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The Story of HIV/TB –
The Terrible Twins

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Abstract

The rising incidence of Tuberculosis (TB) in South Africa is closely linked to the rapid spread of HIV/AIDS that has occurred over the last two decades. Compared to other developing countries in this regard South Africa faces a co-epidemic crisis which must be addressed if HIV/TB is to be fought successfully. It is no longer sufficient to focus on each disease separately while neglecting the issues arising from co-infection. When these two diseases intersect it creates serious problems for TB diagnosis and treatment that are not yet adequately dealt with in the existing treatment frameworks. Moreover, TB is the leading cause of death among AIDS sufferers. There is scope for a broader set of TB diagnostic tools to be prescribed, in particular an urgent need for cheap and accurate TB tests to replace the current 120-year-old sputum microscopy. New tests are becoming available but only for a limited group in the private sector. This paper begins by exploring the link between HIV and TB, the data reveals that a change in HIV prevalence is strongly correlated with a change in the incidence of TB. Two techniques are employed to investigate this. The result is an exceptionally high rate of co-infection in countries such as South Africa, where there is high HIV prevalence and high incidence of active and latent TB. The paper then considers why this HIV/TB overlap is such a serious problem for patients and health care workers beyond the problems caused by each disease separately. In conclusion, four broad solutions are examined which would help to address the co-epidemic and solve some of the key problems.

Introduction

The HIV/AIDS epidemic in South Africa is undoubtedly one of the most pressing national concerns as it devastates a large portion of the adult population, with serious social and economic consequences. Since the first diagnosis in 1982 UNAIDS estimates suggest that over three million South Africans have died from AIDS and the country has a higher number of HIV-infected individuals than any other. At the same time as this HIV crisis unfolds, the incidence of Tuberculosis (TB) is also steadily rising. Data from the National TB Control Programme (NTBCP) show that over the last five years TB case notification has increased by 81%, from 188,695 cases in 2001 to 341,165 in 2006 (National Tuberculosis Policy Guidelines, 2007). A serious concern in this regard is the intersection of HIV and TB, and the extent to which HIV prevalence is driving TB incidence. The overlap of these 'terrible twins' causes numerous problems for the diagnosis of TB and increasingly forces doctors to make clinical decisions on the basis of probability rather than relying on a definitive medical test (WHO, 2004b). Furthermore, serious treatment difficulties can arise such as the development of Immune Reconstitution Inflammatory Syndrome (IRIS) which can be fatal, and TB is the leading cause of death among those infected with HIV in South Africa (3). This paper explores the link between HIV and TB, examines the problems caused by co-infection, and then considers some interventions that could lead to positive change.

The Link between HIV/AIDS and Tuberculosis

The World Health Organisation (WHO) estimates that the annual worldwide incidence of TB is 139 per 100 000; in Africa this rises to 363; while in South Africa there are approximately 948 people per 100 000 diagnosed with TB (WHO, 2009). Table 1, below, gives an overview of the TB burden worldwide and includes a section on South Africa. The table is divided into the 6 WHO regions for which TB incidence and prevalence are reported; in addition the extent of co-infection (patients with TB and HIV) is shown in the "HIV Prevalence" column. Here again the South African figures are higher than average; 73% of patients who are infected with TB are co-infected with HIV. Given the extent of this overlap it is useful to explore whether a change in one of the diseases is associated with a change in the other. Understanding this link would certainly clarify some of the epidemiological problems facing countries like South Africa and thus provide help in responding to the co-epidemic.

Table 1: The Epidemiological Burden of TB[1]

Region	Population	TB Incidence[1] (All Forms)	TB incidence (Smear +ve)	TB Prevalence	HIV Prevalence[2]
	1000s	*per 100,000*	*per 100,000*	*1000s*	*%*
African Region	792,378	363	150	3,766	38
American Region	909,820	32	17	348	11
Eastern Med. Region	555,064	105	47	772	3.5
European Region	889,278	49	21	456	9.8
S.E. Asian Region	1,745,394	181	81	4,881	4.6
Western Pacific Region	1,776,440	108	48	3,500	2.7
GLOBAL	6,668,374	139	61	13,723	15
SOUTH AFRICA	48,577	948	358	336	73

[1] *Incidence is the number per 100 000 population per annum*
[2] *HIV Prevalence within the given TB cases*
Source: WHO 2009

The Physiological Link

The physiological connection between HIV and TB is relatively straightforward and it is widely accepted that a change in HIV prevalence can easily precipitate a change in TB incidence within a given population (Corbett, Mallory, Churchyard, Kleinschmidt, De Cock, 2000; Swaminathan, Ramachandran, Baskaran, Paramasivan, Ramanathan, Venkatesan, Prabhakar & Datta, 2000). The rationale behind this theory is discussed below.

TB is a bacterial disease, primarily transmitted through sputum particles in the air, therefore easily spread and contracted. Once infected with TB a healthy immune system is capable of fighting off the infection and successfully preventing the bacteria from multiplying (WHO, 2004b). Consequently, while the body remains infected with TB the disease is kept under control and the individual does not get sick − this individual is said to have *latent TB (*WHO, 2004b*).* It is estimated that approximately 80% of South Africans have latent

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[1] TB Incidence: this table gives the figures for two kinds of TB incidence - the first includes all forms of TB, pulmonary and extra pulmonary, diagnosed using the sputum smear microscopy as well as through x-rays, and other methods; while the second column, the "smear +ve", indicates the incidence for patients who were diagnosed positively for TB exclusively using the prescribed sputum smear microscopy test.

