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Tuberculosis in South Africa: Pandora's box?

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In most sub-Saharan African countries, including South Africa, TB caseloads and annual TB incidence rates have more than doubled (Figure 1) from relatively high, but stable, pre-HIV era levels in the 1980's (1,2). In South Africa, the high incidence of TB prior to the HIV epidemic was probably a result of a combination of geopolitical factors related to apartheid and migrant labour, but since 1990 the pre-eminent factor contributing to the current massive TB epidemic is HIV infection – the most potent risk factor for TB (3). In a single year (2007), almost half a million South Africans were treated for TB (948/100 000 or ~1% of the population). Moreover, globally South Africa is ranked second, after Swaziland, by TB incidence, both in HIV-infected and uninfected individuals (1). Overall at least 60% of TB patients in South Africa are HIV co-infected. Because of its relatively large population and high HIV prevalence, South Africa alone has 28% of the total HIV-infected TB caseload in the world, by far the largest number of HIV-infected TB patients in a single country. Although the risk of TB disease increases as the immune system deteriorates as a result of HIV infection, a discernable increased risk of TB can be observed one year after HIV infection when it is unlikely that the CD4 count has been reduced substantially (4).

But the risk of TB in HIV-infected adults and children can be reduced. Adults not taking highly active antiretroviral therapy (HAART) have about a 7-10% risk of developing active TB per annum (5,6), whereas the risk of TB in people on long term HAART is reduced by 70-80%. However, even in those taking HAART the risk of developing TB is still many times higher than that of HIV uninfected people.

In people living with HIV, TB is the leading serious opportunistic infection and the leading cause of death, both prior to HAART and while taking HAART. In 2007 112 000 people were reported to have died during their TB treatment of whom an estimated 93 000 were HIV-infected (1). This despite the fact that in South Africa effective TB treatment has been widely available for many years, and HAART since 2004. TB is commonly treated as an outpatient illness with standard TB drug regimens. However, approximately 20% of all adult medical admissions are TB-related of whom ~90% are HIV-infected, and for many patients their admission will be the first confirmation of their HIV-infection. Most hospitalised co-infected TB patients will have severe immune suppression with extensive pulmonary and/or disseminated multi-organ TB (7). A quarter of these patients will die during their hospital admission, most in the first few days or weeks after admission (8,9). This suggests

