of TB and HIV co-infection. Establishing sentinel sites within the TB programme is recommended in countries where the prevalence of TB and HIV co-infection is ≥5% (WHO 1989).

3. Aims of the study

The general aim of the study is to evaluate the occurrence and clinical implications of HIV infection among patients treated for TB in two districts in Somaliland. The results can also be applied in prevention, raising awareness of HIV infection, as well as setting priorities in health service planning.

The specific aims were:

1. To describe the prevalence of HIV infection among TB patients in Somaliland.
2. To compare of disease pattern (pulmonary and extrapulmonary manifestations) and bacteriology (pulmonary smear-positive and smear-negative disease) among HIV seropositive and seronegative TB patients.
3. To compare of treatment response, sputum smear conversion at 2/3 and 5/6 months and treatment outcome after 6/8 months treatment among HIV seropositive and seronegative TB patients.

4. Materials and Methods

4.1 Setting and enrolment

The study was conducted in Somaliland. The country is the former British Somaliland, which after independence in 1960 merged with Italian Somalia as the Somali Republic. After the coup d'etat of 21 October 1968, Somalia was renamed as the Somali Democratic Republic. Somaliland declared itself an independent country after the regime of Mohamed Siyad Barre was ousted in 1991.

Somaliland has a total area of 187,000 square kilometres, with a coastline of 850 km. The republic has borders with Ethiopia, Djibouti and Southern Somalia. The population is estimated to 1.5–2 million. Of the people 55% are nomads and 45% are rural. Life expectancy at birth is estimated to 45–50 years. Population growth rate is 3.1% per year and density is 22 persons per square kilometre (Somaliland National Health Policy 1999, Ministry of National Planning and Coordination 2000, Bradbury 2008). Tuberculosis programme exists in six districts of the country and national TB programme is supported WHO and is fully DOTS (Directly Observed Treatment Short course) approach

The study was conducted in the TB centres of Borama and Hargeisa. The centres have the highest catchments of TB cases, 60% of the TB notifications in the whole country (WHO 2000, unpublished data).

A total of 839 participants were enrolled in the study during period from January to August 2003. The target population was defined as all TB patients diagnosed and treated in the TB centres during the study period. The target sample size was selected in order to achieve sufficient statistical power to distinguish between HIV prevalence of 10% and 8% (alpha 0.05 two-sided, 1-beta 0.8).

The inclusion criteria were the following:

1. Patients residing permanently in Somaliland for at least for one year.
2. Newly diagnosed tuberculosis registered in the TB centres of Borama and Hargeisa during the study period.
3. Age 15 years or older.
4. TB patients under DOTS treatment

A study form was completed for each patient diagnosed by a nurse in Hargeisa and by a medical doctor in Borama, when the TB diagnosis was confirmed. The forms contained demographic information, family contacts, sputum smear results, symptoms present at enrolment, case classification according to the type of disease and sputum smear results as well as HIV serological results.

The staff filling in the forms were briefed and given practical training before conducting the enrolment. Participants enrolled were sent to HIV serological testing in the TB laboratory of Borama and Hargeisa. The HIV testing was anonymous as testing and reporting was done with coded numbers of the patients.

4.2 Ethical considerations

The study protocol was submitted to the Ethical Committee of the Ministry of Health and Labour of Somaliland for permission and the protocol was approved. Patients were informed of the objectives of the study and participants were sent to testing only after they gave written consent. Participants were informed of their HIV status in case they requested the information. This study did not possess the resources for providing treatment for diagnosed HIV cases, which is unfortunate, but this is consistent with standard practice in the centres. In other words, participation in the study did not affect the treatment the patients received.

4.3 Diagnosis

4.3.1 Tuberculosis

The diagnosis of tuberculosis was based on the WHO case definitions of tuberculosis, according to disease type or pulmonary smear status.

4.3.2 Selection of TB suspect cases

All suspected cases of pulmonary and extrapulmonary tuberculosis were received at the TB centres, by a medical doctor in Borama and by a nurse in Hargeisa. All pulmonary TB suspect cases were sent to make sputum smear examination at the TB centres laboratory. All extrapulmonary were examined by the medical officer of the TB centre (Figure 3).

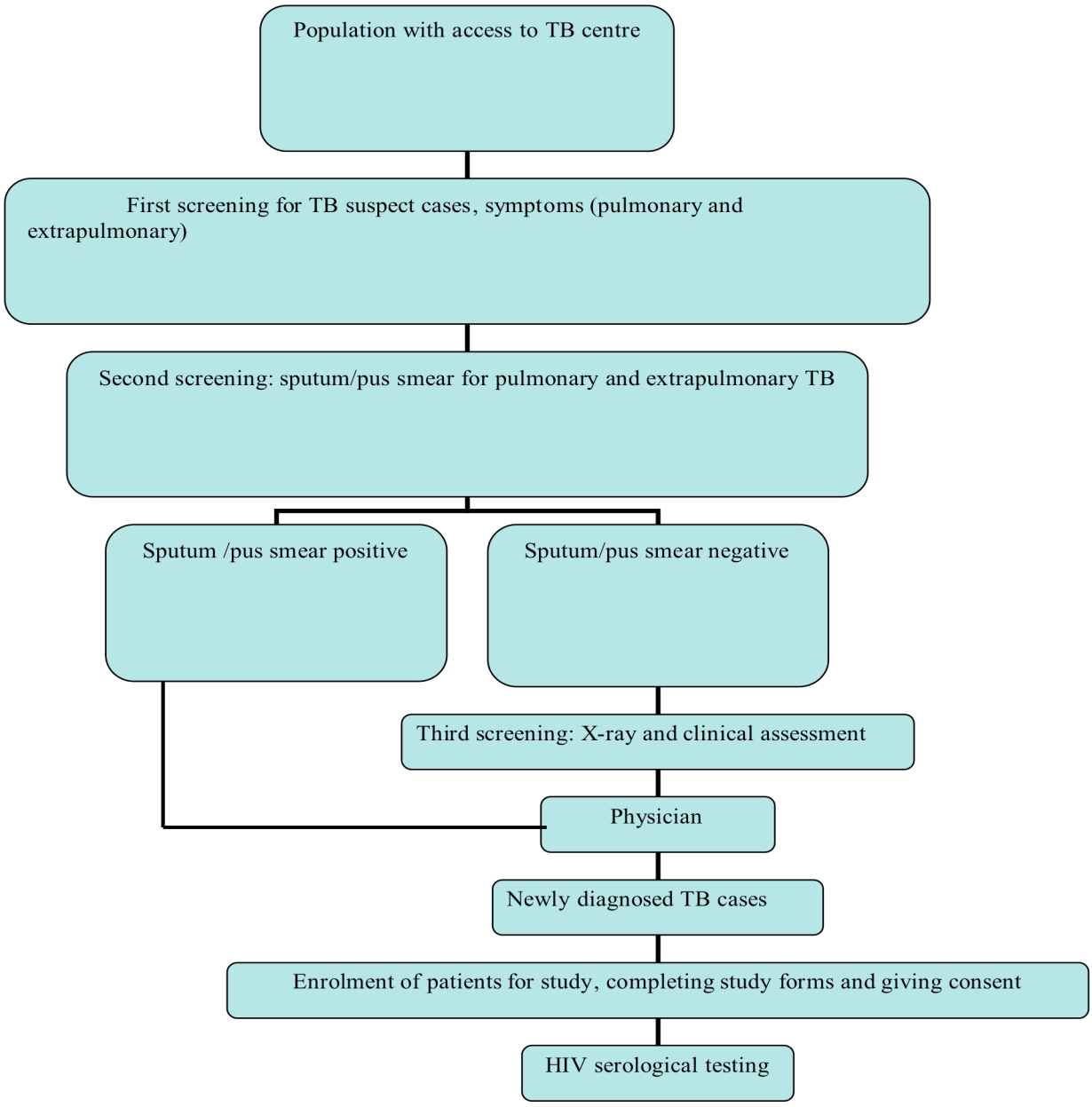

Figure 3. Scheme of participant enrolment

4.3.3 Pulmonary tuberculosis

All suspect cases of pulmonary tuberculosis gave three sputum specimens to the TB laboratory. Sputum collection was accepted with sputum collection form (TB05) which is was also used for reporting results (Pio and Chaulet 1998). The sputum smears were prepared by the Ziehl-Neelsen method (Bates 1979, Mitchison 1982, Allen 1984).

Sputum smear results were classified into four grades: 1. Negative: no acid fast bacilli (AFB) found (0); 2. Scanty positive: 10 AFB found (+); 3. Moderate positive: 100 AFB in all fields of the slide combined (++); 4. Heavy positive: 100 AFB found per field (+++) (Aber et al. 1980).

4.3.4 Pulmonary smear- negative tuberculosis

Pulmonary smear-negative disease was defined as cases that had a negative result in all three sputum specimens and still presented with symptoms consistent with tuberculosis. The cases were considered as TB when they fulfilled the following criteria: (1) Chest x-ray which shows changes consistent with TB and (2) The medical officer decided to start TB treatment. The medical officer of each TB centre read chest x-ray films following the forms for evaluating chest x-ray changes adapted from other studies (Woodring et al. 1986, Harries and Maher 1996).

4.3.5 Diagnosis of extrapulmonary tuberculosis

Extrapulmonary tuberculosis is classified into miliary, lymph nodes, abdominal, urinary tract, skin, bone and joints, and pleurisy (Davies 1971, Grange 1988, Sharma and Mohan 2004). The diagnosis of pulmonary miliary TB and TB pleurisy were made with chest x-ray and clinical diagnosis. Lymph node involvement was confirmed clinically. Bone and joint TB was diagnosed with x-rays and clinical examination. Abdominal cases were only considered if the case was confirmed by a surgeon in laparotomy. Urinary tract and skin were excluded, as diagnostic tools were not available.

4.3.6 Quality control of tuberculosis microscopy

The tuberculosis control programme in Somaliland is well functioning and the tuberculosis laboratory is supported by WHO in material and equipment. A WHO laboratory expert makes regular quality control visits. All TB sputum smear positive slides and 10% of the smear negative cases are stored for quality control (Mitchison 1982)

4.3.7 HIV serological testing

Two simple rapid immunobinding assays were selected for the HIV serological testing. The first test was Hexagon HIV-1 and 2, (Human GmbH, Wiesbaden Germany) and the second kit was Capillus HIV-1/HIV-2 (Cambridge Diagnostics, Galway, Ireland). The approach was consistent with WHO recommendations regarding HIV testing for research purposes. It has been suggested that two tests with different antigen preparations or different principles should be used (WHO 1992, 1998).

The results of the testing were evaluated according to the WHO recommendations for selection and use of HIV antibody testing (WHO 1992, 1997). I used the II strategy which was made in the following procedure:

1. All samples were analysed with Hexagon simple rapid test
2. Serums found positive in the first test were retested with the second test Capillus HIV-1/HIV-2.
3. Samples found in both tests positive were considered HIV seropositive TB cases
4. HIV seronegative cases were those that were negative in the first test and those with positive results in the first but were negative in the second test.

4.4 Antituberculosis treatment

All the patients in the study were treated according to the DOTS system, the current strategy of WHO (Pio and Chaulet 1998, Elzinga et al. 2004). The patients were assigned to the treatment category according to the case classification, smear status (smear-positive or smear-negative), disease (pulmonary/extrapulmonary) and disease course (relapses and failure). New sputum smear-positive cases and seriously ill extrapulmonary and smear negative cases were under Category I. Re-treatment pulmonary smear-positive cases (relapses, recurrent and treatment failures) were

assigned to Category 2. Smear negative cases and non-severe extrapulmonary cases were treated under Category 3. The treatment regimen for category 1 consisted of four drugs and category 2 patient were treated with five drugs and category 3 received a three-drug regimen (Maher et al. 1997) (Table 1).

Table 1. Treatment regimens by case category

Treatment category	Case classification	Treatment regimen: Initial phase	Treatment regimen: Continuation phase	Total duration of treatment in months
1	New smear positive, seriously ill smear-negative and extrapulmonary	HRZE(2)	HR (4)	6
2	Re-treatment (Relapses and failures)	HRZSE*(3)	HRE (5)	8
3	Smear-negative and non-severe extrapulmonary	HRZ (2)	HR (4)	6

* Number in brackets is duration of treatment in months and abbreviations for anti-TB essential drugs (H) isoniazid, (R) rifampicin, (Z) pyrazinamide, (S) streptomycin and (E) ethambutole.

4.4.1 Treatment dosage

Isoniazid was given with a dose of 5 mg/kg/day, not exceeding a daily dose of 300 mg/day. Rifampicin was given 10 mg/kg/day not exceeding 600 mg daily. Pyrazinamide was given with a dose of 20–30 mg/kg/day up to 2500 mg/day. Ethambutole was given 25–25 mg/kg/day and streptomycin given with dose of 15 mg/kg /day (Maher et al. 1997, Pio and Chaulet 1998).