TB[2] (Coetzee, Nachega, Adendorff, Msandiwa, Gray, Intyre & Chaisson, 2002). In contrast if the immune system is weak when the disease is contracted, or becomes weak with latent TB present in the body, the TB bacteria begin to multiply and this causes the infected person to become sick – this is called *active TB,* the extent of which was illustrated in Table 1 (WHO, 2004b). In the case of HIV infected individuals, the immune system can become very frail in the early and late stages of the disease, thereby rendering the individual more vulnerable to TB.

HIV infection leads to progressive immunodeficiency and increased susceptibility to infections such as TB. HIV positive people are thus at high risk of infection and when their immune systems are weak the disease will not be suppressed. It is estimated by the WHO that on average there is a 50% chance of contracting TB if one is HIV positive compared to between a 5% and 10% chance if one is HIV negative (WHO, 2004b). A previous study by Grange et al also asserts that the risk of developing TB if one is HIV positive is 20.6 times higher than if one is HIV negative (Grange, Henderson, Malon & Zumla, 2000). In countries where a large proportion of the population already have latent TB, such as South Africa, the problem is more acute and these odds may be even higher. The spread of HIV and consequent weakening of the immune system causes latent TB to become reactivated; therefore, as HIV spreads in a population with high rates of latent TB the extent of co-infection also increases. In addition, when active TB becomes more prevalent the problem is perpetuated because those with active TB easily infect others.

What the data suggests

The medical explanation of this link is well founded, widely accepted, and appears to be supported by the high percentage of co-infections in South Africa. However, it is useful to explore the empirical association between HIV and TB in more detail. Two approaches are used to investigate this:

1. Examining the HIV and TB data over time for South Africa and Uganda. Fitted curves are plotted using Spectrum[3] to observe and compare the trends.

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[2] A major factor contributing to the high rate of TB infections is the socio-economic conditions facing many South Africans, where living conditions are poor, crowded and thus relatively unhygienic. TB is more easily contracted and spread in such settings (7).

[3] Spectrum is an epidemiological modelling tool which can be downloaded from hhtp://www.policyproject.com/software.cfm?page=Software&ID=Spectrum.

2. Formulating a cross country regression to examine the effect of a change in HIV prevalence on the change in TB incidence[4].

Spectrum HIV/TB Curves

Comparing trends in HIV prevalence and TB in Uganda and South Africa serves as a useful test of the relationship between these two diseases. If the medical explanation is correct, then the trends in TB cases should mirror trends in HIV cases. As Uganda's HIV epidemic peaked in the late 1990's, whereas South Africa's peaked a decade later, we should expect TB cases to have fallen in Uganda and risen in South Africa over the past decade in line with trends in HIV cases.

Using Spectrum the HIV prevalence and TB incidence curves for each country were generated with data from the WHO and UNAIDS (WHOSIS, 2009; UNAIDS/WHO, 2008). The curves in Figure 1 show the HIV prevalence and TB incidence for South Africa from 1990-2009 and 1980-2009, respectively.

Figure 1   (a)   Number of HIV Cases in South Africa

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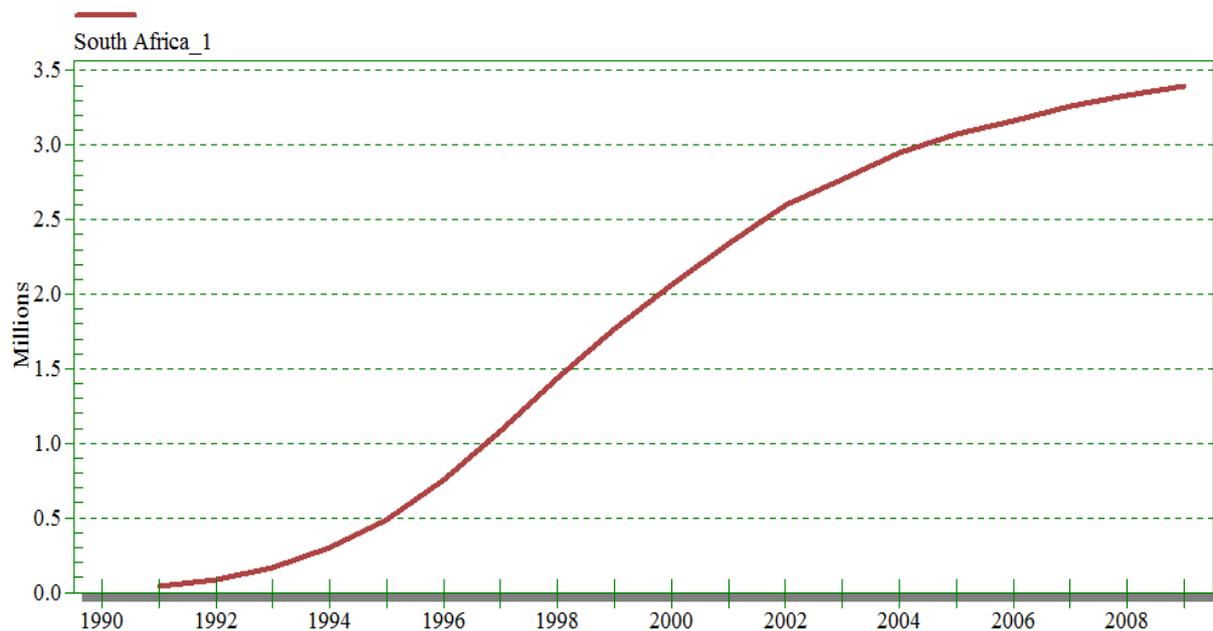
[4] 'Incidence' reports the number of new cases of a disease per year, while 'prevalence' gives the total number of people infected in a given population. Incidence is thus used to measure the extent of TB − because TB is curable so the patients who have it in one year may not have it the following year -; while Prevalence is used to measure the extent of HIV infection− given that once a patient is HIV positive they remain infected for life.

