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Antiretroviral Drugs for Tuberculosis Control in the Era of HIV/AIDS

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HIV/AIDS has dramatically increased the incidence of tuberculosis (TB) in sub-Saharan Africa where up to 60% of TB patients are co-infected with HIV and each year 200,000 TB deaths are attributable to HIV co-infection. Now HIV threatens TB control in Asia, Eastern Europe and Latin America. Antiretroviral (ARV) drugs can prevent TB by preserving immunity but cohort analysis shows that early therapy, plus high levels of coverage and compliance, will be needed to avert a significant fraction of TB cases. However, ARVs could enhance the treatment of TB while TB programmes provide an important entry point for the treatment of HIV/AIDS.

In the decades leading up to 1980 TB was in decline throughout the world. There was reason to believe that if control efforts were maintained, and where necessary strengthened, TB would be driven steadily towards elimination. However, 30% of people in sub-Saharan Africa are latently infected with *Mycobacterium tuberculosis* (*1*) and the rapid spread of HIV during the 1980s and 1990s led to a similarly rapid increase in the incidence of TB, with notification rates in some countries increasing by more than five times in ten years (*2*). HIV/AIDS control strategies have not substantially reduced the prevalence of HIV in sub-Saharan Africa (*3*), and the decline in immunity in people co-infected with HIV and TB has meant that even good TB control programs based on short-course chemotherapy (*4*) have not been sufficient to contain the rising incidence of TB (*5*). As HIV spreads through Asia, Eastern Europe and Latin America (*3*) TB control could be compromised there also. The development of new classes of ARV drugs (*6*), the availability of cheap generic equivalents (*7*), and the increasing commitment of international donors to making ARV drugs widely available in poor countries (*8*) should all help to reduce HIV-related illness and death over the next few years. Whether ARVs have a significant impact on TB depends on their efficacy in preventing disease and prolonging life, on population coverage and patient compliance, and on synergies between the treatment of TB patients and the provision of ARV therapy to those patients who are HIV positive.

HIV infects and kills $CD4^+$ T-lymphocytes, and the concentration of $CD4^+$ cells declines as HIV infection progresses; this breakdown of immunity increases susceptibility to new *Mycobacterium tuberculosis* infection, and permits the reactivation of latent infection. ARVs block virus replication and reduce the plasma viral load to undetectable levels allowing a degree of immune reconstitution. Here we bring together data of four kinds, within a single analytical framework, in order to determine the potential, population-level impact of ARVs on TB.

First, the rate of decline of $CD4^+$ count in people infected with HIV has been determined at different levels (*9–13*) and over different ranges of $CD4^+$ count (*14–19*). The form of the decline through time has been characterized as exponential (*20*), quadratic (*19*), and linear or piece-wise linear (*15*, *18*). The rates of decline of $CD4^+$ count from ten studies are shown in Fig. 1A [Supporting Online Material (SOM) Text]. The aggregated data suggest that, as the $CD4^+$ count declines from 800/μl to 300/μl, the rate of decline slows from about 100/μl/yr to 60/μl/yr. Below 300/μl, the rate of decline, measured over a few months, increases again to 150/μl/yr as $CD4^+$ count approaches 100/μl. At very low $CD4^+$ count the rate of decline is between 150 and 250/μl/yr. On the basis of these data, our best estimate of the decline of $CD4^+$ count with time is as shown in Fig. 1B, which predicts a median survival time after infection with HIV of 9 years (range 7 to 13 years), consistent with independent estimates of the median time to death from cohort studies (*21*, *22*).

Second, the incidence of culture-positive TB as a function of $CD4^+$ count has been estimated in three studies, among which the incidence of TB varies by a factor of sixty. For a reduction of 200 $CD4^+$ cells/μl, the incidence of TB in these studies increased by factors of 1.6 (1.0–2.5) (*9*), 2.4 (1.2–4.7) (*23*), and 2.1 (1.6–2.8) (*24*) (here and elsewhere ranges are 95% confidence limits) [Supporting Online Material (SOM) Text]. It is also important to know if the variation of TB incidence with $CD4^+$ count depends on whether or not people are infected, uninfected or anergic, with regard to TB, as determined by skin testing with purified protein derivative (PPD). In a study in Italy (*23*) the incidence of TB increased by a factor of 3.2 (1.3–8.1) when comparing PPD-negative with anergic people, and by about the same factor in a comparison of anergic and PPD-positive people. This was true across all levels of $CD4^+$ count and the interaction between PPD status and $CD4^+$ count was not significant

[Supporting Online Material (SOM) Text]. In a study of HIV-positive patients in the United States (*25*) the incidence of TB was 11.3 (3.8–33.7) times higher in PPD-positive than in PPD-negative patients in agreement with the Italian study. In sum, these data suggest that the incidence of TB increases by a factor of 2.1 (1.4–3.0) for each reduction of 200/µl in the $CD4^+$ count (weighted geometric mean) as shown in Fig. 1C, and that this increase is independent of PPD status or the background incidence of TB.