4.4.2 Follow-up of treatment

The follow-up of TB treatment and sputum smear control was done by nurses and the physician at each TB centre. The treatment card was marked daily when patients received their medication under the observation of a nurse. Sputum smear positive patients were sent to sputum smear control according to category of treatment. For patients in category 1, sputum smear control was collected by the end of the 2nd month (end of the initial phase of treatment) and at the end of the 5th month, one month before the end of the continuation phase. For category 2 patients, sputum

smear control was made after the 3rd month and at the end of the 5th month of treatment (Pio and Chaulet 1998).

Treatment was changed from the initial phase to the continuation phase after completion of 2/3 months of treatment depending on smear conversion of each patient. The sputum control results and new treatment for the continuation phase were recorded in the TB register and in the treatment card of each patient.

At the end of the treatment period, treatment outcome was evaluated as: (1) Patient cured, if the case was pulmonary smear-positive at beginning of treatment, (2) Treatment completed, in the case of extrapulmonary and smears-negative cases, (3) Died, (4) Treatment interruption, (5) Transferred out. Follow-up results were collected between January 2003 and August 2004, allowing time for all patients to complete the treatment.

4.5 Statistical methods

Confidence intervals for prevalence estimates were calculated based on the variance of proportion. Unconditional logistic regression analysis was used to analyse differences between HIV seropositive and seronegative TB patients in disease characteristics and treatment outcome. Odds ratio was used as the effect measure and 95% CI for OR was estimated using SPSS. Attributable fraction in the exposed population i.e. proportion of TB cases attributable to HIV was calculated from the formula $AF = (I_E-I_0)/I_E$, where I_E is incidence in the exposed (in this case HIV seropositive patients), I_0 incidence in the unexposed (in this case seronegative patients). Population-attributable fraction was calculated as the attributable fraction multiplied the exposure prevalence (P_E proportion of all seropositive TB patients), i.e. $PAF = AF \cdot P_E = P_E (I_E-I_0)/I_E$.

5. Results

5.1 Enrolment and socio-demographic characteristics of TB patients

5.1.2 Enrolment

A total of 839 TB patients were identified during January-August 2003 and among them 31 (3.6%) withdrew from the study before serological HIV testing. Eight (1%) patients were excluded due to missing information and data from 800 (95%) TB patients were used for the study. During the treatment, 35 (4.4%) were transferred to other centres and sputum smear results were not available from 22 (5%) out of 475 smear-positive patients.

5.1.3 Demographic characteristics

Results of TB diagnostic confirmation and HIV serological test were obtained from 800 TB patients. A total of 510 patients (64%) were examined in the Hargeisa TB centre and 290 (36%) in the Borama TB centre.

Among the 800 patients examined, 536 (67%) were men and 264 (33%) women. Age distribution shows the largest number of patients (N=713, 89%, 95% CI 86.7–91.1) in the age groups between 15–54 years (Table 2). There was a larger number of elderly cases in Borama compared to Hargeisa. The mean age of all cases was 32 years, with a median of 28 years and standard deviation of 14.89 (Figure 4).

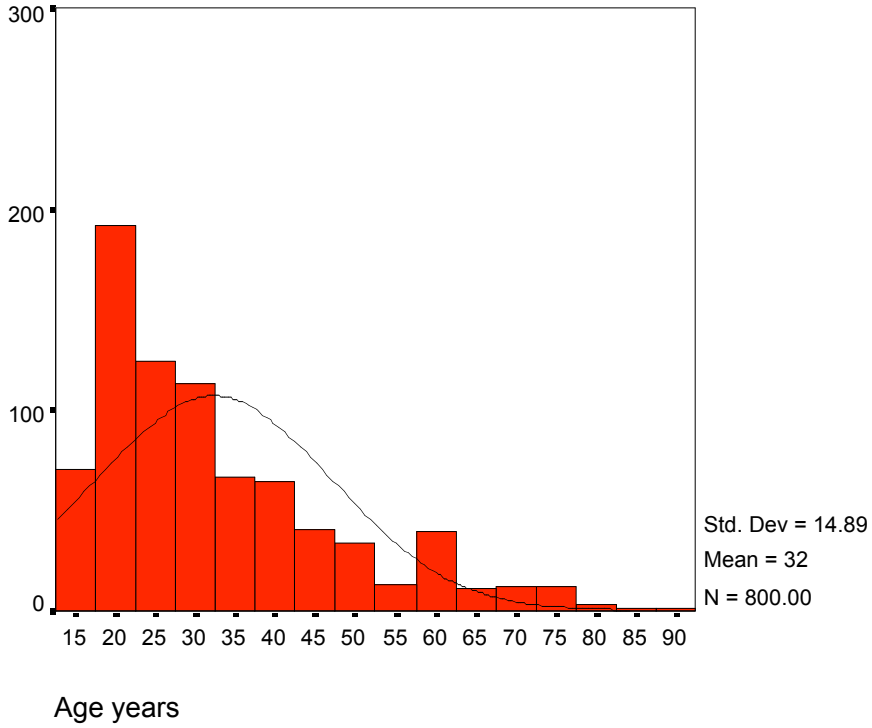

Figure 4. Age distribution of TB patients with mean and standard deviation

Table 2. Age and gender distribution of TB patients by centre

	TB centre								Total	
	Borama				Hargeisa					
	Males		Females		Males		Females			
Years	N	%	N	%	N	%	N	%	N	%
15–24	59	30.1	25	26.6	152	44.7	69	40.6	305	38.1
25–34	56	28.6	24	25.5	89	26.2	52	30.6	221	27.6
35–44	28	14.3	18	19.1	50	14.7	30	17.6	126	15.8
45–54	16	8.2	10	10.6	24	7.1	11	6.5	61	7.6
55–64	22	11.2	10	10.6	13	3.8	7	4.1	52	6.5
65+	15	7.7	7	7.4	12	3.5	1	0.6	35	4.4
Total	196	24.5	94	11.8	340	42.5	170	21.3	800	100

5.1.4 Other socio-demographic characteristics of patients

TB patients treated at the Borama centre came from nine different districts, while the source population for Hargeisa comprised 11 districts. The majority of the patients came from districts of Borama and Hargeisa (78% and 89% respectively). In Borama TB centre, 14% came from other districts within the Awdal region, of which Borama is the provincial capital. Among Hargeisa cases, 5% came from Gebilay district, which is within the same Northwest region as Hargeisa, and the remaining cases (4%) came from districts of Burao and Odwayne in the region of Togdheer (Table 3).

The type of home in which the patient resided was classified into permanent (stone or brick building), cottage (corrugated iron or wooden) and hut (collapsible straw and curved wooden sticks), which are typical nomadic Somali "Aqal". One-third of the patients (34%, 95% CI 30.5–37.1) resided in nomadic huts "Aqals", which are common in poor quarters of towns and rural areas. The proportion of patients living in cottages was 22% (95% CI 18.7–24.4) and 45% (95% CI 41.3–48.2) in permanent buildings. There were some differences in the type of housing by centre. Proportion with permanent homes is 41% in Borama and 47% in Hargeisa (Table 3).

Approximately half of the cases were married (49%, 95% CI 45.3–52.2). The remaining were mainly single (46%, 95% CI 42.7–49.5) and a few were widowed/divorced (5%, 95% CI 3.8–6.8). Patients seen at the Borama TB centre were more frequently widowed or divorced compared to those in Hargeisa (Table 3).

Among all TB cases, 43% (95% CI 39.2–46.0) were unemployed, 13% (95% CI 10.6–15.2) employed in transportation and construction work, 12% (95% CI 10.1–14.7) worked in private business, 16% (95% CI 13.5–18.5) depended on farming and livestock raising. Hargeisa TB centre had a higher proportion of unemployed patients (55%, 95% CI 50.1-58.7) compared to Borama (22%, 95% CI 17.3-26.8). The percentages of students were similar in both centres. Borama had a higher number of patients in other skills (Table 3).

Most (68%, 95% CI 64.1–70.6) of the patient were without formal education, 24% (95% CI 21.2–27.2) had primary education, 7% (95% CI 5.9–9.6) secondary level education and 6 (1%) had university or college level education. There was a marked difference in level of education between the two TB centres. Hargeisa TB centre had a higher proportion of patients without formal education (70%, 95% CI 65.8–73.8) compared to Borama (63%, 95% CI 58.8–69.7). There was a marginal difference in secondary and university level (Table 3).

Table 3. Other characteristics of patients by TB centre

Characteristics	TB Centre				Total	
	Borama		Hargeisa			
	N	%	N	%	N	%
District of residence						
Baki	10	3.4	-		10	1.3
Berbera	2	0.7	4	0.8	6	0.8
Buhoodle	-		1	0.2	1	0.1
Borama	225	77.6	-		225	
Burao	2	0.7	13	2.5	15	1.9
Aynabo	-		2	0.4	2	0.0
Gebilay	14	4.8	23	4.5	37	4.6
Hargeisa	4	1.0	451	88.4	455	56.9
Lasaanood	-		1	0.2	1	0.1
Lughaya	18	6.0	3	0.6	21	2.6
Odwayne	-		9	1.8	9	1.1
Sheikh	3	1.0	2	0.4	5	0.6
Zeila	12	4.1	1	0.2	13	1.6
Marital status						
Married	132	45.5	258	50.6	390	48.8
Single	125	43.1	244	47.8	369	46.1
Divorced/widowed	33	11.4	8	1.6	41	5.1
Education Level						
Illiterate	183	63.1	357	70.0	540	67.5
Primary school	78	26.9	115	22.5	193	24.1
Secondary school	26	9.0	35	6.9	61	7.6
University	3	1.0	3	0.6	6	0.8
Occupation						
Unemployed	63	21.7	278	54.5	341	42.6
Student	27	9.3	47	9.2	74	9.3
Construction/transport	49	16.9	53	10.4	102	12.8
Business	57	19.7	41	8.0	98	12.3
Farming/nomadism	67	23.1	60	11.8	127	15.9
Civil servant	27	9.3	31	6.1	58	7.3
Type of dwelling						
Permanent	119	41.0	239	46.9	358	44.8
Cottage	60	20.7	112	22.0	172	21.5
Hut	111	38.3	159	31.2	270	33.8
Total	290		510		800	

Information on number of family members were obtained from 775 (94%) of the patients. The mean number of family members was 6.1 for all cases and the median was 6. The mean and median number of family members in Borama was 5.5 and 5 respectively, and the corresponding figures in Hargeisa were 6.4 and 6.

Children under five years were reported by 357 (45%, 95% CI 40.8–47.7) of the patients. The mean number of children under five was 1.8 and the median was two. The number of patients with one child under five years of age was 155 (43%, 95% CI 38.3–48.6) and those with two were 133 (37%, 95% CI 32.4–42.3). Fifty (14%, 95% CI 10.7–17.9) patients reported having three small children (Table 4).

Table 4. Number of children under five years per household of TB patients by centre

Number of children	TB centre				Total	
	Borama		Hargeisa			
	N	%	N	%	N	%
1	61	46	94	42	155	43
2	46	35	87	39	133	37
3	17	13	33	15	50	14
4	6	5	9	4	15	4
5	1	1	2	1	3	1
6	1	1	-		1	

5.2 Disease characteristics

5.2.1 Symptoms at presentation

Nearly all patients had weight loss (98%, 95% CI 97.0–98.9), night sweating (97%, 95% CI 94.9–97.5) and coughing (90%, 95% CI 87.4–91.6). Persistent diarrhoea, mouth lesions, tongue lesions and pain in swallowing were also frequent with 15–25% of the patients affected (Table 5). Other less frequent common symptoms were itching, skin rashes and loss of sensation. Patients at the two TB centres had similar symptoms, with the exception of a higher proportion of mouth lesion in Hargeisa (31%) compared to Borama (13%).

Table 5. Clinical symptoms of TB patients by centre

	TB Centre					
	Borama		Hargeisa		Total	
Symptom	N	%	N	%	N	%
Cough	260	89.7	458	89.8	718	89.8
Night sweating	282	97.2	490	96.1	772	96.5
Weight loss	282	97.6	504	98.8	786	98.2
Diarrhoea	60	20.7	96	18.8	156	19.5
Mouth lesion	39	13.4	158	31.0	197	24.6
Difficult swallowing	29	10.0	89	17.5	118	14.8
Lymphadenopathy	17	5.9	78	15.3	95	11.9
Itching	13	4.5	42	8.2	55	6.9
Skin rash	8	2.8	43	8.4	51	6.4
Sensation loss	8	2.8	68	13.3	76	9.5
Tongue lesion	34	11.7	97	19.1	131	16.4
Total	290	100	510	100	800	100

5.2.2 Type of disease (pulmonary/extrapulmonary)

Among the 800 TB patients examined, 650 (81.3%, 95% CI 78.4–83.8) had pulmonary tuberculosis and 150 (18.8%, 95% CI 16.2–21.6) cases were extrapulmonary (Table 6). The proportion of extrapulmonary disease among men was 17.2% (95% CI 14.3–20.7) and 21.5% (95% CI 17.0–26.9) among women. Correspondingly, the proportions of pulmonary tuberculosis among men and women were 82.6% (95% CI 79.2–85.6.4) and 78.4% (95% CI 73.0–82.9). The difference between the two TB centres in disease distribution was small.