(b)   Number of TB Cases in South Africa
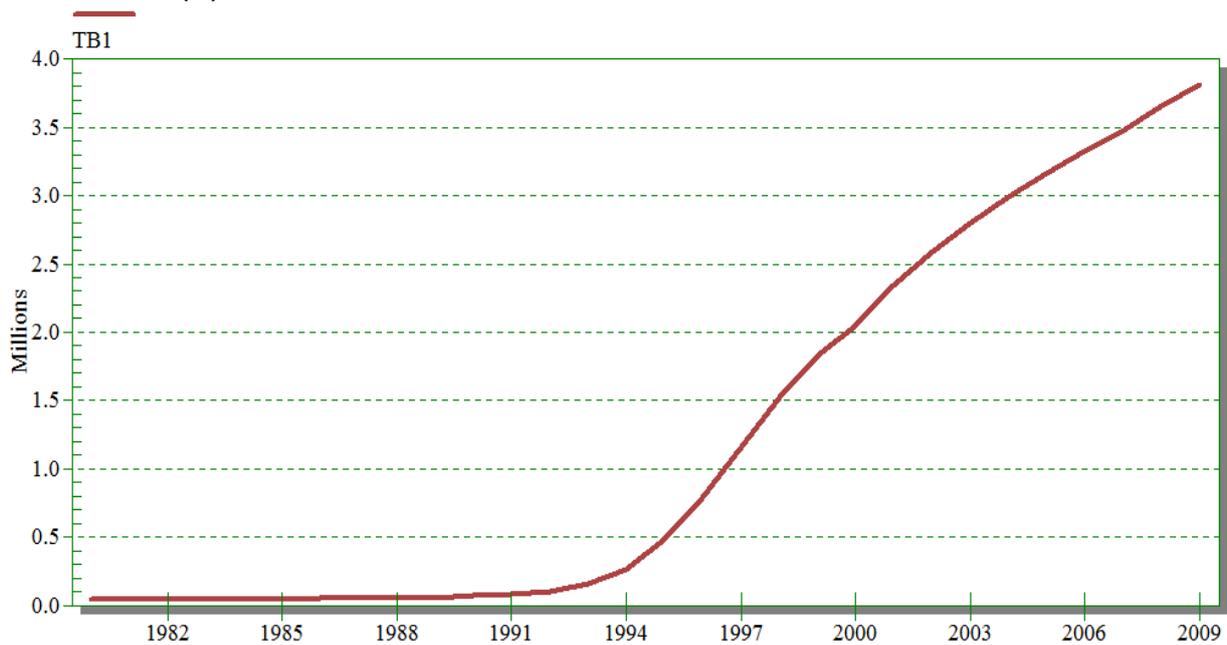
It is clear that the extent of both HIV and TB in South Africa has increased significantly over the past two decades with a correlation coefficient of 0.93. This suggests that the increasing HIV prevalence is closely linked to the rise in TB incidence. However, one must be careful to assume causation from correlation, or to rule out the effect of some external factor/s which may affect both diseases.

The curves for Uganda from 1982-2007 are shown below.