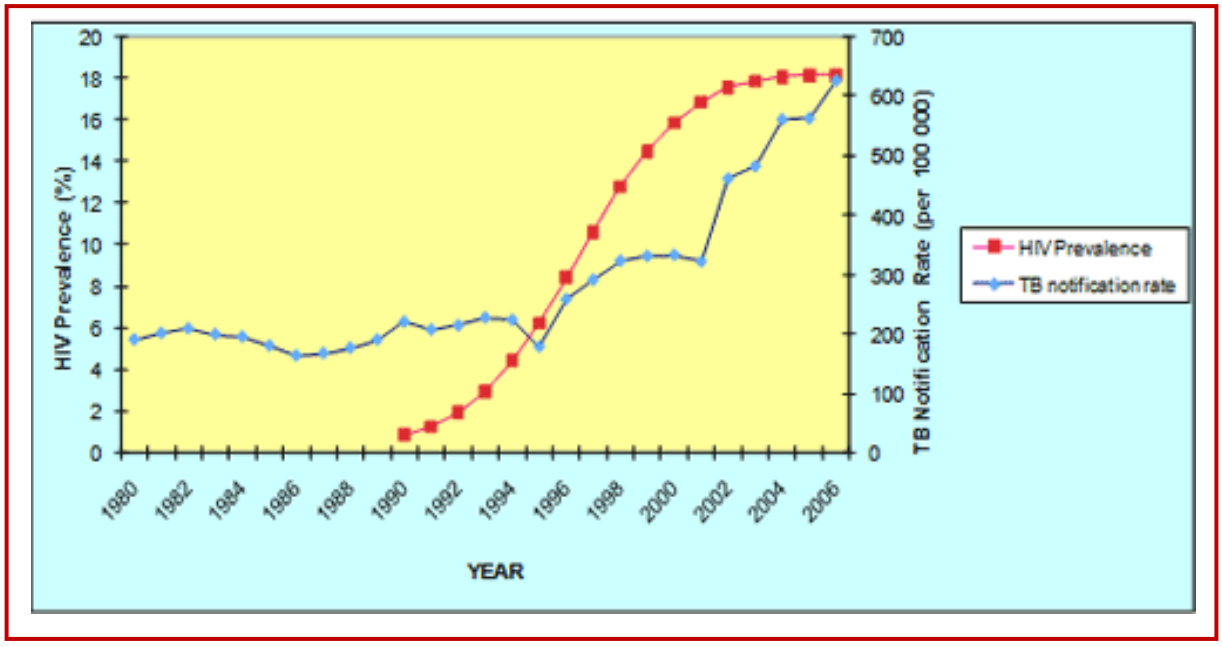

Figure 1: TB notification rate and antenatal HIV seroprevalence in South Africa

that delays in presentation and diagnosis of both HIV and TB combined with rapid progression of TB are major obstacles to improving the prognosis of co-infected adults. Moreover, overloaded health systems raise barriers to access care. The real tragedy is that if these patients survived their admission and were started on HAART, they would probably survive for years on HAART. So, initiating HAART in patients with TB and HIV saves lives. Unpublished data from a randomised control trial from Durban shows that early initiation of HAART soon after a diagnosis of TB is made, prevents mortality in those co-infected with both TB and HIV. It would even be better if they were identified as being HIV-infected and started on HAART prior to becoming ill: both their hospitalisation and TB could be avoided.

3 I's Strategy

Taking into account that earlier diagnosis of TB in high HIV prevalence settings can prevent transmission of TB and may reduce mortality, together with the fact that the Directly Observed Treatment Short course (DOTS) strategy is insufficient to halt the rise of the TB epidemic, the World Health Organisation's (WHO) Stop TB Department now proposes the 3I's strategy: Intensified Case Finding, Isoniazid preventive treatment, and TB Infection Control. However, the 3I's strategy has some pitfalls.

Mass screening campaigns for HIV and TB with earlier initiation of treatment are likely to be beneficial, but confirming TB in HIV-infected patients is more difficult than in uninfected patients. The diagnostic mainstay of TB has been microscopy of a stained sputum specimen (or smear), which is a cheap, low-tech investigation, easily undertaken in most settings. However, microscopy is less reliable in HIV-infected patients and paradoxically, the lower the CD4 count, the less reliable microscopy is (10). The definitive diagnosis of TB relies on culturing this slow growing organism and identifying the presence of mycobacteria and then confirming Mycobacterium tuberculosis. A positive result usually takes about 14 days and a negative result, up to 50 days, which is too late to impact on treatment decisions in ill people. Moreover, depending on whether the test is positive or not, the cost of culture and mycobacterial identification is 4-6 times that of microscopy. As a result many patients are initiated on TB treatment on their clinical picture alone, without laboratory confirmation. Clearly, there is a critical need for novel, rapid TB diagnostics at the bedside, preferably using urine or saliva that are not as hazardous to collect, transport or process as blood or sputum. What makes diagnosis even more complex is that there are reports of the presence of asymptomatic TB in a proportion of HIV-infected adults making it even more difficult to clearly identify who should and who should not be further investigated for TB. Furthermore, data from Zimbabwe (11) suggest that HIV-infected adults bear the burden of TB disease by becoming ill rapidly, and either seeking medical assistance or dying relatively quickly, thereby limiting opportunities for transmission, whereas HIV uninfected adults with TB progress more slowly and spend more time in the community during which to transmit the infection. To prevent TB transmission by HIV-uninfected patients, and to reduce morbidity and mortality in HIV-infected patients, intensified case finding for TB should include simultaneous HIV testing with TB screening for both HIV-infected and uninfected patients.

Isoniazid preventive treatment (The second "I": providing one drug therapy for six months to eradicate dormant or latent TB bacilli in the lungs) has, in multiple randomized trials, been shown (12) to be an efficacious intervention to prevent new cases of TB. Unfortunately the duration of effect is limited to about two years.

TB infection control (The third "I") is a response to recent reports from the Church of Scotland in Tugela Ferry, describing a severe outbreak of extremely drug resistant TB (XDR) (13). In this outbreak, virtually all the XDR patients were HIV-infected, and the virulence of the TB strains was high (most patients died within two months of being diagnosed). Furthermore XDR was easily transmitted, as about half of the patients had not received prior TB treatment, suggesting that many patients had contracted their resistant TB in hospital. Authorities responded immediately with a variety of interventions that have been adopted countrywide. A key intervention is environmental management: dilution of potentially contaminated air in wards, consulting rooms and waiting areas by opening windows and mechanical external venting, and installation of ultra violet lights which are mycobactericidal. These environmental interventions should also be used in other settings such as work places, public waiting areas and even bars and shebeens.

The TB epidemic in South Africa is unlikely to be controlled until the HIV prevalence is dramatically lowered and/or the immune status of HIV-infected individuals can be restored to that of uninfected individuals. TB statistics from Uganda, a country where a sustained reduction in HIV prevalence has been achieved, show that reductions in TB incidence were only seen 12 years after the first indications of a sustained reduction in HIV prevalence. South Africa, therefore, is likely to have several years of increasing TB caseloads, incidence and mortality, unless widespread preventive strategies such as intensified case finding for both HIV and TB with early initiation of HAART and widespread use of preventive treatment are aggressively implemented.

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