Table 6. Distribution of disease pulmonary and extrapulmonary tuberculosis by age

	Extra-pulmonary		Pulmonary		Total	
	N	%	N	%	N	%
Age (years)						
15–24	48	16	257	84	305	38.1
25–34	50	23	171	77	221	27.6
35–44	24	19	102	81	126	15.8
45–54	13	21	48	79	61	7.6
55–64	10	19	42	81	52	6.5
65+	5	14	30	86	35	4.4
Gender						
Male	93	17	443	83	536	67.0
Female	57	22	207	78	264	33.0
Total	150	19	650	81	800	100

5.2.3 Distribution of pulmonary smear-positive and negative tuberculosis

The number of pulmonary TB cases was 650 (81%, 95% CI 78.4–83.8). Of these, 475 (73%, 95% CI 69.5–76.3) were sputum smear-positive and 175 (27%, 95% CI 23.6–30.4) smear-negative cases (Table 7). The proportions of pulmonary smear-positive cases among men and women were 73.3% (95% CI 69.0–77.2) and 72.4% (95% CI 66.0–78.1).

There was a marked difference between the TB centres in proportions of pulmonary smear-positive and smear-negative cases, with a higher fraction of smear-negative cases in Hargeisa (34%) compared with Borama (14%).

Table 7. Distribution of pulmonary smear-negative and smear-positive cases by age and gender

	Pulmonary smear-negative		Pulmonary smear-positive		Total	
	N	%	N	%	N	%
Age (years)						
15–24	66	25.8	190	74.2	256	40.0
25–34	42	24.6	129	75.4	171	26.4
35–44	31	30.4	71	69.6	102	15.7
45–54	21	42.9	28	57.1	49	7.5
55–64	9	21.4	33	78.6	42	6.5
65+	6	20.0	24	80.0	30	4.6
Gender						
Males	118	26.6	325	73.4	443	68.5
Females	57	27.5	150	72.5	207	31.5
Total	175	27.0	475	73.0	650	100

5.3 Prevalence of HIV among TB patients

A total of 800 patients were tested for HIV, among them 290 in Borama and 510 in Hargeisa. The total number of HIV seropositive cases was 87 (prevalence 10.9%, 95% CI 89.0–13.2). In Borama, the number of HIV seropositive cases was 42 (14.5%, 95% CI 10.9–19.0) and in Hargeisa 45 (8.8%, 95% CI 6.6–11.6, Table 8). The HIV prevalence was 11.2% (95% CI 8.8–14.1) among men and 10.2% (95% CI 7.1–14.4) among women.

Table 8. Prevalence of HIV infection among TB patients by TB centre

TB Centre	HIV					
	Seronegative		Seropositive		Total	
	N	%	N	%	N	%
Borama	248	85.5	42	14.5	290	36.3
Hargeisa	465	91.2	45	8.8	510	63.7
Total	713	89.1	87	10.9	800	100

5.3.1 Association between HIV infection and socio-demographic characteristics

Logistic regression modelling was used to analyse the association between socio-demographic characteristics and HIV infection. All the variables were mutually adjusted (entered into the model simultaneously). Factors analysed included marital status, occupation, education, age, and gender (Table 9).

Characteristics significantly associated with HIV infection were age and occupation (Table 9). Age groups 25–34, 35–44 and 45–54 years showed the highest frequency of HIV infection with odds ratios 5.46, 3.73 and 5.44, respectively relative to the oldest age group (55+). No HIV-positive cases occurred in the age group 65 years or older. Transport and construction workers, as well as businessmen were a high-risk group for HIV-infection, with odds ratios of 1.92 and 1.97 respectively. No cases were seen among students. Widowed or divorced subjects were also more frequently HIV-positive than single patients (odds ratio 3.43).

Table 9. HIV serostatus by socio-demographic factors with odds ratio from multiple logistic regression modelling

Demographic characteristics	HIV positive		Odds ratio	95% CI
	N	%		
Age (years)				
15-24	10	3.3		Reference
25–34	35	15.8	5.46	2.31-12.88
35–44	28	22.2	3.73	1.71-8.12
45–54	14	23.0	5.44	2.00-14.78
55+	1	1.1	0.21	0.02-1.82
Occupation				
Unemployed	33	9.7		Reference
Student	-		0	
Transport/construction	22	21.6	1.92	1.03-3.58
Business	19	19.4	1.97	1.01-3.82
Farming/nomadism	4	3.1	0.27	0.09-0.80
Civil servant	9	15.5	1.13	0.49-2.61
Marital status				
Single	52	13.3		Reference
Married	25	6.8	1.15	0.63-2.08
Divorced/widowed	10	24.4	3.43	1.30-9.02

5.4 Disease characteristics by HIV status

5.4.1 Disease distribution by HIV status

There was no marked difference between HIV seronegative and HIV seropositive tuberculosis in the proportion of extrapulmonary and pulmonary TB. The total number of HIV seronegative TB cases was 713 and among them 581 (81.5%, 95% CI 78.4–84.1) presented with pulmonary tuberculosis and 132 (18.5%, 95% CI 15.2–21.5) with extrapulmonary tuberculosis. Of the TB cases, 87 were HIV seropositive and among them 69 (79%, 95% CI 69.6–86.4) had pulmonary tuberculosis and 18 (21%, 95% CI 13.5–30.3) extrapulmonary tuberculosis (Table 10). The odds ratio of extrapulmonary tuberculosis among HIV seropositive cases was 1.17 (95% CI 0.65–2.09).

Table 10. Distribution of disease (extrapulmonary/pulmonary) among the HIV seropositive and HIV seronegative TB patients

HIV	Extrapulmonary		Pulmonary		Total	
	N	%	N	%	N	%
Negative	132	18.5	581	81.5	713	89.1
Positive	18	20.7	69	79.3	87	10.9
Total	150	18.8	650	81.3	800	100

5.4.2 Smear results of pulmonary TB by HIV status

A wide difference was observed in the proportion of smear-positive and smear-negative pulmonary TB by HIV status (Table 11). Of the 650 pulmonary TB cases, 581 (89.4%, 95% CI 86.7–91.5) were HIV seronegative and 69 (10.6%, 95% 8.4–13.2) seropositive. Among the HIV seronegative cases, 76% (95% CI 72.9–79.8) had smear-positive pulmonary TB and 24% (95% CI 20.1–27.0) smear-negative pulmonary TB. The corresponding figures among the HIV seropositive cases were 44% (95% CI 32–55) smear-positive and 56% (95% CI 45–68) smear-negative. The odds ratio for pulmonary smear-negative TB among HIV seropositive cases was 4.17 (95% CI 2.43–7.19).

Table 11. Pulmonary smear-positive and smear-negative TB among HIV seropositive and HIV seronegative TB patients

HIV	Smear-negative		Smear-positive		Total	
	N	%	N	%	N	%
Seronegative	136	23.4	445	76.6	581	89.4
Seropositive	39	56.5	30	43.5	69	10.6
Total	175	27.0	475	73.0	650	100

5.5 Disease and treatment outcome by TB centre

5.5.1 Smear conversion outcome at 2/3 months of TB treatment

The number of sputum smear-positive cases evaluated for smear conversion was 453 (95%, 95% CI 93.0–96.9 of all smear-positive). Of these, 194 (43%, 95% CI 38.3–47.4) were from Borama and 259 (57%, 95% CI 52.5–61.6) from Hargeisa. Of the smear-positive cases, 397 (88%, 95% CI 84.2–90.3) were new patients and 56 (12%, 95% CI 9.6–15.7) relapses. The smear conversion probability for all cases was 93% (95% CI 90.7–95.3). There was a large difference in smear conversion between the two TB centres. In Hargeisa, smear conversion after 2/3 months of treatment was 99% (95% CI 96.6–99.6) compared to 86% (95% CI 80.5–90.2) in Borama. The patients with new sputum smear-positive TB had a slightly higher conversion probability (94%, 95% CI 91.1–95.9) than the relapses (89%, 95% CI 78.5–95.0). Smear conversion probability also varied significantly by age group, with lower conversion proportions among older ages (Table 12). Men had non-significantly lower frequency of smear conversion than women (92%, 95% CI 88.7–94.7 and 96%, 95% CI 91.2–98.0 respectively).

Variation of smear conversion was found with other demographic features. In terms of occupation, higher proportions of smear conversions were observed among the unemployed (97%, 95% CI 93.1–98.5), students (95%, 95% CI 84.0–97.9), as well as construction and transport workers (94%, 95%, CI 84.5–98.7). Low smear conversion proportions were seen among businessmen, farmers/nomads and civil servants. Education was inversely associated with smear conversion. Being illiterate or having completed only primary school was related to non-significantly higher smear conversion proportions (93%, 95% CI 90.1–95.7 and 95%, 95% CI 86.6–98.0, respectively). Those with secondary/university education had lower conversion proportions (87%, 95% CI 73.2–94.4).

Table 12. Smear conversion at 2/3 months of TB treatment by TB Centre and demographic characteristics, with odds ratio and 95% confidence interval

Demographic factor	Smear conversion		Odds ratio	95% CI
	No N (%)	Yes N (%)		
TB Centre				
Borama	27 (13.9)	167 (86.1)	13.80	3.91-58.01
Hargeisa	3 (1.2)	256 (98.8)	1	Reference
Case status				
New cases	24 (6.0)	373 (94.0)	0.54	0.20-1.54
Relapses	6 (10.7)	50 (89.3)	1	Reference
Gender				
Males	24 (7.8)	285 (92.2)	1.94	0.73-5.42
Females	6 (4.2)	138 (95.8)	1	Reference
Age group				
15-24	4 (2.2)	176 (97.8)	1	Reference
25-34	6 (4.7)	121 (95.3)	2.18	0.53-9.42
35-44	9 (13.6)	57 (86.4)	6.95	1.86-28.01
45-54	4 (16.0)	21 (84.9)	8.38	1.61-44.06
55-64	5 (16.1)	26 (83.9)	8.46	1.81-40.76
65+	2 (8.3)	22 (91.7)	4.07	0.48-28.20
Occupation				
Unemployed	6 (3.2)	179 (96.8)	1	Reference
Student	2 (4.7)	41 (95.3)	1.46	0.20-8.41
Construction/transport	3 (5.9)	48 (94.1)	1.86	0.35-8.82
Business	6 (9.8)	55 (90.2)	3.20	0.89-11.98
Farming/nomadism	10 (12.3)	71 (87.7)	4.20	1.34-13.58
Civil servant	3 (9.4)	29 (90.6)	3.09	0.57-15.03
Education				
Illiterate	20 (6.5)	286 (93.5)	1	Reference
Primary school	5 (4.6)	103 (95.4)	0.70	0.22-2.05
Secondary/university	5 (13.0)	34 (87.0)	2.13	0.65-6.52
Marital status				
Single	4 (1.8)	215 (98.2)	1	Reference
Married	22 (10.6)	186 (89.4)	6.36	2.03-22.20
Divorced/widowed	4 (15.4)	22 (84.6)	9.77	1.88-51.05
Type of dwelling				
Permanent	11 (5.6)	185 (94.4)	1	Reference
Cottage	6 (6.0)	94 (94.0)	1.07	0.34-3.26
Hut	13 (8.3)	144 (91.7)	1.52	0.62-3.76

There was no difference in smear conversion according to the type of dwelling. In the analysis by marital status, lower conversion rates were seen among married and widowed/divorced patients (89%, 95% CI 84.5–92.9 and 85%, 95% CI 66.4–93.8, respectively).

Regression modelling was used to evaluate the associations between socio-demographic characteristics and smear conversion. Cases were defined as those with positive smear and high odds ratio indicating increased probability of treatment failure. For the TB centres, Borama had a higher frequency of failure with odds ratio 13.80, (95% CI 3.91–58.01). Of the occupational groups, those involved in farming and nomadism had increased rate of failure (OR 4.20, 95% CI 1.34–13.58). In the analysis by marital status, married and widowed/divorced patients had more frequent unfavourable outcome, odds ratio 6.36, (95% CI 2.03–22.20) and 9.77 (95% CI 1.88–51.05).

5.5.2 Smear results at 5/6 months of TB treatment

Sputum smear outcome at 5/6 months of TB treatment was available from 411 TB patients (86.5%). Smear conversion at 5/6 months of TB treatment was less frequent in Borama (93%, 95% CI 88.2–96.0) than Hargeisa (99%, 95% CI 97.0–99.9). The corresponding OR for treatment failure in Borama was 8.89 (95% CI 1.85–58.3). The sputum smear conversion at 5/6 months among new sputum smear positive cases was achieved in 97% (95% CI 94.6–98.2) and among the relapses in 94% (95% CI 84.0–97.9). The gender difference was very slight, with a smear conversion in 97% (95% CI 94.3–98.5) among men and 96% (95% CI 90.7–97.9) among women. The greatest success was among the younger age groups 15–24 years, with a conversion of 99%, 95% CI 96.5–99.8 and the lowest conversions were among the age group 65 years and older (Table 13).