Figure 2   (a)   Number of HIV Cases in Uganda

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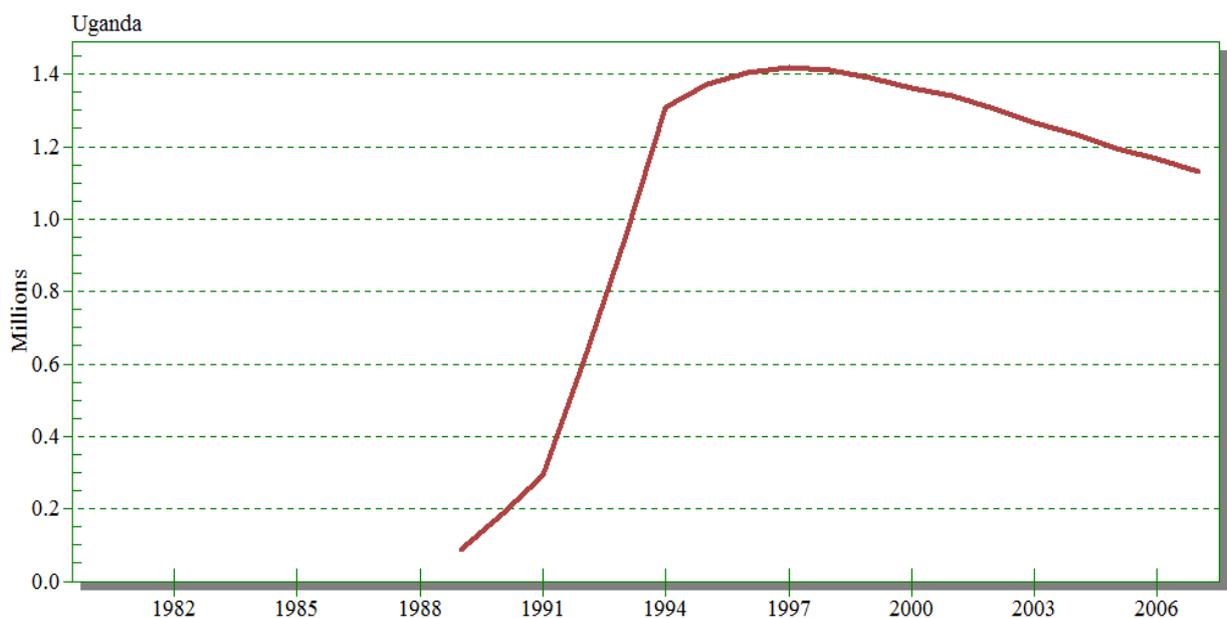
(b)   Number of TB Cases in Uganda
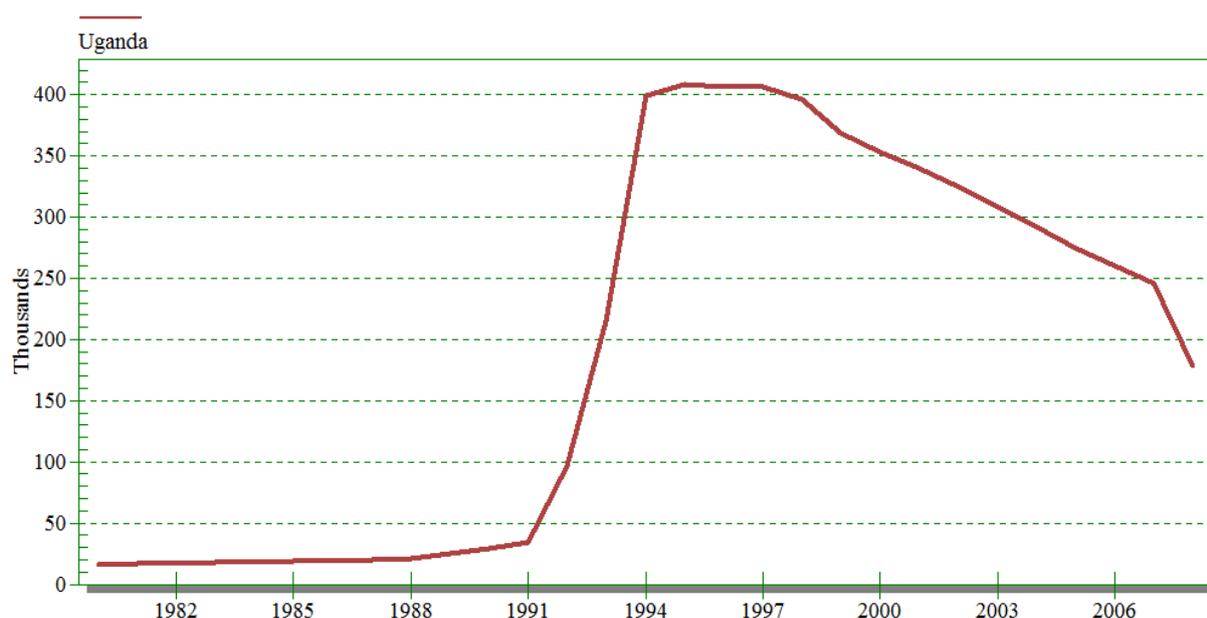
The cubic nature of both curves is immediately clear. It can be seen in figure (a) that after rising steeply in the first half of 1990, by 1996 the number of people with HIV in Uganda begins to decline. After 1999 TB incidence also begins to fall[5]. This sheds more light on the relationship between the two diseases because we can see that in both countries the progression of TB follows that of HIV. This comparative evidence from South Africa and Uganda bolsters the medical argument for a strong HIV-TB causal link.

Regression Analysis

Cross country regression analysis enables us to explore the link further. This regression explores the relationship between the change in HIV prevalence and the change in TB incidence over the period 1994 – 2007, controlling for relevant socio-economic variables. Data was obtained for 51 African countries from UNAIDS, the WHO and the World Bank (WHOSIS, 2009). All data for the

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[5] The TB curve for Uganda shown in Figure 2(b) begins declining slightly earlier than the overall data suggests – around 1998 instead of after 2000. This has to do with the method Spectrum uses to calculate the incidence curve: inputs for the TB incidence *with HIV* and the incidence *without HIV* are required; one is thus forced to split up the total incidence into these categories. But while TB incidence without HIV continues to increase up until 2003 in Uganda, the incidence in people with HIV falls after 1998. It appears that for some reason Spectrum weights the latter more heavily than the former which produces the curve shown in Figure 2(b) where the decline begins just after 1998. The curve would otherwise have only begun to fall a few years later.

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independent economic variables were for the year 2004. The general regression equation is formulated as follows:

Δ*TB Incidence = C + β1(level of healthcare) + β2(%urban population) + β3(life expectancy) + β4(GNI per capita) + β5(ΔHIV prevalence) + ε.*

In short, this regression uses cross country data and observes to what extent changing HIV prevalence can "explain" changes in the TB incidence, while controlling for other aggregate socio-economic factors potentially linked to TB. It is important to keep this general aim in mind when reading the results, which are presented and discussed below. Table 2 presents the list of variables and the results of 3 multivariable OLS (Ordinary Least Squares) regression specifications.

Table 2: Cross Country Regression Analysis

Dependent Variable: Change in TB Incidence (1994-2007)	1	2	3
Change in HIV Prevalence (1994-2007)	26.082** (4.202)	28.615** (4.040)	33.316** (4.035)
GNI per capita	-0.007 (0.004)	-0.001 (0.004)	-0.004 (0.193)
Number of Physicians per 1000 people		-26.997 (54.63)	-39.22 (75.64)
% of the population that is urban	0.13161 (1.126)	0.6483 (1.150)	0.4288 (0.006)
Per Capita Health Expenditure	-3.5142 (7.436)		
Life Expectancy	-6.6053* (2.396)	-6.569 (2.369)	
Constant	408.22 (119.8)	385.67 (97.76)	103.31 (43.32)
Number of Observations (N)	50	42	42
Adjusted R^2	0.711	0.704	0.649

Coefficients are shown, with standard errors in parenthesis()
*5% significance
**1% significance

All three specifications report an adjusted R^2 of 65% or more. Put differently, the independent variables explain at least 65% of the variation in TB incidence over time. No heteroscedasticity was present in the models[6] and a correlation matrix is presented in the Appendix to show that there was no significant correlation between the independent variables.

