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Modelling the impact of HIV and ART on TB

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Models of HIV can be very simple (1) or very detailed (2,3). The simple models give a good overall understanding of the drivers of the epidemic while the detailed models allow one to explore the impact of different structures, transmission networks and interventions. The standard model of TB (4), even in its simplest form, can involve many different transition states for fast and slow progressors, latent TB and TB disease, those on treatment and those that fail treatment. Since all of these models are well established, it is tempting to model the combination of HIV and TB by repeating a suitable TB model a number of times corresponding to the various states of HIV: uninfected, early infection and various states corresponding to the progression of HIV through the various clinical stages of infection to death. This can, however, lead to a very complex model with tens, if not hundreds of parameters, requiring considerable computing power to run. Fortunately, the time scales over which the two infections progress are very different, allowing us to greatly simplify the problem.

Rising incidence of TB due to HIV has no impact on TB in HIV negatives

Very early in the epidemic of HIV it was clear that HIV was driving the incidence of TB rapidly upwards. Given the already very high rates of TB in countries like South Africa, and within South Africa in the gold-mines, people were concerned that the increase in TB resulting from the severe epidemic of HIV would spread TB throughout the population. Fortunately, this turned out not to be the case and the key study in this regard was carried out by Elizabeth Corbett studying the gold miners in the town of Welkom. Corbett carried out a retrospective analysis of the incidence and prevalence of TB in HIV-positive and HIV-negative miners (5) between the years 1990 and 2000. As expected, the incidence of TB in men with HIV increased, over this period, from 2.2% per annum (p.a.) in 1991–1997 to 5.9% p.a. in 1998–1999 to 9.4% p.a. in1999–2000. But, unexpectedly, the incidence of TB in men without HIV remained constant at 1.0% p.a., 1.1% p.a. and 1.1% p.a. Since this study covered the time when the epidemic of HIV was taking off it gave us a number of key insights. In 1990 most people with HIV must have been recently infected suggesting that soon after infection the risk of developing TB doubles. As time passes, more and more men have more advanced HIV-disease and, as their immune systems collapse, their risk of developing TB continues to increase. All of this was confirmed in subsequent studies that showed that a person's CD4+ cell count drops by about 25% immediately after infection with HIV and then decreases almost linearly, on average reaching zero over about ten years – the untreated life expectancy. Further studies showed that the incidence of TB increases exponentially with declining CD4+ cell counts and this enables one to fit the observed epidemic trends quite well (6-8).

Just as important, however, was Corbett's quite unexpected observation (5) that the dramatic rise in the incidence of TB, resulting from the rising epidemic of HIV, had no impact on TB in HIV negative people. The reason for this soon became clear: as people's CD4+ cell counts decline their risk of developing TB rises, but the mortality of co-infected people increases so that they die that much more quickly. Since the prevalence of disease is roughly equal to the incidence times the duration of infectiousness, prevalence, and hence infectious pressure, would be the same even if the incidence increases by a factor of, say, ten, provided provide the mortality increases and the duration of infectiousness decreases, by the same factor.

Simple model to estimate impact of HIV on TB epidemic

This insight gives us a very simple way to model the impact of HIV on TB. First we note that TB is a very slow disease, with characteristic times of the order of decades, compared to HIV, with characteristic times of the order of years. Second, for the reasons given above, TB in HIV-positive people does not add to the incidence and therefore the risk of TB in other people We can therefore use whatever model we like for TB in HIV-negative people, ignoring the epidemic of HIV completely. For the HIV-positive people we assume: 1. That the incidence of TB disease doubles (7) immediately after the two week acute phase of HIV (9.10); 2. That the incidence of TB increases exponentially with time since infection using the stage of infection as a surrogate for the time since infection; 3. That the duration of TB disease in HIV positive people is less than in HIV-negative people; 4. ART reduces the incidence of TB in people with HIV (8). To model the epidemic of TB in HIV-positive people, given the epidemic of TB in HIV-negative people, we then have only two fixed and one variable parameter in model. The factor of 2 in the first assumption we take as fixed. The exponential rate of increase of TB with declining CD4+ cell counts in the second assumption is the only variable parameter. The increase in morality and the reduction in disease duration, the 'Corbett factor' appears to be the same

over a number of different countries and can be taken as fixed (1). When we introduce ART the corresponding reduction in the incidence of TB appears also to be fixed at about 60%.

So given a model of what we expect to happen to TB without HIV and considering only the comparatively short time scale of HIV compared to TB, we can model the impact of HIV on TB with a model that requires three fixed but only one variable parameter and this has been shown to give very good fits to the TB epidemics in all of southern Africa (2) and indeed East Africa as well (Williams, unpublished).

The important lesson for modellers is that one is tempted to start with detailed models of TB and HIV and then combine them into one even more detailed TB-HIV model, giving a model with tens of parameters, and this is what the present author initially did (8). But clear thinking and a better understanding of the natural history of HIV and TB, drawing on the critical work of Corbett, makes it possible to model the epidemic of TB in the context of HIV with only a single variable parameter (1) which is not only much easier to do but gives greater insight into the way in which the two epidemics interact.

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