In the analysis by marital status, the divorced/widowed patients had the lowest (81%, 95% CI 7.1–16.8) and singles the highest (99%, 95% CI 96.3–99.7) proportion of smear conversion. In the analysis by occupation, the smear conversion rate among students was 100%. Farmers and nomads had lower results than other groups (Table 13). Education was associated with higher sputum smear conversion, with 100% success rate among the secondary school and university graduates.

In the regression modelling, the only factors significantly associated with lower results were Borama TB centre (OR 8.89, 95% CI 1.85–58.29) and marital status (odds ratio for married patients 4.19, 95% CI 0.81–28.98, and divorced/widowed OR 21.56, 95% CI 3.08–184.45). The differences between age groups were also significant despite small numbers of events.

Table 13. Smear results at 5/6 months of TB treatment by TB centre and demographic characteristics

Factor	Smear conversion		Odds ratio	95% CI
	No	Yes		
TB Centre				
Borama	12 (7.0)	160 (93.0)	8.89	1.85-58.29
Hargeisa	2 (0.8)	237 (99.2)	1	Reference
Case status				
New cases	11 (3.1)	349 (96.9)	0.50	0.12-2.37
Relapses	3 (5.9)	48 (94.1)	1	Reference
Gender				
Males	8 (2.9)	267 (97.1)	0.65	0.22-2.16
Females	6 (4.4)	130 (95.6)	1	Reference
Age group				
15-24	1 (0.6)	161 (99.4)	1	Reference
25-34	3 (2.6)	141 (97.4)	3.43	0.31-86.43
35-44	4 (6.6)	57 (93.4)	11.30	1.15-271.1
45-54	2 (8.7)	21 (91.3)	15.33	1.02-448.1
55-64	2 (6.9)	27 (93.1)	11.93	0.81-345.1
65+	2 (10.5)	17 (89.5)	18.94	1.25-559.5
Occupation				
Civil servant	1 (3.8)	25 (96.2)	1	Reference
Unemployed	6 (3.5)	165 (96.5)	0.91	0.10-20.88
Student	-	40 (100)	Not estimated	
Construction/transport	2 (4.3)	45 (95.7)	1.22	0.16-7.03
Business	1 (1.8)	55 (98.2)	0.52	0.02-4.32
Farming/nomadism	4 (5.6)	67 (94.4)	1.61	0.47-5.52
Education				
Illiterate	11 (3.9)	269 (96.1)	1	Reference
Primary school	3 (3.2)	91 (96.8)	1.24	0.31-5.74
Secondary/university	-	37 (100)	Not estimated	
Marital status				
Single	2 (1.0)	194 (99.0)	1	Reference
Married	8 (4.1)	185 (95.9)	4.19	0.81-28.98
Divorced/widowed	4 (18.2)	18 (81.8)	21.56	3.08-184.5
Type of dwelling				
Permanent	6 (3.4)	171 (96.6)	1	Reference
Cottage	1 (1.1)	90 (99.0)	0.32	0.01-2.71
Hut	7 (4.9)	136 (95.1)	1.44	0.43-5.06

5.5.3 Treatment outcome

Treatment results were obtained from 800 patients, of whom 727 (90.9%) were new TB cases (with category 1 treatment) and 73 (9.1%) relapses (category 2 treatment). A total of 398 (49.8%, 955 CI 46.2–53.2) were cured and 249 (31.1%, 95% CI 28.0–34.4) completed treatment. Of the other patients, 20 (2.5%, 95% CI 1.6–3.8) defaulted, 14 (1.8%, 95% CI 1.0–2.9) failed, 36 (4.4%, 95% CI 3.2–6.1) died. Thirty-five cases (4.4%) were transferred and 48 (6%) could not be evaluated.

The treatment success proportion among the smear-positive cases was 87% (95% CI 84.5–90.5) and among all cases 80% (95% CI 78.0–83.4) were cured or successfully completed treatment.

5.5.4 Treatment outcome by TB centre and demographic characteristics

The treatment outcome was divided into unsuccessful (defaulted, failed, deaths and not-evaluated) and successful (cured and completed treatment). A total of 765 (95.6%) TB patients were evaluated for treatment outcome and those 35 (4.4%) transferred to other centres were excluded.

Successful treatment outcome was more common in Hargeisa 87% (95% CI 83.6–89.5) compared to Borama 81% (95% CI 75.8–85.0). Treatment outcome difference was narrow according to disease characteristics. The treatment success rate was comparable among patients with extrapulmonary and pulmonary TB: 83% (95% CI 78.2–89.8) and 85% (95% CI 81.9–87.5), respectively. Among the pulmonary TB patients, the smear-positive patients had higher treatment success than smear-negative patients, 88% (95% CI 84.5–90.5) compared to 77% (95% CI 69.9–82.7) (Table 14). Best treatment success was seen among age groups 15–24 and 25–34 years (90%, 95% CI 85.6–92.6 and 89%, 95% CI 88.6–92.2). Other demographic characteristics did not substantially affect treatment results. Divorced/widowed patients had poorer treatment outcome (69%, 95% CI 53.5–81.4) compared to other patients. In the analysis by occupation, the best treatment success was among students (97%, 95% CI 89.9–99.1) and poorer among the business workers and civil servants (80%, 95%, CI 70.2–0.86.6 and 79%, 95% CI 65.9–87.7). No major differences were observed by level of education (Table 14).

In the regression modelling, sputum smear negative cases were associated with significantly higher frequency of unfavourable treatment outcome (OR 2.17, 95% CI 1.34–3.52). Other factors with high odds ratios were Borama TB centre (OR 1.57,

95% CI 1.03–2.38), married (OR 1.67, 95% CI 1.07–2.61) or divorced/widowed marital status (OR 3.50, 95% CI 1.54–7.90), as well as age 35–44 (OR 2.61, 95% CI 1.42–4.81) and 45–54 years (OR 4.35, 95% CI 2.14–8.81). However, when all the factors were included in one regression model, only sputum smear negative disease was significantly associated with unsuccessful treatment.

5.6 Treatment outcome and smear conversion by HIV status

5.6.1 Smear conversion at 2/3 months of treatment by HIV status

The total number of smear-positive cases was 475 and of these 445 (94%, 95% CI 91.1–95.5) were HIV seronegative and 30 (6%, 95% CI 4.4–8.8) seropositive. Smear conversion results were obtained from 453 patients, including 427 (96%) HIV seronegative and 26 (87%) HIV seropositive TB patients. A total of 22 patients were excluded for missing information, death and transfer.

Among the HIV seronegative patients, 27 (6.3%, 95% CI 4.3–9.0) had sputum conversion failure at 2/3 months of TB treatment and 400 (93.7%, 95% CI 90.9–95.6) cases were sputum smear-negative. Among the HIV seropositive cases evaluated, 3 (12%, 95% CI 4.0–28.9) were smear conversion failures at 2/3 months of TB treatment and 23 (88%, 95% CI 71.0–96.0) were sputum-smear negative.

The smear conversion failure rate at 2/3 months of treatment was higher among the HIV seropositive patients than among the HIV seronegative (Table 15). The odds ratio for smear conversion at 2/3 months was 1.9 (95% CI 0.43–7.38) among HIV seropositive patients.

5.6.2 Smear results at 5/6 months of TB treatment by HIV status

Smear results were obtained at 5/6 months from 411 TB patients of whom 388 (94%, 95% CI 91.7–96.2) were HIV seronegative and 23 (6%, 95% CI 3.7–8.2) were HIV seropositive. At 5/6 months of treatment, 13 (3.4%, 95% CI 1.9–5.6) of the HIV seronegative TB patients were failures in terms of sputum smear results, compared to 1 (4.3%) among the HIV seropositive patients (Table 16). Odds ratio was 1.3 (95% CI 0.46–9.75) among HIV seropositive relative to seronegative patients for smear conversion at 5/6 months.

Table 14. Treatment outcomes by TB centre and demographic characteristics

Factor	Treatment outcome		Odds ratio	95% CI
	Unsuccessful	Successful		
Disease status				
Pulmonary	93 (15.0)	526 (85.0)	1	Reference
Extrapulmonary	24 (16.4)	122 (83.6)	1.11	0.66-1.86
Case status				
New cases	105 (15.1)	591 (84.9)	1	Reference
Relapses	12 (17.4)	57 (82.6)	1.18	0.58-2.37
Smear status				
Smear–positive	55 (12.1)	399 (87.9)	1	Reference
Smear–negative	38 (23.0)	127 (77.0)	2.17	1.34-3.52
TB centre				
Hargeisa	64 (13.1)	424 (86.9)	1	Reference
Borama	53 (19.1)	224 (80.9)	1.57	1.03-2.38
Gender				
Females	40 (15.7)	215 (84.3)	1	Reference
Males	77 (15.1)	433 (84.9)	0.96	0.62-1.48
Age group				
15-24	30 (10.3)	261 (89.7)	1	Reference
25-34	24 (11.4)	187 (88.6)	1.12	0.61-2.03
35-44	27 (23.1)	90 (76.9)	2.61	1.42-4.81
45-54	20 (33.3)	40 (66.7)	4.35	2.14-8.81
55-64	8 (15.4)	44 (84.6)	1.58	0.62-3.90
65+	8 (23.5)	26 (76.5)	2.68	1.01-6.91
Occupation				
Civil servant	11 (21.2)	41 (78.8)	1	Reference
Unemployed	51 (15.4)	281 (84.6)	0.68	0.31-1.50
Student	2 (2.9)	66 (97.1)	0.11	0.02-0.58
Construction/transport	16 (16.2)	83 (83.8)	0.72	0.28-1.84
Business	19 (20.4)	74 (79.6)	0.96	0.39-2.40
Farming/nomadism	18 (14.9)	103 (85.1)	0.65	0.26-1.62
Education				
Illiterate	80 (15.4)	438 (84.6)	1	Reference
Primary school	28 (15.4)	154 (84.6)	1.00	0.61-1.63
Secondary/university	9 (13.6)	56 (86.1)	0.88	0.39-1.93
Marital status				
Single	40 (11.3)	315 (88.7)	1	Reference
Married	65 (17.5)	306 (82.5)	1.67	1.07-2.61
Divorced/widowed	12 (30.8)	27 (69.2)	3.50	1.54-7.90
Type of dwelling				
Permanent	53 (15.5)	290 (84.5)	1	Reference
Cottage	16 (9.8)	147 (90.2)	0.60	0.31-1.11
Hut	48 (18.5)	211 (81.5)	1.24	0.79-1.95

Table 15. Smear conversion rate at 2/3 months of TB treatment among HIV seropositive and seronegative TB patients

HIV	Smear conversion				Total	
	Yes		No			
	N	%	N	%	N	%
Seronegative	400	93.7	27	6.3	427	94.3
Seropositive	23	88.5	3	11.5	26	5.7
Total	423	93.4	30	6.6	453	100

Table 16. Smear results at 5/6 months of TB treatment among HIV seropositive and HIV seronegative TB patients

HIV	Smear conversion				Total	
	Yes		No			
	N	%	N	%	N	%
Negative	375	96.6	13	3.4	388	94.4
Positive	22	95.7	1	4.3	23	5.6
Total	397	96.6	14	3.4	411	100

5.6.3 Treatment outcome by HIV status

Treatment results were obtained from 713 HIV seronegative and 87 seropositive TB patients. Among all HIV seronegative cases, 377 (53%, 95% CI 49.2–56.5) were cured and 225 (32%, 95% CI 28.2–35.0) completed treatment. Among the HIV seropositive cases, 21 (24.1%, 95% CI 16.3–34.1) were cured and 24 (27.6%, 95% CI 19.2–37.7) completed treatment. The HIV seropositive status was associated with a higher frequency of default, deaths and non-evaluated cases (Table 17).

Treatment failure among smear-negative HIV seropositive patients was 63% (95% CI 46.3–76.8) and 27.6% (95% CI 14.7–45.7) among smear-positive HIV seropositive TB patients (Table 18). Sputum smear-negative HIV seropositive TB patients had a higher probability of unsuccessful treatment, with an odds ratio 4.44 (95% CI 1.36–14.96).

Treatment success among the HIV seropositive and seronegative TB was analysed with stratification by treatment category. The difference in treatment failure between the new cases and relapses of smear-positive TB among HIV seropositive patients was small, 45.5% and 43.8%. The corresponding odds ratio was 1.08 (95% CI 0.47–3.61) (Table 19).