In comparing the models one can observe that Equation 1 has the highest R^2 and most number of significant variables. However, it suffers from the risk of a two-way (endogenous) relationship between Health Expenditure and TB incidence in

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[6] Results of White's test for heteroscedasticity are shown in the Appendix for equation 1; the result was the same for equations 2 and 3.

that higher levels of health expenditure may affect TB incidence, but TB incidence may also affect the level of health expenditure. This means that health expenditure may be correlated with other factors that explain TB incidence, which violates the OLS assumption of there being no relationship between the explanatory variables and the disturbance term (which *inter alia* picks up the effect of unmeasured variables). To overcome this problem Equation 2 uses a variable related to the level of healthcare in a country (which is what health expenditure is being used to capture) but not directly to health expenditure, namely the 'number of physicians per 1000 people'.

In addition to omitting the health expenditure variable, Equation 3 omits 'Life Expectancy' because it is also most likely influenced by both TB incidence and HIV prevalence. This equation has an adjusted R^2 of 0.65 and the four independent variables report results similar to Equations 1 and 2. As should be expected the coefficient of 'HIV prevalence' increases when independent variables are dropped but it maintains a range of 26 to 33 over the three equations, which is a relatively large coefficient value in each case. The variables from equation 3 are explained and interpreted here.

- GNI per capita. This variable is used as a broad measure of development given that other poverty measures are not readily available for many African countries. The coefficient of GNI per capita is negative (-.004), suggesting that poorer populations experience higher levels of TB incidence. While the sign is as expected, the variable is not statistically significant and the coefficient is small.
- Physicians per 1000. Used instead of Health Expenditure this variable tries to capture the level of healthcare in each country and the effect of this on TB incidence. Although it solves the problem of endogeneity the data available on 'physicians per 1000' is not available for all countries so the number of observations falls to 42. The adjusted R^2 is not negatively affected, as Equation 2 proves. The variable itself is not significant at the 5% level and has an extremely high standard error, which may be due to the small sample size, but it does suggest that having more physicians is related to a small decrease in TB incidence, which is what one would expect.
- Urban Population. Higher proportions of urban population are related to higher TB incidence. This may be because TB spreads more easily in areas where people live in close proximity to one another such as cities, particularly in crowded informal settlements which are a salient feature of most South African cities (WHO, 2009). But while the variable reflects this relationship with a positive coefficient of 0.42, it is statistically insignificant and the effect is fairly small.

- Change in HIV prevalence. Finally, and most importantly, the output shows that, controlling for the other variables, a positive change in HIV prevalence is linked to a positive change in TB incidence. The interpretation is that a 1% increase in HIV prevalence in Africa is associated with an increase in TB incidence of 33.3. This means that on average 33 more people out of 100,000 contract TB when HIV prevalence increases by 1%. The variable is significant at the 1% level and has a relatively small standard error; this is also the case in equations 2 and 3.

The regression results, while facing certain data constraints, undoubtedly support the medical hypothesis regarding the link between HIV and TB given the strong positive co-efficient of "Change in HIV Prevalence". This, together with the comparative time-series curves for South Africa and Uganda, and the medical argument, strongly suggests that changes in HIV prevalence can lead to changes in TB incidence. While this does not imply that in attempting to fight both diseases countries could simply focus all efforts on reducing HIV prevalence, it does suggest that progress against HIV/AIDS will result in lower rates of TB incidence. Accepting this link, the paper now turns to examine some of the major problems caused by HIV/TB co-infection, explaining why it is such a serious concern.

The Problems of HIV/TB

TB is the most common form of HIV-associated infection and the leading cause of AIDS-related death in South Africa (Corbett, Watt, Walker, Maher, Williams, Raviglione & Dye, 2003; Harries, Hargreaves, Kaluwa, Nyangulu & Salaniponi, 2003). Ironically, HIV is easy to diagnose using accurate serological tests but there is no cure for the disease, while TB is curable using freely available anti-tuberculosis treatment but it can be very difficult to diagnose – especially in HIV positive patients (Wilson, 2005). This section examines the problems caused by HIV/TB co-infection, particularly in diagnosis and treatment of TB.

The most problematic cases for health workers are those where a patient is HIV positive and is suspected of having TB, but the TB cannot be accurately diagnosed. Increasingly in such cases health workers are forced to make treatment decisions on the basis of probability, instead of relying on the prescribed diagnostic tests required by the National TB Control Program (NTBCP) to place a patient on treatment (Wilson, 2005). Evidence from Table 1 showed that in 2008 only 37% of the incident TB cases in South Africa were diagnosed positively using the prescribed Sputum Smear Microscopy Test.

TB is a disease most commonly contained in the lungs - this is known as pulmonary TB (PTB) (WHO, 2004b). But the disease can also be contained in other parts of the body such as the abdomen, bone marrow, or around the heart - this is known as extra pulmonary TB (EPTB) (WHO, 2004b). Pulmonary and extra pulmonary TB are diagnosed using different methods, with EPTB being harder to diagnose accurately (unfortunately EPTB is becoming more prevalent among HIV positive patients as the TB spreads easily in a weak immune system) (National Tuberculosis Policy Guidelines, 2007; WHO, 2004b).

Currently there are several ways in which TB is diagnosed and healthcare workers have a brief window of opportunity in which to make a diagnostic decision before patients could become too ill to visit healthcare facilities (Corbett, Charalambous, Moloi, Fielding, Grant, Dye, De Cock, Hayes, Williams & Churchyard, 2004). Unlike TB in HIV negative patients, which is usually an indolent disease developing over months, HIV-associated TB is aggressive and can render immune-compromised patients moribund within weeks (Corbett, et al., 2004). In an HIV positive patient the presence of TB may also allow the HIV to multiply more quickly resulting in rapid progression of the virus (WHO, 2004b). This makes early diagnosis and treatment crucial.