Table 17. Treatment outcome difference between HIV seronegative and seropositive cases

	HIV					
	Seronegative		Seropositive		Total	
	N	%	N	%	N	%
Cured	377	52.9	21	24.1	398	49.8
Completed	225	31.6	24	27.6	249	31.1
Defaulted	16	2.2	4	4.6	20	2.5
Failed	13	1.8	1	1.1	14	1.8
Died	19	2.7	17	19.5	36	4.4
Transferred	30	4.2	5	5.7	35	4.4
Not evaluated	33	4.6	15	17.2	48	6.0
Total	713	100	87	100	800	100

Table 18. Treatment success by HIV serostatus and sputum smear status

Smear	HIV serostatus	Treatment outcome				Total
		Unsuccessful		Successful		
		N	%	N	%	N
Negative	Negative	16	12.3	114	87.7	130
	Positive	22	62.9	13	37.1	35
	Total	38	23.0	127	77.0	165
Positive	Negative	47	11.1	378	88.9	425
	Positive	8	27.6	21	72.4	29
	Total	55	12.1	399	87.9	454

Table 19. Treatment outcome among HIV seropositive and HIV seronegative TB patients by treatment category

Treatment category	HIV serostatus	Treatment outcome				Total	
		Unsuccessful		Successful			
		N	%	N	%	N	%
New cases	Negative	75	11.9	555	88.1	630	100
	Positive	30	45.5	36	54.5	66	100
	Total	105	15.1	591	84.9	696	100
Relapses	Negative	5	9.4	48	90.6	53	100
	Positive	7	43.8	9	56.3	16	100
	Total	12	17.4	57	82.6	69	100

Attributable fraction is the disease burden caused by the exposure in the exposed population and it was calculated as the difference in the successful treatment outcome achieved. Among HIV seronegative (unexposed) TB patients, treatment outcome was unfavourable (died, failed or defaulted) in 7.4% overall (48/650 evaluated patients, excluding those transferred), while the corresponding figure among HIV seropositive patients was 32.8% (22/67). The attributable risk was thus (32.8%–7.4%)/32.8% = 77% – in other words, HIV infection caused three quarters of treatment failures among seropositive patients.

The population-attributable fraction indicates the proportion of disease burden in the entire population caused by the exposure. Of all treatment failures in the patients treated for TB, HIV infection accounted for 0.109*0.77 = 0.084 or 8.4% of treatment failures in the two TB centres. Without HIV infection, 17 fewer treatment failures would have occurred among the 717 patients evaluated.

6. Discussion

6.1 Methodology and limitations of the study

The patients enrolled into the study represented a large majority of the patients treated in the two TB centres and 50% of the expected incident TB cases in the whole of Somaliland during the study period (WHO 2005). The sample surveyed should be representative of the TB patients in Somaliland, provided that there were no major differences between centres. However, a limitation of the study was the fact that it was conducted in two regions and could not cover the situation in other regions.

The socio-demographic characteristics of the sample are consistent with the findings in other surveys (UNDP 2003). The age distribution of the study subjects is comparable with the age structure of the Somali population (Figure 5). The demographic pyramid for the Somali population and study participants is typical for a developing country.

The diagnosis of the smear-negative and extrapulmonary TB cases is a concern in terms of misclassification, because the smear-negative TB cases could not be confirmed bacteriologically by culture. Some inter-observer variability may occur in the diagnosis of smear-positive or negative TB cases between the two centres, similar to that reported in other studies (Chum et al. 1996, Harries et al. 1998). The possibility of both extrapulmonary and pulmonary in the same patient could result in classification of pulmonary cases as extrapulmonary, or vice versa. The likely effect of non-differential misclassification is attenuation of the differences between study groups. However, also differential misclassification is a possible, as HIV/TB co-infection also makes the diagnosis of sputum smear-negative cases more uncertain (Harries et al. 1998). The impact of non-differential misclassification on the findings is difficult to predict, as it may distort the result to any direction.

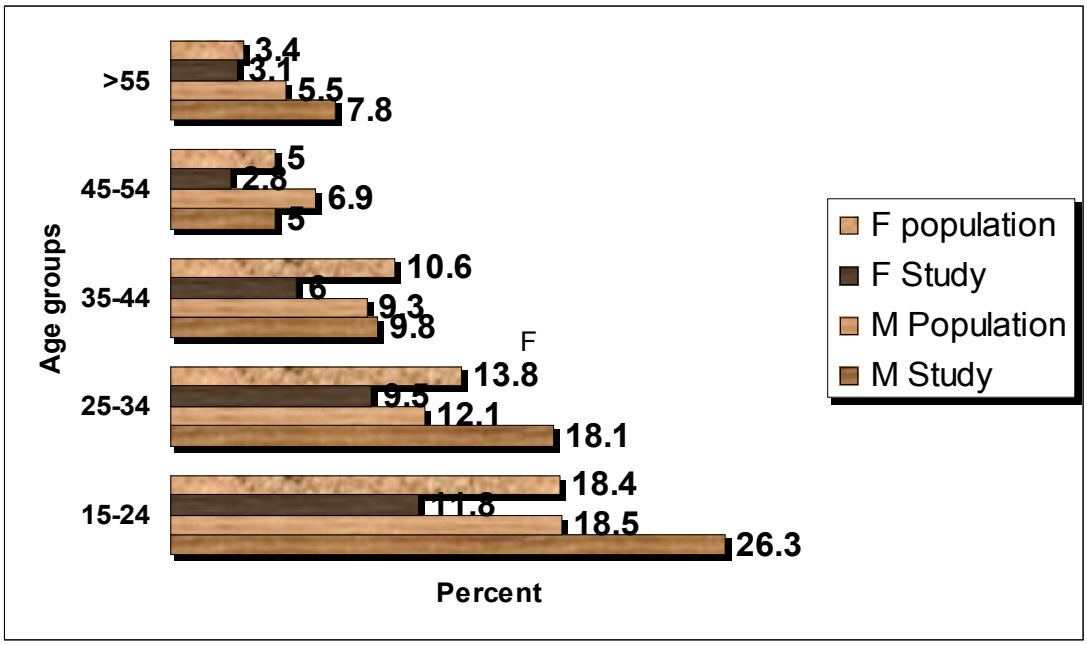

Figure 5. Age distribution of the Somali population and study participants (%), Somali population data adopted from UNDP survey 2003

The diagnosis of tuberculosis in the study was made with the Ziehl-Neelsen method, which is less sensitive than other methods e.g. fluorescent microscopy with auramine (Koche and Cote 1964, Mitchison 1966, Bates 1979). Fluorescent microscopy has approximately 8% higher sensitivity than the conventional microscopy with Ziehl-Neelsen staining, with 9% higher positivity rates (Steingart et al. 2006). This may be particular importance for HIV-positive cases, who typically have low bacterial concentration. Other novel methods include rapid culture system, antigen detection, immune-base assays and nucleic acid amplification tests (Pai et al. 2006). Direct microscopy is still more feasible in the developing countries since it detects pulmonary TB cases, which are responsible for transmission. The Ziehl-Neelsen method is simple and the cost of the examinations is low. However, fluorescent microscopy is recommended for larger centres that receive higher numbers of specimens for sputum examination (Mitchison 1982). Lack of such technique may lead to under-ascertainment of smear-positive cases.

Radiological findings can contribute to the diagnosis of tuberculosis and were used where both clinical assessment and X-ray film were consistent with TB. The diagnosis of pulmonary tuberculosis can be established with sputum smear examinations in 50–80% of cases, but in smear-negative cases radiological changes suggestive of TB disease together with clinical symptoms make up a sufficient indication for treatment (Gordin et al. 1989, Tiruviluamala and Reichman 2002). The

spectrum of TB radiological manifestation of the pre-HIV era appears different from that in the current HIV era. In the pre-HIV era, two thirds of x-ray abnormalities showed cavitations while currently atypical primary lesions are more common (Harries et al. 1998).

6.1.1 Validity of HIV serological testing

There has been a major development in HIV antibody testing assays since 1985 (WHO 1997, 1998). The recent technology has made possible the use simple/rapid test in conditions, where laboratory services are inadequate and do not meet the requirements for use of enzyme-linked immunosorbent assay (ELISA) (Constantine and Zink 2005). The simple and rapid test is considered equivalent in performance of HIV antibody testing with ELISA and also in confirmatory testing (WHO 1998, Constantine and Zink 2005).

In the present study, two simple and rapid tests were used. Both tests were based on recombinant proteins, but with different principles (WHO 1998). The field conditions are not expected to affect the performance of the tests, as the simple tests do not require specialised staff. In other studies, short training for non-laboratory staff was adequate to perform simple tests, and inter-observer discordance was reported as 0.7% (Kanal et al. 2005). Hence, it has been concluded that a simple test could be successfully used by non-laboratory staff.

In the present study, the two simple tests were performed according to strategy II for HIV antibodies testing (WHO 1997). There were no discordant results between the two tests. This part of the study was up to the current standard of HIV antibody testing and presents very little uncertainty or error.

6.2 Main findings

Two thirds of the TB patients in the study were men, which may reflect differences in either disease risk or access to care. Globally, the number of male TB cases exceeds that among women in all age groups except children (WHO 2008). This could represent either probability of transmission or diagnosis and notification, but given the consistent pattern male predominance appears more likely to reflect a genuine difference in risk. A possible explanation for higher incidence among men is more common smoking.

In terms of age distribution, the largest number of TB patients belonged to the younger age groups, 15–24 years, followed by 25–34 and 35–44 years. This reflects both population structure and incidence pattern of TB. In other studies, incidence of tuberculosis has been higher in the age groups 30–44 (Chum et al. 1996, Glynn et al. 2004).

In terms of disease presentation, extrapulmonary TB was not as frequent as reported in some other studies. The proportion of extrapulmonary cases was 18.7%, which corresponds to the pattern seen in populations with a low HIV prevalence. The proportion of extrapulmonary disease has been between 15–20% among HIV seronegative TB patients and among immunocompromised patients it may increase to 50% (Yassin et al. 2003, Sharma and Mohan 2004). The proportion of pulmonary smear-positive cases was 73%, while in a low HIV prevalence situation the proportion is expected to be close to 80% (Kenyan/British Medical Research Council Cooperative Investigation 1989).

The study findings demonstrate an increase of HIV seroprevalence in the TB centres since the last WHO survey of 1999 (WHO 1999). The HIV seroprevalence for all cases in this study was 10.9%, which is 1.6 times higher compared to 6.9% in the year 1999 (WHO 1999). The HIV seroprevalence in both TB centres has increased since the previous survey. In the study, HIV seroprevalence among the patients in Borama and Hargeisa was 14.5% and 8.8% respectively, while the earlier figures were 8.9% in Borama and 7% Hargeisa. The tested used could detect both HIV-1 and HIV-2 and especially the Hexagon kit could distinguish between HIV-1 and HIV-2, but all confirmed tests were HIV-1. The seroprevalence among the TB patients is higher than that among blood donors. The national HIV seroprevalence among the blood donors in Somalia was estimated at 0.8% in the first survey (WHO 1999). Higher figures have been reported more recently with seroprevalence 1.2% in Hargeisa and 2.4% in Bosaso (UNICEF 2003).

The HIV seroprevalence among TB patients varies between African countries, with highest prevalence in the sub-Saharan countries. The estimate in Tanzania was 32%, Zambia 60%, Malawi 64%, Kenya 28–50% and Ivory Coast 38% (Elliot et al. 1990, Lucas et al. 1993, Chum et al. 1996, Odhiambo et al. 1999, Glynn et al. 2004). Other countries of the Horn of Africa, Ethiopia, Djibouti and Somalia belong to the fifteen countries with the highest estimated TB incidence. The HIV seroprevalence among TB patients in Ethiopia was 42% and that of Djibouti was estimated as 25% (WHO 2002 and 2003). The prevalence in Somaliland has been lower than that of other countries in the eastern southern African countries, but shows an increasing trend of HIV seroprevalence among TB patients. The situation in Somaliland appears similar to that in other African countries during the late 1980's and early 1990's,

when an increase of trend of HIV among TB patients was observed with parallel to the increase of HIV infection in the population (Glynn et al. 2004).

The reasons why Somaliland and Somalia have lower HIV seroprevalence could be the closed situation under the military regime and the restriction in cross-border traffic between neighbouring countries. Due to the civil war, a mass exodus of Somali refugees took place to Ethiopia, Kenya and Djibouti in 1990. Afterwards the cross-border population movement and trade were open. Population movements, forced migration, displacement and interaction of communities through commercial routes could be a mechanism of transmission in host-migrant interactions (Salama and Dondero 2001). The prevalence of HIV was also higher in the towns near to borders of Djibouti and Ethiopia, Hargeisa and Borama (WHO 2000). Regarding sexual risk behaviour, there could be differences between the neighbouring populations due to cultural factors, but such conclusion remains to be confirmed by a comparative survey of knowledge, attitudes and behaviour.