PTB in a relatively healthy immune system is diagnosable through a Sputum Smear Microscopy Test, where laboratory technicians use a microscope to identify Acid-Fast Bacilli (AFB) in the sputum (National Tuberculosis Policy Guidelines, 2007). This is the test recommended by the WHO and is required by the NTCP. The South African TB guidelines stress: "…bacteriological confirmation of disease is the standard required for the diagnosis of pulmonary TB in adults." (National Tuberculosis Policy Guidelines, 2007) It is approximately 60% accurate in testing HIV negative patients (WHO, 2004b). However, the rapid spread of HIV in South Africa has challenged this strategy and the data in Table 1 confirm this. HIV positive patients are far more likely to have extra pulmonary infection and, given their weakened immune systems, they are also less able to contain the TB bacteria within the lungs, which is essential for diagnosis using this test (Corbett, et al., 2004). The sputum smear has therefore become considerably less effective as an accurate test for TB in patients who are infected with HIV.

Dr Laurel Giddy, director of the Knysna HIV and TB clinics affirms this, "The probability of TB increases as the CD4 count drops below 350, and increases exponentially as the CD4 drops below 100. Any TB patient can be sputum negative if the sputum collection method is faulty. However, many patients with CD4s fewer than 50 may be sputum negative as they don't have enough immunity to confine TB to their lungs and it becomes disseminated for example,

in other organs like the spleen, in lymph nodes, etc. These sites are less directly accessible, and this makes diagnosis more difficult" (Giddy, 2009).

This leaves a large number of people with TB undiagnosed and untreated. Furthermore, the current treatment policy only allows a patient to be pronounced "cured" if they were initially sputum positive and become sputum negative after completing their treatment (National Tuberculosis Policy Guidelines, 2007). The smear positive cure rates are reported below and should be judged against the accepted WHO cure rate target of 85%.

Table 3: South African TB Smear Positive Cure Rates[7]

Year	2000	2001	2002	2003	2004	2005	2006
Cure Rates	54.0%	53.7%	54.1%	56.7%	50.8%	57.6%	62.9%

Source: South African Department of Health, 2009

Without the change from sputum positive to negative a patient cannot officially be said to be cured of TB and thus the current statistics on "cure rates" in Table 3 only reflect the fraction of patients who are initially diagnosed as smear positive. Increased co-infection therefore makes it difficult to be sure of the total cure rates, especially since such a small percentage of TB infections in South Africa are diagnosed as smear positive.

In addition to taking sputum smears from patients the NTCP recommends a chest radiograph (x-ray) if the first two smears are negative (National Tuberculosis Policy Guidelines, 2007). A third smear is suggested if the x-ray is suggestive of TB (National Tuberculosis Policy Guidelines, 2007). Following these guidelines TB can be diagnosed in many HIV-infected patients (Corbett, et al., 2004). However, the gold standard for diagnosing TB is through a mycrobacterial culture. This method accurately diagnosis over 80% of TB cases and is the only way to diagnose Multi-Drug Resistant TB (MDR-TB) (Corbett, et al., 2004). The reason it has not replaced the sputum smear for general diagnosis is that a culture can take up to 6 weeks to return results and is also prohibitively expensive (Iseman, 2000). While it is prescribed for patients who have had TB previously, many co-infected patients do not have such time to spare and may die before the results become available (Giddy, 2009). New diagnostic tools are slowly being discovered but as yet no cheap, accurate tests are available to the general population.

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[7] Definition: The percentage of smear positive TB patients who are proven to be cured using sputum smear microscopy at the end of treatment.

In many cases doctors face a serious dilemma when seeing an HIV positive patient who is sick with possible TB; a typical scenario is described here in order to explain the problems more clearly.

Following standard procedure a patient suspected of having TB will be tested using the sputum smear microscopy and a chest radiograph. If the tests confirm TB then a six month treatment regime follows for the patient and if they adhere to this they will be cured. However, assuming the smear returns negative, the x-ray is inconclusive, and they cannot wait for a culture result, the doctor or nurse now faces a difficult choice. The physical symptoms may suggest that TB is present but the prescribed tests do not confirm this. There are thus three possibilities:
- The tests failed to pick up the TB (as they are only 60% accurate),
- The patient has some form of EPTB and further testing is necessary,
- It may be that the physical symptoms are due to the HI-virus and an opportunistic infection such as *pneumocystis carinii* pneumonia (PCP), not TB.
Either way, a decision must be made to place the patient on a full 6-month course of TB chemotherapy, or not.

If the doctor decides not to treat for TB and the patient does in fact have TB it is almost certain that this patient will spread the disease to others and if the TB remains undiagnosed for long enough it may eventually result in death. Also, if we assume that the patient is HIV positive and gets put onto ART at some point with undiagnosed TB there is a risk that they may acquire Immune Reconstitution Inflammatory Syndrome, which can be fatal[8] (Balakrishnan, Kumarasamy, Lloyd, Murugavel, Shankar, Sekar, Solomon & Vignesh, 2007). Dr Giddy, when questioned on how doctors make such decisions explains: "One has to be extremely careful when putting a patient on ARVs. Generally we err on the side of caution and give 'unnecessary' TB treatment first, because TB IRIS untreated can be deadly." (Giddy, 2009)

If, as Dr Giddy suggests, the patient is treated for TB as a precaution but it turns out that no TB was present the patient suffers 6 months of unnecessary treatment, which is preferable given the risks but can have various side effects. These include liver and kidney toxicity, skin rashes, pill burden, and the delayed diagnosis of other causes of symptoms. If this treatment coincides with ART

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[8] IRIS can occur when a patient is taking ART but has untreated TB. The ART begins to reconstitute the patient's immune system and as the immune system begins operating again it is able to recognise existing TB bacteria which it could not do when it was overwhelmed by the HI-virus. It then tries to fight the TB bacteria and in doing so the TB can overwhelm the already fragile immune system and cause the patient to die.

there are also possible drug interactions where the efficacy of the ART is compromised. Furthermore, the likelihood of the said patient defaulting on either treatment is higher, and if the patient does default on their TB medication then drug resistant strains of TB can develop and spread more easily (WHO, 2004b). This scenario highlights the difficulties faced in diagnosis of TB and the need for development of a rapid, cost-effective diagnostic test.