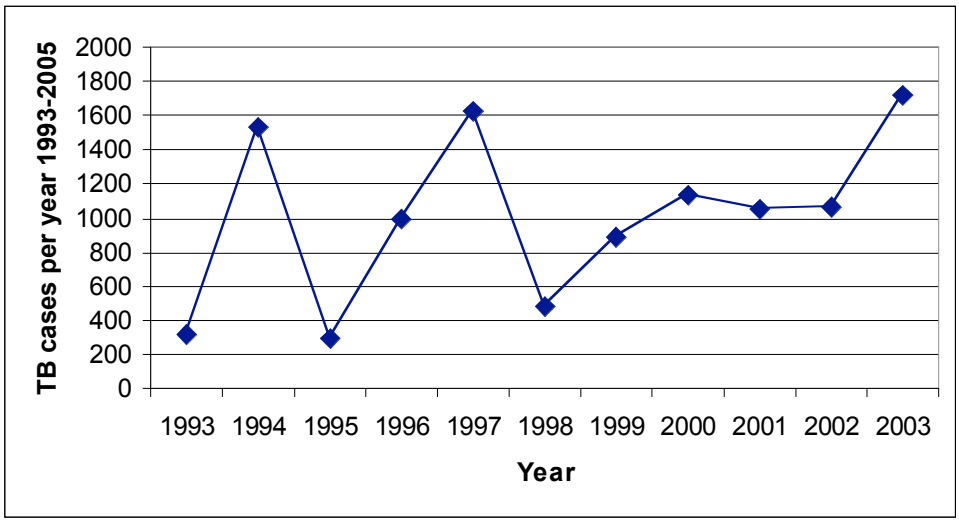

Figure 6. Annual number of tuberculosis cases from Hargeisa TB hospital 1993–2005.

The age distribution among the HIV and TB co-infected cases was consistent with findings in other studies. In this study, the age groups with most frequent HIV infection were 25–44 years, which is similar to a Tanzanian study (Chum et el. 1996). In the Malawian survey, the age groups most frequently co-infected were 30–44 years (Glynn et al 2004). Higher prevalence among the younger age groups is indicative of higher transmission of HIV infection among young adults (WHO 1999).

6.3 The pattern of disease among co-infected TB patients

TB disease classification is an important feature among the HIV and TB co-infected patients, as earlier studies have revealed an altered pattern of clinical presentation. Higher proportions of extrapulmonary disease are reported among the HIV and TB co-infected patients (Chum et al. 1996, Whalen et al. 1997, Harries et al. 1998). In this study there was no significant difference in the proportion of extrapulmonary and pulmonary disease among the co-infected and seronegative cases (21% vs. 19%).

Smear-negative tuberculosis is typical in immunocompromised patients, but because of the lack of laboratory examinations for CD4 count it was not possible to classify the immunostatus (or stage of HIV infection) among the smear-negative and extrapulmonary patients. The proportion of smear-negative cases was twice as high among the HIV seropositive as among the seronegative patients. In a study in North-Eastern Brazil, the proportion of smear-negative cases was 55% among HIV seropositive TB patients (Liberato et al. 2004). In the Tanzanian study, pulmonary smear negative cases had a higher HIV prevalence compared to pulmonary smear positives case (40% versus 28%). Other studies have shown an increased risk of sputum negative and extrapulmonary TB associated with HIV/AIDS (Chum et al. 1996).

6.4 Impact of HIV on smear conversion and treatment results

In the present study, HIV seronegative cases had a higher smear conversion rate at the 2/3 months of TB treatment, but no difference between HIV positive and negative patients was seen in sputum smear results at 5/6 months of treatment. In other studies, no marked difference has been reported. Follow-up smear results and proper management of treatment were crucial for the outcome of the results. Results were missing from 48 (6%) of the TB patients, of whom 15 were HIV seropositive. In a study carried out in South Africa, the conversion rate at two months was comparable for the HIV seropositive and seronegative TB cases (87.6% versus 88.5%). The results after six months of TB treatment were also similar (99% for both groups). It was also reported that being smear positive at two months did not predispose to relapses or death (Connolly et al. 1999).

The HIV seropositive cases had a lower treatment success rate at 5/6 months compared to HIV seronegative patients (6% versus 12% smear-positive). The main reason was more frequent deaths and treatment interruptions among the HIV

seropositive cases. A higher CFR among the HIV seropositive cases has also been reported in other studies ranging 23–34% compared to 10% among HIV seronegative cases (Harries et al. 1998, Ponziak et al. 1999). The treatment success has been reported to differ between the HIV seropositive and seronegative TB patients. HIV seropositive cases had higher failures and relapses in Zaire (Perriens et al. 1995). A study in North-Eastern Brazil showed a higher number of treatment failures among the HIV seropositive cases (Liberato et al. 2004). The HIV seropositive smears-negative cases had a higher CFR compared to HIV seropositive smear-positive patients (Mukadi et al. 2001).

Antiretroviral therapy was not available in either of the TB centres during the study period. The treatment could have reduced mortality and improved TB treatment outcome. Reduced mortality from tuberculosis has been reported with combination antiretroviral therapy in co-infected patients (Girardi et al. 2001, Dean et al 2002, Dheda et al. 2004).

Treatment and smear conversion by TB centre show differences and Borama had lower smear conversions 93% versus 99%. The treatment results at 5/6 months of TB treatment were also lower in Borama. In other treatment indicators, number of defaulters, failed treatments and deaths were all higher in Borama. The higher HIV seroprevalence in Borama could be the reason for the poorer results. Borama had a higher proportion of cured than Hargeisa and also fewer results not evaluated. This suggests better follow-up and treatment management in Borama than Hargeisa.

6.5 Public health relevance

HIV and TB represent both an immense public health burden. Their interrelation is well established and HIV infection fuels tuberculosis (Styblo 1990, Odhiambo et al. 1999, WHO 2002). Particularly in sub-Saharan Africa, the HIV epidemic has increased tuberculosis incidence and deaths (Shafer et al. 1996, Gilks et al. 1997, Glynn et al. 2004, Williams et al. 2005). Corbett et al. (2003) reported that globally nine percent of all new TB cases were attributable to HIV infection in 2000. Others have shown that approximately two thirds of new smear-positive cases were directly attributable to HIV infection (Chum et al. 1996). The estimated number of TB cases attributable to HIV was 264 excess cases of all forms of TB in the Somaliland population of 1,500,000 in 2003 (WHO 2007). The results of the current study show that HIV infection caused 77% of all treatment failures among those infected and 7.8% of all the treatment failures among evaluated.

National surveillance is important to indicate the magnitude and burden of both diseases. The sentinel data in many countries comprise HIV and TB co-infection rates in addition to HIV prevalence figures from antenatal care and blood donors (WHO 1989). To control the problem, the WHO recommends the establishment of a coordinated strategy for both diseases, as otherwise many national health targets will not be achieved (Walker et al. 2002, WHO 2004a, Williams et al. 2005).

In Somaliland, very few studies have been carried out on HIV and tuberculosis co-infection. This study is the second on HIV and TB co-infection carried out in Somaliland. The earlier study addressed the impact of the HIV and TB co-infection on the clinical pattern of tuberculosis, but without evaluating treatment outcome (WHO 1999). Policymakers and health authorities need surveillance data for planning and setting targets for the control of high burden diseases. The results from this study indicate an increase of the prevalence of HIV infection among TB patients. Data from other sources have also shown an increase of HIV prevalence among pregnant women in three regions of Somaliland during the same period (WHO 1999). The prevalence among antenatal sentinel sites increased from 0.8% in 1999 to 1.1%–2.3% in 2003 (WHO survey 2003, UNAIDS 2007). These results represent a warning signal to the health authorities on the HIV and TB co-infection, and stress the importance of continued surveillance of the burden of TB and HIV (WHO 2002).

The study indicates a need to start HIV prevention and awareness raising within the TB control programme. Counselling and voluntary HIV testing with in the TB programmes could facilitate in reducing TB burden among HIV infected individuals and reduction HIV burden on TB patients (Harries et al. 2002, WHO 2004a).

Data on the burden and magnitude of co-infection provide a basis for planning and response to the increasing HIV and TB co-infection that could have a negative impact on the TB control programmes (Harries et al. 1998). The co-infection results in increasing need for hospitalisation and extra costs for the care of the co-infected cases (Harries et al. 1998). The national programmes will not achieve the target set for reducing TB cases and mortality unless the current situation of co-infection is adequately addressed (Williams et al. 2005). The current study contributes to the literature available for the local situation and provides information to the health personnel especially in the HIV and TB programmes. Periodic and sentinel surveys are recommended for countries where HIV testing and counselling is not well established (WHO 2004a). The largest clusters of patients with HIV/AIDS are the HIV and TB co-infected patients at hospitals, as they are not scattered as other HIV infected from the community. The co-infected cases benefit from the antiretroviral therapy, which is known to reduce mortality (Girardi et al. 2001). During the study, provision of ARV was not feasible even if the cases identified could have benefited

from treatment, which could have reduced mortality and could have improved treatment outcome. Social support for the people living with HIV/AIDS may reduce the socioeconomic burden of the disease, but needs of the orphans and affected households remain a major problem (Sewankambo et al. 2000, Grassly et al. 2003, Zaba et al. 2004).

Antiretroviral treatment reduces mortality among the HIV infected and also the risk of tuberculosis (Girardi et al. 2000, Harries et al. 2002). Chemoprophylaxis with isoniazid among HIV infected people reduces the risk of developing TB (Foster et al. 1997, Harries et al. 2002, WHO 2002, Padmapriyadersini and Swaminathan 2005). Trimethoprim-sulphamethoxazole prophylaxis reduces opportunistic infections (Anglaret et al. 1999, Wiktor et al. 1999). Table 20 shows WHO recommendations for collaboration in HIV and TB activities.

Somaliland is a country emerging from a civil war and after the war health care services and other infrastructure is being slowly re-instituted. An important step in the recovery process was organisation of five reconciliation conference between 1991 and 1999 with re-establishment of the parliament and house of elders was. Currently, Somaliland has an elected parliament, president and a cabinet of ministers. National government institutions including a judicial system, police and military forces are functioning. Educational sector covers three universities established and also a strong private schooling system. The major constraint is the weak government revenue and high unemployment (Euser et al. 2002, Bradury 2008.)

The health authority is functional up to the regional level and includes 7 regional hospitals, 7 TB centres, 71 maternal and child health centres (MCHs) and 140 health posts (Ministry of Health and Labour annual health report 2006, unpublished data). There is an inadequate institutional capacity for lack of health financing and poor infrastructure and health workers capacity. There is a wide involvement of international NGOS and UN Agencies in the health sector. The primary health care and the TB programme are funded by UNICEF, WHO and the Global Fund with aid from several international organizations. There is good feasibility to establish VCT sites within the TB program under the Global Fund. Yet, there is still need for improved infrastructure and supplies and human resources capacity building.

Table 20. Recommended collaborative TB/HIV activities*

A. Establish the mechanism for collaboration between tuberculosis and HIV/AIDS programmes
A1. Set coordinating bodies for TB/HIV effectives activities at all levels
A2. Conduct surveillance of HIV prevalence among Tuberculosis patients
A3. Carry out joint TB/HIV planning
A4. Monitor and evaluate collaboration TB/HIV activities
B. Decrease the burden of tuberculosis in people living with HIV/AIDS
B1. Establish intensified tuberculosis case-finding
B2. Introduce isoniazid preventive therapy
B3.Ensure tuberculosis infection control in health and congregate settings
C. Decrease the burden of HIV in tuberculosis patients
C1. Provide HIV testing and counselling
C2. Introduce HIV prevention methods
C3. Introduce co-trimoxazole prevention therapy
C4. Ensure HIV/AIDS care and support
C5. Introduce antiretroviral

* *Sources from WHO (Weekly Epidemiological Record NO. 1/2, 9 January 2004)*

7. Conclusions

The findings of this study permit the following conclusions to be drawn:

1. The HIV prevalence among TB patients has increased since the last WHO survey of 1999 in the districts of Borama and Hargeisa in Somaliland.
2. The TB and HIV clinical pattern influences TB disease and case classification, increasing the proportion of sputum smear negative and extrapulmonary TB.
3. Sputum conversion failure rates and unsuccessful treatment outcome were higher in HIV seropositive TB patients and sputum smear-negative HIV seropositive tuberculosis have a higher tendency for treatment failure.

TB and HIV co-infection is responsible for increased deaths of the HIV seropositive patients. TB and HIV co-infection is a new public health challenge to TB control programmes and TB hospitals due to increased patient care demand among HIV seropositive TB patients. The people mostly affected are young adults, which suggests higher transmission of both diseases in this age group and will require interventions targeting youth and young adults. There is a justification for starting TB and HIV collaboration program in TB centres and TB hospitals, and to establish preventive VCT services. This study provided basic indicators of the current situation and may serve to stimulate further investigation on the subject. However, there is a need to establish HIV sentinel sites and combine data from all health sectors including STI, antenatal care and blood donors. Such a system would create a basis for a national surveillance system.