It is argued by activists that the reason doctors still use a 120-year-old TB test, and no new drugs have reached the market in 35 years, is because TB does not affect rich countries therefore drug companies see no profit in new TB research (Achmat & Roberts, 2005). Whether or not this is true it is surprising that satisfactory TB tests are not yet widely available. A Médicins Sans Frontiéres (MSF) poster captures this attitude toward the state of TB drugs and tests: it shows the picture of a young, solemn, female doctor and the print reads, "Don't tell me TB is under control. The TB drugs I'm prescribing were invented before I was born. And we have to rely on a TB test that was developed 120 years ago." (Equal Treatment, 2005) The fact that current tests and drugs are inadequate to deal with the co-infection epidemic is undeniable and highlighted by the numerous problems encountered. In general the consequences of co-infection include the following:

- Over-diagnosis of sputum smear-negative TB (due to difficulties in diagnosis);
- Under-diagnosis of sputum smear-positive TB (due to excess laboratory workload);
- Inadequate supervision of anti-TB chemotherapy;
- Low cure rates;
- High mortality rates during treatment;
- High default rates because of adverse drug reactions, high pill-taking burden, and HIV dementia;
- High rates of TB recurrence;
- Increased transmission of drug-resistant TB strains among HIV-infected patients. (WHO, 2004b)

In addition to these issues the number of clinical visits which co-infected patients must make requires substantial absence from work which could become a growing problem for both employers and employees. The problems highlighted in this section are numerous and potential solutions must be discussed and adopted if any ground is to be made against the co-epidemic in South Africa and elsewhere.

Possible Solutions

The extent of HIV/TB co-infection, the fact that TB incidence is rising due to increased HIV prevalence, and the serious problems that HIV/TB create, call for a bold approach in tackling the co-epidemic. Dr Giddy comments on what she would like to see as a response to the problems of co-infection: "I would like to see a focus on new diagnostic tools and better treatment support. Unlike HIV, we are all at risk for TB, especially people using public transport in winter, living in over-crowded conditions, or working in health care facilities." (Giddy, 2009) Four possibilities are briefly outlined in this section.

The first of these is the implementation of earlier ARV treatment (perhaps even as soon as a person's positive status is known). In addition to the required expansion of ART in South Africa and many developing countries, there have been calls for earlier ARV treatment to be implemented as a way to reduce the spread of HIV, lengthen lives, and fight TB. It is argued that patients should start treatment before their CD4+ count falls below 350 cells per μL, and a recent study published in *The Lancet* shows that earlier treatment appears to keep patients healthier for longer (Lawn & Wood, 2009). Granich et al (2006) in a somewhat controversial paper have gone beyond this and suggested immediate ART as a preventative measure, given that HIV infectiousness falls close to zero once treatment has begun (Granich, Gilks, Dye, De Cock & Williams, 2008). Both of these measures would be helpful in the case of HIV and TB infection. Given that decreasing HIV prevalence seems to result in decreasing TB incidence, as argued earlier, if earlier ART can help to prevent the spread of HIV this will also impact positively on TB infection. Furthermore, healthier immune systems due to earlier treatment would also play a large role in preventing many HIV positive patients from contracting TB. The possibility of earlier treatment appears to be one which requires serious consideration as a solution and is being considered; it was proposed at the 2009 National AIDS conference in Cape Town.

Secondly, a solution which would involve substantial investment and potentially take some time is the development of new TB diagnostic tests which are accurate, fast, and affordable for developing countries. It has been 20 years since the first HIV test was invented, and already there are inexpensive tests which have been developed and can diagnose a patient's HIV status with more than 99% accuracy in less than 20 minutes (Achmat & Roberts, 2005; Centre for Disease Control and Prevention, 2006). No laboratories or skilled technicians are required. But there has not been similar investment and development into TB diagnostics, this has been pointed out already, and more funding for research into new TB tests is vital (while there have been recent developments in this

field nothing is available to the general public). With better diagnostics TB can be much more easily treated and overcome. In addition to new diagnostic tests, newer TB drugs aimed at shortening the treatment period of 6 months and decreasing the side-effects would also contribute to faster eradication of TB, lower default rates, and decreased development of MDR-TB.

Thirdly, there is need for a greater level of integration between HIV and TB treatment, and an expansion of the current TB treatment framework. The extent of HIV/TB in South Africa must be recognised and all health facilities should strongly encourage both TB and HIV testing. The current strategy to treat TB is Directly Observed Treatment Short-course (DOTS), which requires TB patients to be observed while taking their treatment every weekday for six months (WHO, 2004). It also was intended to be used with patients who tested smear positive for TB, thus excluding many HIV positive patients. The framework should be broadened to include everyone on TB treatment. Greater integration would mean that patients are treated at the same health facility for both HIV and TB, thus ensuring that the treatment problems already mentioned are minimized. President Jacob Zuma in a national address on World Aids Day 2009 committed to a move in this direction where greater integration will be facilitated and co-infected patients will be treated when their CD4 count is 350 or less. "All patients with both tuberculosis and HIV will get treatment with anti-retrovirals if their CD4 count is 350 or less. At present treatment is available when the CD4 count is less than 200. TB and HIV/AIDS will now be treated under one roof". (Zuma, 2009)