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9. References

Aber VR, Allen BW, Mitchison, Ayuma P, Edwards EA and Keyes AB (1980): Quality control in Tuberculosis bacteriology 1. Laboratory studies on isolated positive cultures and the efficiency of direct smear examination. Tubercle 61:123–133.

Adjuik M, Smith T, Clark S, Todd J, Garrib A, Kinfu Y, Kahn K, Mola M, Ashraf A, Masanja H, Adazu K, Sacarial J, Alam N, Marra A, Gbangou A, Mwangeni E and Binka F (2006): Cause specific mortality rates in Sub-Saharan Africa and Bangladesh. Bull World Health Organ 84(3):1–17.

Allen BW (1984): Tuberculosis bacteriology in developing countries. Med Lab Science 41:400–409.

Anglaret X, Chene G, Attia A, Toure S, Lafont S, Combe P, Manlan K, N'Dri-Yoma T, Salamon R and Cotrimo-Cl Study Group (1999): Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Lancet 353:1463–468.

Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chmaret S, Dauguet C, Axeler-Blin?, Vezinet-Brun F, Rouzioux C, Rozenbaum W and Montagnier L (1983): Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome. Science 220:868–871.

Bass JB, Laurence S, Hopewell PC, Jacobs RF and Snider DE (1990): Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis 142:725–735.

Bates JH (1979): Diagnosis of tuberculosis. Chest 79:757–763.

Borgdorff MW, Floyd K and Broekmans JF (2002): Interventions to reduce tuberculosis mortality and transmission in low-and middle-income countries. Bull World Health Organ 80:217–227.

Bradbury M (2008): Becoming Somaliland – (African issues). ISBN 978-99700-02-724-8, Malaysia.

Breman JG (2001): The ears of hippopotamus: Manifestations, determinants, and estimates of malaria burden. Am J Trop Med Hyg 64(Supppl 1-2):1–11

Carter R and Mendis KN (2002): Evolutionary and historical aspects of the burden of malaria. Clin Microbiol Rev 15(4):564–594.

CDC (2006a). Twenty-five years of HIV/AIDS − United States, 1981-2006. MMWR Weekly 55(21):585–589.

CDC (2006b). Epidemiology of HIV/AIDS − United States, 1981–2005. MMWR Weekly 55(21):589–592.

Christopher DD, Scheele S, Dolin P, Pathania V and Raviglione MC (1999): Global burden of tuberculosis. J Am Med Assoc 282: 677–686.

Chum HJ, O'Brien RJ, Chonde TM, Graf P and Rieder HL (1996): An epidemiological study of tuberculosis and HIV infection in Tanzania, 1991–1993. AIDS 10:299–309.

Connolly C, Reid A, Davies A, Strum W, McAdam KPWJ and Wilkinson D (1999): Relapse and mortality among HIV infected and uninfected patients with tuberculosis successfully treated with twice weekly directly observed therapy in rural South Africa. AIDS 13:1543-1547.

Constantine NT and Zink H (2005): HIV testing technology after two decades of evolution. Indian J Med Res 121:519–538.

Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC and Dye C (2003): The growing burden of tuberculosis global trends and interactions with the HIV epidemic. Arch Intern Med 163:1009–1021.

Daley CL, Small PM, Schecter GF, Schoolnik GK, MacAdam RA, Phil D, Jacobs WR and Hopewell PC (1992): An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. N Engl J Med 326:231–235.

Davies PDB (1971): Clinical presentation of tuberculosis. Br J Hosp Med 9:749–760.

De Cock KM, Binkin NJ, Zuber PLF, Tappero JW and Castro KG (1996): Research issues involving HIV-associated tuberculosis in resource-poor countries. J Am Med Assoc 276:1502–1507.

De Cock KM, Gnaore E, Adriolo G, Braun MM, Lafontaine MF,Yesso G, Bretton G, Coulibaly IM, Gershy-Damet GM, Bretton R and Heyward WL (1991): Risk of tuberculosis in patients with HIV-I and HIV-II infections in Abidjan, Ivory Coast. Br Med J 302:496–499.

Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, Fisher M, Taylor GP, Miller R, Taylor CB, de Ruiter A and Pozniak AL (2002): Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS 16:75–83.

Dheda K, Lampe FC, Johnson MA and Lipman MC (2004): Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. J Infect Dis 190:1670–1676.

Dixon S, McDonald S and Roberts J (2002): The impact of HIV and AIDS on Africa's economic development. Br Med J 324:232–234.

Doctor HV and Weinreb AA (2003): Estimation of AIDS adult mortality by verbal autopsy in rural Malawi. AIDS 17:2509–2513.

Drobniewski FA, Caws M, Gibson A and Young D (2003): Modern laboratory diagnosis of tuberculosis. Lancet Infect Dis 3:141–147.

Dye C, Garnett GP, Sleeman K and Williams BG (1998). Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Lancet 352:1886–1891

Elliott AM, Hayes RJ, Halwiindi, Luo N, Tembo G, Pobee JOM, Nunn N and McAdam KPWJ (1993): The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. AIDS 7:981–987.

Elliott AM, Luo N, Tembo LG, Halwiindi B, Steenbergen G, Machiele L, Pobee J, Nunn P, Hayes RJ and MacAdam KPWJ (1990): Impact of HIV on tuberculosis in Zambia: a cross-sectional study. Br Med J 301:412–415.

Elzinga G, Raviglione MC and Maher D (2004): Scale up: meeting targets in global tuberculosis control. Lancet 363:814–819.

Eriki PP, Okwera A, Aisu T, Morrissey AB, Ellner JJ and Daniel TM (1991): The influence of human immunodeficiency virus infection on tuberculosis in Kampala, Uganda. Am Rev Respir Dis 143:185–187.

Espinal MA, Perez EN, Baez J, Henriquez L, Femandez K, Lopez M, Olivo P and Reingold AL (2000). Infectiousness of Mycobacterium tuberculosis in HIV-1-infected patients with tuberculosis: a prospective study. Lancet 358:275–280.

EuroHIV (2003): HIV/AIDS surveillance in Europe, mid-year report No. 69.

Euser BJ, Lages P and Jin M (2002): Somaliland. Writers Center of Martin, California.

Festenstein F and Grange JM (1991): Tuberculosis and the acquired immune deficiency syndrome. J Appl Bacteriol 71:19–30.

Foster S, Godfrey-Faussett P and Porter J (1997): Modelling the economic benefits of tuberculosis preventive therapy for people with HIV: the example of Zambia. AIDS 11:919–925

Frieden TR, Sterling TR, Munsiff SS, Watt CJ and Dye C (2003): Tuberculosis. Lancet 362:887–899.

Gallo RC (2002): The early years of HIV. Science 298: 1728–1730.

Gallo RC and Montagnier L (2003): Discovery of HIV as the cause of AIDS. N Engl J Med 349(24): 2283–2285.

Gilks CF, Godfrey-Faussett P, Batchelor BIF, Ojoo JC, Ojoo SJ, Brindle RJ, Paul J, Kimari J, Bruce MC, Bwayo J, Plummer FA and Warrell DA (1997): Recent transmission of tuberculosis in a cohort of HIV-1-infected female sex workers in Nairobi, Kenya. AIDS 11:911–918.

Gilks FG, Brindle RJ, Otieno LS, Bhatt SM, Newnham RS, Simani PM, Lule GN, Okel GBA, Watkins WM, Waiyaki PG, Were JOB and Warrell DA (1990): Extrapulmonary and disseminated tuberculosis in HIV-1-seropositive patients presenting to the acute medical services in Nairobi. AIDS 4:981–985.

Girardi E, Palmieri F, Cingolani A, Ammassaro A, Petrosillo N, Gillini L, Zinzi D, de Luca A, Antinori A and Ippolito G (2001): Changing clinical presentation and survival in HIV-associated tuberculosis after highly active antiretroviral therapy. J Acquir Immune Defic Syndr 26:326–331.

Girardi E, Antonucci G, Vanacore P, Libanore M, Errante I, Matteelli A and Ippolito G (2000): Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. AIDS 14:1985–1991

Glynn JR, Crampin AC, Ngwira BMM, Mawaungulu FD, Mwafulirwa DT, Floyd S, Pönnighaus JM, Warndorff DK and Fine PEM (2004): Trends in tuberculosis and the influence of HIV infection in northern Malawi, 1988-2001. AIDS 18:1459–1463

Godfrey-Faussett P, Maher D, Mukadi YD, Nunn P, Perriens J and Raviglione M (2002): How human immunodeficiency virus voluntary testing can contribute to tuberculosis control. Bull World Health Organ 80:939–945

Gordin FM, Slutkin G, Schecter G, Goodman PC and Hopewell PC (1989): Presumptive diagnosis and treatment of pulmonary tuberculosis based on radiographic findings. Am Rev Respir Dis 139:1090–1093

Grange JM (1988): Mycobacteria and human disease. Edward Arnold, London.

Grassly NC, Desai K, Pegurri E, Sikazwe A, Malambo I, Siamatowe C and Bundy D (2003): The economic impact of HIV/AIDS on the education sector in Zambia. AIDS 17:1039–1044.

Harries AD and Maher D (1996): TB/HIV A clinical manual. World Health Organization. WHO/TB96.200.

Harries AD, Maher D and Nunn P (1998): An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high-HIV prevalence settings in Sub-Saharan Africa. Bull World Health Organ 76(6):651–662.

Harries AD, Hargreaves NJ, Chimzizi R and Salaniponi FM (2002): Highly active antiretroviral therapy and tuberculosis control in Africa: Synergies and potential. Bull World Health Organ 80(6):464–470.

Hawken MP, Meme HK, Elliot LC, Chakaya JM, Morris JS, Githui WA, Juma ES, Odhiambo JA, Thiong'o LN, Kimari JN, Ngugi EN, Bwayo JJ, Gilks CF, Pulmmer FA, Porter JDH, Nunn PP and MacAdam KPWJ (1997): Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomised controlled trial. AIDS 11:875–882.

Hosegood V, Vanneste AM and Timaeus IM (2004): Levels and causes of adult mortality in rural South Africa: the impact of AIDS. AIDS 18:663–671.

Jordan-Harder B, Maboko L, Mnbando D, Riedner G, Nägele E, Harder J, Kuchen V, Kilian A, Korte R and Sonneburg FV (2004): Thirteen years HIV-1 sentinel surveillance and indicators for behavioural change suggest impact of programme activities in south-west Tanzania. AIDS 18:287–294.

Kamenga M, Ryder RW, Jingu M, Mbuyi N, Mbu L, Behets F, Brown C and Heyward WL (1991). Evidence of marked sexual behaviour change associated with low HIV-1 seroconversion in 149 married couples with discordant HIV-1 serostatus: experience at an HIV counselling centre in Zaire. AIDS 5:61–67

Kanal K, Chou TL, Sovann L, Morikawa Y, Mukoyama Y and Kakimoto K (2005): Evolution of the proficiency of trained non-laboratory health staff and laboratory technicians using a rapid and simple HIV antibody test. AIDS Res Ther 2:5 (htt://www.aidsrestherpy.com/content/2/1/5).

Kenya/British Medical Research Council Cooperative Investigation (1989): Tuberculosis in Kenya, 1984: a third national survey and comparison with earlier surveys in 1964 and 1974. Tubercle 70:5–20.

Kim JM, Cho GJ, Hong SK,Chang KH, Chung JS, Choi YH, Song YG, Yeom JS, Lee KS and Choi JY (2003): Epidemiology and clinical features of HIV infection/AIDS in Korea. Yonsei Med J 44:363–370.

Koch MI and Cote RA (1964): Comparison of fluorescent microscopy with Ziehl-Neelsen stain for demonstration of acid-fast bacilli in smear preparations and tissue sections. Am Rev Respir Dis 91: 283–284.

Kochi A (1991): The global tuberculosis situation and the new control strategy of the World Health Organisation. Tubercle 72:1–6.

Laga M, Alary M, Nzila N, Manoka AT, Tuliza M , Behets F, Goeman J, St Luis M and Piot P (1994). Condom promotion, sexually transmitted disease treatment, and declining incidence of HIV infection in female Zairean sex workers. Lancet 344:246–248.

Lal RB, Chakrabarti S and Yang C (2005): Impact of genetic diversity of HIV-1 on diagnosis, antiretroviral therapy & vaccine development. Indian J Med Res 121:287–314.

Liberato IRO, Albuquerque MFM, Campelo ARL and Melo HRL (2004): Characteristics of pulmonary tuberculosis in HIV seropositive and seronegative patients in a northeastern region of Brazil. Rev Soc Bras Med Trop 37:46–50.

Lindan CP, Lieu TX, Giang LT, Lap VD, Thuc NV, Thinh T, Lurie P and Mandel JS (1997): Rising HIV infection rates in HO Chi Minh City herald emerging AIDS epidemic in Vietnam. AIDS 1(suppl 1):S5–S13.

Lucas SB, Hounnou A, Peacock C, Beaumel A, Djomand G, N'Gbichi JM, Yaboue K, Honde M, Diomande M, Giordano C, Doorly R, Brattegaard K, Kestens L, Smithwick R, Kadio A, Ezani N, Yapi A and De Cock KM (1993): The mortality and pathology of HIV infection in a West African city. AIDS 7:1569–1579.

Maher D, Chaulet P, Spinact S and Harries A (1997): Treatment of tuberculosis: Guidelines for national programmes. Geneva, WHO/TB/97,220.

Marks J (1972): Classification of the mycobacteria in relation to clinical significance. Tubercle 53:259–264.

Marks J (1976): A system for the examination of tubercle bacilli and other mycobacteria. Tubercle 57:207–225

Miller FJW and Thompson MD (1992): Decline and fall of the tubercle bacillus: Newcastle story 1882-1988. Arch Dis Child 67:251–255.

Ministry of National Planning and Coordination (2000): Somaliland in figures. MOPC, Hargeisa.

Mitchison DA (1966): Standard smear for grading the content of acid – fast bacilli in sputum. Tubercle 47:289–291

Mitchison DA (1982): Organization of tuberculosis laboratory services in developing countries. Bull Int Union Tuber 57:140–146.

Mukadi YD, Maher D and Harries A (2001): Tuberculosis case fatality rates in high HIV prevalence population in sub-Saharan Africa. AIDS 15:143–152.

Nicoll A, McGarrigle C, Brady AR, Ades AE, Tookey P, Duong T, Mortimer J, Cliffe S, Goldberg D, Tappin D, Hudson C and Peckham C (1998): Epidemiology and diction of HIV-1 among pregnant women in the United Kingdom: results from national surveillance 1988–96. Br Med J 316:253–258.

Niemann S, Richter E and Riisch-Gerdes (2000a): Differentiation among members of the Mycobacterium tuberculosis complex by molecular and biological features: Evidence for two pyrazinamide–susceptible subtypes of M. bovis. J Clin Microbiol 38:152–157.

Niemann S, Riisch-Gerdes S, Joloba ML, Whalen CC, Guwatudde D, Ellner JJ, Eisenach K, Fumokong N, Johnson JL, Aisu T, Mugerwa RD, Okwera A and Schwander SK (2000b): Mycobacterium Africanum subtype II is associated with two distinct genotypes and is a major cause of human tuberculosis in Kampala, Uganda. J Clin Microbiol 40(9):3398–3405.

Notkola V, Timaeus IM and Siiskonen H (2004): Impact on mortality of the AIDS epidemic in northern Namibia assessed using parish registers. AIDS 18:1061–1065.

Odhiambo JA, Borgdroff MW, Kiambih FM, Kibuga DK, Kwamanga DO, Ng'ang'a L, Agwanda R, Kalsivaart NA, Mislijenovic O, Nagelkerke NJD and Bosman M (1999): Tuberculosis and the HIV epidemic: increasing annual risk of tuberculosis infection in Kenya, 1989–1996. Am J Public Health 89:1078–1082.

Padmapriyadersini C and Swaminathan S (2005): Preventive therapy for tuberculosis in HIV infected individuals. Indian J Med Res 121:415–423.

Pai M, Kalantri S and Dheda K (2006). New tools and emerging technologies for the diagnosis of tuberculosis. Expert Rev Mol Diag 6:423–423.

Peeters M and Sharp PM (2000): Genetic diversity of HIV-1. AIDS 14(suppl 3): S31–44.

Peeters M, Courgnaud V, Abela B, Auzel P, Pourrut X, Bibollet-Ruche F, Loul S, Liegeois F, Butel C, Koulagna D, Mpoudi-Ngole E, Shaw GM, Hahn BH and Delaporte E (2002): Risk to human health from a plethora of simian immunodeficiency viruses in primate bushmeat. Emerg Infect Dis 8:451–457.

Peltola H, Mohamed ON, Kataja M, Salminen S, Tuittula T, Peltola TL and Brander E (1994): Risk of infection with mycobacterium tuberculosis among children and mothers in Somalia. Clin Infect Dis 18:106–111.

Perriens JH, Colebunders RL, Karahunga C, Willame JC, Jeugmans J, Kaboto M, Mukadi Y, Pauwels P, Ryder RW, Prignot J and Piot P (1991). Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with "standard" chemotherapy in Kinshasa, Zaire. Am Rev Respir Dis 144:750–755.

Perriens JH, St. Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, Portaels F, Willame JC, Mandala JK, Kaboto M, Ryder RW, Roscigno G and Piot P (1995): Pulmonary tuberculosis in HIV-infected patients in Zaire – A controlled trial of treatment for either 6 or 12 months. N Engl J Med 332:779–784.

Pettifor AE, van der Straten A, Dunbar MS, Shiboski SC and Padian NS (2004): Early age of first sex: a risk factor for HIV infection among women in Zimbabwe. AIDS 18:1435–1442.

Phillips AN, Lepri AC, Lampe F, Johnson M and Sabin CA (2003): When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies. AIDS 17:1863–1869.

Pio A and Chaulet P (1998): Tuberculosis Handbook. Geneva, WHO/TB98.235.

Pozniak AL, Miller R and Ormerod P (1999): The treatment of tuberculosis in HIV-infected persons. AIDS 13:435–445.

Raviglione MC, Dixie E, Snider JR and Kochi A (1995): Global epidemiology of tuberculosis. J Am Med Assoc 273: 220–226.

Riley RL (1982): Disease transmission and contagion control. Am Rev Respir Dis 125:16–19.

Rosen S, Vincent JR, Macleod W, Fox M, Thea DM and Simon JL (2004): The cost of HIV/AIDS to businesses in southern Africa. AIDS 18:317–324.

Sakula A (1982): Robert Koch: Centenary of the discovery of the tubercle bacillus, 1882. Thorax 37:246–251.

Salama P and Dondero T (2001): HIV Surveillance in complex emergencies. AIDS 15 (suppl 3):S4–S12.

Sewankambo NK, Gray RH, Ahmad S, Serwadda D, Wabwire-Mangen F, Nalugoda F, Kiwanuka N, Lutalo T, Kigozi G, Li C, Meehan MP, Brahmbatt H and Wawer MJ (2000): Mortality associated with HIV infection in rural Rakai District, Uganda. AIDS 14:2391–2400.

Shafer RW, Bloch AB, Larkin L, Vasudavan V, Seligman S, Dehovitz JD, Diferdinando G, Stoneburner R and Cauthen G (1996): Predictors of survival in HIV-infected tuberculosis. AIDS 10:269–272.

Sharma SK and Mohan A (2004): Extrapulmonary tuberculosis. Indian J Med Res 120:316–353.

Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE and Hopewell PC (1991). Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. N Engl J Med 324(5):289–294

Snider GL (1997): Tuberculosis then and now: A personal perspective on the last 50 years. Ann Intern Med 126 (3):237–243.

Somaliland National Health Policy, Ministry of Health, 1999.

Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, Urbanczik R, Perkins M, Aziz MA and Pai M (2006): Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 6:570–581

Styblo K (1990): The global aspects of tuberculosis and HIV infection. Bull Int Union Tuberc Lung Dis 65:28–31.

Tan DHS, Upshur REG and Ford N (2003): Global plagues and the Global Fund: Challenges in the fight against HIV, TB and malaria. BMC Int Health Hum Rights 3(1):2

Ten Dam HG and Hitze KL (1980): Does BCG vaccination protect the newborn and young infants? Bull World Health Organ 58(1): 37–41.

Tiruviluamala P and Reichman LB (2002): Tuberculosis. Annu Rev Public Health 23:403–426

Trivedi SS (1988): Primary antituberculosis drug resistance and acquired rifampicin resistance in Gujarat, India. Tubercle 69:37–42.

UNAIDS (2001). AIDS epidemic update. UNAIDS/01.74E. Geneva

UNAIDS (2002): AIDS Epidemic update.UNAIDS 02/58E Geneva.

UNAIDS (2003): AIDS epidemic update. UNAIDS/03.39E. Geneva.

UNAIDS (2007): AIDS epidemic update. UNAIDS/07.27E. Geneva.

UNICEF (2003): Strategic framework for the prevention and control of HIV/AIDS and STIs within Somali population. English press Ltd, Nairobi, Kenya.

UNDP Programme Somalia Country Office (2003): Socio-Economic Survey 2002 Somalia. Report No.1 Nairobi, Kenya.

Volberding PA, Baker KR, and Levine AM (2003): Human immunodeficiency virus haematology. ISSN 1520-4391:294–313, American Society of Hematology Education Program Book, San Francisco.

Walker N, Schwartländer B and Bryce J (2002): Meeting international goals in child survival and HIV/AIDS. Lancet 360:284–289.

Wayne LG (1982): Microbiology of tubercle bacilli. Am Rev Respir Dis 125(3):31–41.

Weber J (2001): The pathogenesis of HIV-1 infection. Br Med Bull 58:61–72.

Weltman AC and Rose DN (1994): Tuberculosis susceptibility patterns, predictors of multidrug resistance, and implications for initial therapeutic regimens at a New York City Hospital. Arch Intern Med 154:2161–2167.

Whalen C, Horsburg Jr CR, Hom D, Lahart C, Simberkoff M and Ellner J (1997): Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis. AIDS 11:455–460.

Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Mauirce C, Djomand G, Ackah A, Domoua K, Kadio A, Yapi A, Combe P, Tossou O, Roels TH, Lackritz EM, Coulibaly D, De Cock KM, Coulibaly IM and Greenberg AE (1999): Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet 353:1469–1475.

Williams BG, Granich R, Chauhan LS, Dharmashaktu NS and Dye C (2005): The impact of HIV/AIDS on the control of tuberculosis in India. Proc Natl Acad Sci 102:9619–9624.

Woodring JH, Vandiviere HM, Fried AM, Dillon, Williams TD and Melvin IG (1986): Update: The radiological features of pulmonary tuberculosis. Am J Roentgenol 146:497–506.

World Health Organization (WHO) (1989): Global programme on AIDS and TB Tuberculosis programme. Weekly Epidemiol Rec 64:125-132

World Health Organization (1992): Global programme on AIDS. Weekly Epidemiol Rec 20:45–148.

World Health Organization (1995): Global tuberculosis programme and global programme on vaccines. Weekly Epidemiol Rec 70: 230–236.

World Health Organization (1997): Joint United Nations programmes on HIV/AIDS (UNAIDS) – WHO: Revised recommendations for the selection and use of HIV antibody tests. Weekly Epidemiol Rec 12 (21):81–88.

World Health Organization (1998): The importance of simple/rapid assays in HIV testing. Weekly Epidemiol Rec 42(16):321–326.

World Health Organization Somalia Office (1999): TB and HIV a deadly partnership. TB Newsletter – Somalia 1(3): 11–12

World Health Organization (2000): Global tuberculosis control: WHO Report. Communicable Diseases, Geneva WHO/CDS/TB/2000.275.

World Health Organization (2002): HIV/AIDS Epidemiological, Surveillance Update for the WHO African Region. ISBN 92 9023 100 9, Harare, Zimbawe.

World Health Organization (2003): Global tuberculosis control: Surveillance, Planning and Financing. Geneva, WHO/CDS/TB/2003.316.

World Health Organization (2004a): Recommendations of the interim policy on collaborative TB/HIV activities. Weekly Epidemiol Rec 79(1/2):6–12.

World Health Organization (2004b). Global tuberculosis control: WHO Report 2004. Communicable Diseases, Geneva WHO/HTM/TB2004.331.

World Health Organization (2004c): The World Health Report: A changing history. Geneva ISBN 92-4-156265.

World Health Organization Somalia Office (2005): TB Guidelines for Somalia. WHO, Nairobi.

World Health Organization (2007): Global tuberculosis control: Surveillance, Planning and Financing. Geneva, WHO/THM/TB/2007.376.

World Health Organization (2008): Global tuberculosis control: Surveillance, Planning and Financing. Geneva, WHO/HTM/TB/2008.393.

Worobey M, Gemmel M, Teuwen DE, Haselkorn T, Kunstman K, Bunce M, Muyembe JJ, Kabongo JMM, Kalengay T, Marck EV, Gilbert MTP, and Wolinsky SM (2008): Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. Nature 455: 661–664.

Yassin Ma, Olobo JO, Kidane D, Negesse Y, Shimeles E, Tadesse A, Demissie A, Britton S, Harboe M and Abate G (2003): Diagnosis of tuberculous lymphadenitis in Butajira, rural Ethiopia. Scand J Infect Dis 35(4):240–243.

Zaba B and Gregson S (1998): Measuring the impact of HIV on fertility in Africa. AIDS 12(suppl 1):541–550.

Zaba B, Whiteside A and Boerma JT (2004): Demographic and socioeconomic impact of AIDS: taking stock of the empirical evidence. AIDS 18(suppl 2): S1–S7.