Lastly, there is the possibility of using preventative TB therapy as a way to tackle the epidemic. People at high risk of developing TB, such as HIV positive individuals, may benefit significantly from Isoniazid Preventive Treatment (IPT) (WHO, 2004b). IPT is likely to provide protection against the risk of developing TB through two mechanisms; firstly, it decreases the risk of progression of infection, and secondly, it decreases the risk of reactivation of latent TB (WHO, 2004b; WHO/UNAIDS, 1999). However, in populations with high TB prevalence, such as South Africa, the duration of benefit following completion of a 6-month course of IPT is limited to around 2.5 years (WHO, 2004b). The short duration is probably due to continued exposure to TB infection – also the period of protection depends on the length of preventive treatment (WHO, 2004b). Taking IPT after a course of anti-TB therapy has been completed can also decrease the risk of TB recurrence in HIV-infected individuals, although it does not prolong survival (WHO, 2004b). The possibility of preventative treatment in HIV positive individuals could be examined in the South African case not only as an individual measure but also as an epidemiological measure. Individuals on IPT would reduce their risk of getting active TB, and in this way

the spread of TB could be contained as well. Given the high TB prevalence in South Africa and the risks faced by HIV positive individuals, IPT is a realistic option; furthermore, such treatment is relatively inexpensive.

Conclusion

This paper has examined the link between HIV and TB by investigating the theory behind it and analyzing the data. It is found that a change in HIV prevalence is associated with a change in TB incidence, in the same direction. The empirical link was established firstly through a comparison of South Africa and Uganda's infection rates over time where it was clear that the progression of TB followed that of HIV, and secondly by using a cross country regression of African countries in an attempt to isolate the effect of HIV on TB cases. The regression reported a large positive coefficient for "change in HIV prevalence" when controlling for other variables linked to TB incidence suggesting that a small change in the percentage of HIV prevalence is related to a significant change in the incidence of TB. This provides strong support to the medical arguments for a clear link between HIV and TB.

The numerous problems created by the 'terrible twins' were then examined in an effort to highlight the severity of HIV/TB co-infection. HIV positive individuals are at much higher risk of TB infection; the diagnosis of TB which is already challenging becomes even more so when a patient is HIV positive, and the TB progresses more quickly in an immuno-compromised body leading to many deaths. It is also increasingly difficult to measure South Africa's progress against TB since an overall TB cure rate does not exist; only patients diagnosed positively using the sputum smear test are included in the current cure rate statistics and high levels of co-infection impair the accuracy of this measure considerably.

Finally, four interventions which would confront, and help to solve, the problems of co-infection were suggested. Firstly the implementation of earlier ARV treatment was discussed as a way to simultaneously combat the HIV epidemic and stop TB. The second intervention was the development of new TB diagnostic tests and the roll-out of new tests which have already been developed. Developing cheap and accurate TB testing technology may not be achievable in the short term but is a vital part of the fight against co-infection in the long run. Thirdly, an issue which has long been advocated by organizations such as the WHO, is the focus on treating HIV and TB together. Recognizing the difficulties posed by co-infection and the danger of TB in HIV positive patients this approach would broaden the current framework and allow for more

comprehensive treatment. This has recently been highlighted by President Jacob Zuma as one of South Africa's national healthcare goals. Fourthly there is opportunity to make use of preventative TB therapy for individuals. Such prophylactic treatment could play an important role in protecting HIV positive people who face a high risk of TB infection.

Appendix

(I)

Correlation Coefficents						
	Change in Hiv Prev.	GNI per capita	Physicians per 1000	Urban Pop	Life Expectancy	Exp. on Health
Change in Hiv Prev.	1					
GNI per capita	0.3432	1				
Physicians per 1000	0.1606	0.2238	1			
Urban Pop	0.0959	0.5711	0.2932	1		
Life Expectancy	-0.2943	0.0498	0.193	0.2857	1	
Exp. on Health	0.19	-0.1609	0.0547	-0.1929	-0.0671	1

(II)

White's Test for Heteroscedasticity				
Dependent Variable: Residual Squared	Coefficient	Std.Error	t stat	P>t
GNI per capita*Change in HIV Prev.	0.00533	0.00	2059	0.014
GNI per capita*Life Expectancy	0.00163	0.00	2.15	0.038
GNI per capita*Urban Pop	-0.00014	0.00	-0.4	0.689
GNI per capita*GNI per capita	0.00000	0.00	1.04	0.303
Change in HIV Prev.*Life Expectancy	-0.21183	0.92	-0.23	0.821
Change in HIV Prev.*Urban Pop	-0.49642	0.41	-1.2	0.237
Change in Hiv Prev.*Change in HIV Prev.	1.06988	0.76	1.4	0.17
Life Expectancy*Urban Pop	-0.22057	0.16	-1.36	0.181
Life Expectancy*Life Expectancy	-0.01854	0.18	-0.1	0.921
Urban Pop*Urban Pop	0.06458	0.05	1.28	0.208
GNI per capita	-0.10193	0.05	-2.24	0.031
Change in HIV Prev.	-3.45888	39.57	-0.09	0.931
Urban Pop	7.69124	6.22	1.24	0.224
Life Expectancy	7.98172	16.74	0.48	0.637
Constant	-302.10630	419.68	-0.72	0.476
R-Squared	0.47360			
Adjusted R-Squared	0.31020			
N	51			

The White's test statistic is $N*R^2 = 51*0.4736 = 24.15$. Comparing this with the χ^2 critical value, at the 5% level, of 31.3193 we do not reject the null hypothesis of no heteroscedasticity. On the basis of the White test we therefore conclude that there is no heteroscedasticity at the 5% level.

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