Combining the decline in $CD4^+$ count over time (Fig. 1B) with the increase in TB incidence as a function of $CD4^+$ count (Fig. 1C) gives TB incidence as a function of time since infection (Fig. 1D) [Supporting Online Material (SOM) Text]. We calculate that the median $CD4^+$ count at which HIV-infected people develop TB is 256/µl (207–310/µl), higher than, but not significantly different from, the median $CD4^+$ count of 202/µl (136–269/µl) observed in HIV-positive TB patients [Supporting Online Material (SOM) Text]. Since the onset of severe pulmonary TB is known to be associated with a fall in $CD4^+$ count (*26*), the difference is in the expected direction.

The third set of data describes the efficacy of ARVs in preventing TB. In a study in Cape Town, South Africa (*24*) ARV therapy for patients with $CD4^+$ count below 200/µl, between 200 and 350/µl, and above 350/µl, reduced the incidence of TB in all three groups to that in the group with the highest $CD4^+$ count [Supporting Online Material (SOM) Text]. This suggests that ARV therapy reduces the incidence of TB to the level observed soon after sero-conversion.

he fourth piece of information is the survivorship of persons infected with HIV. In an earlier study we found that, without antiretroviral therapy, and for a mean age at seroconversion of 30 years, survivorship follows a Weibull distribution with a median survival time of 10.2 ± 0.5 years. The Weibull shape parameter was 2.28 ± 0.12 implying that the increase of mortality with time since infection is close to linear. With ARV therapy, the shape of the survivorship curve remains the same but life-expectancy increases to 19.8 ± 2.2 years (*27*).

These four groups of data can be combined to calculate the incidence of TB over time in a cohort of HIV-infected patients, allowing the time at which ARV therapy is provided after HIV infection to vary [Supporting Online Material (SOM) Text]. Given the evidence that ARV therapy reduces the incidence of TB to the level immediately after HIV sero-conversion (*24*) the risk of TB per person alive will be constant through time in cohorts that start ARV therapy immediately after HIV sero-conversion (line 8, Fig. 2). The total number of TB cases then follows the Weibull survivorship curve with a median of about 20 years. In cohorts that start ARV therapy at lower $CD4^+$ count, the number of TB cases initially increases while most people are still alive and their $CD4^+$ count is falling, but declines once they start ARV therapy, and declines further as they die (lines 7 to 1, Fig. 2). Without ARV therapy, and assuming a life expectancy of 10 years, the mean time between HIV infection and the development of TB is 6.0 years, consistent with the observed time lag of about six years between rising TB notifications and HIV incidence in East Africa (*28*). With ARV therapy, the mean time between HIV infection and the development of TB varies from 7.2 to 8.6 years depending on the $CD4^+$ count at which therapy is started.

Using the data in Fig. 2 we can determine the reduction in the incidence of TB over twenty years as a function of the $CD4^+$ count at which ARV therapy is initiated and the effective coverage, i.e. the product of population coverage and compliance (Fig 3A). Current recommendations for developing countries are that ARV therapy should begin when the $CD4^+$ count falls below 200/µl (*29*). With complete coverage and perfect compliance this would reduce the cumulative incidence of TB in people infected with HIV by just 22% over 20 years; with an effective coverage of 50%, only 11% of TB cases would be prevented (Fig. 3A). To have a substantial impact on the incidence of TB in high burden countries it will therefore be necessary to start therapy early and to achieve high coverage and compliance. But even if ARV therapy begins at 500 $CD4^+$ cells/µl with 85% effective coverage TB incidence would be cut by only 50% over 20 years (Fig. 3A). The explanation for this low impact is that ARVs suppress TB but extend life expectancy, so HIV-infected individuals on treatment develop TB at a lower rate but over a longer period of time (Fig. 2). Because this is a cohort model it does not include the additional impact of ARVs on TB transmission. However, that additional impact is likely to be small, even in sub-Saharan Africa, because the proportion of TB transmission events from people dually infected with HIV is estimated to be less than 10% (*1, 28*).

Much of the TB arising in HIV-positive individuals is due to the breakdown of latent infections, so it should be possible to reduce TB incidence further by treating these latent infections, for example with isoniazid as an adjunct to ARV therapy (*30*). Furthermore, there is evidence for a significant decline in $CD4^+$ count and a corresponding increase in TB incidence soon after sero-conversion [Supporting Online Material (SOM) Text]. If we assume, optimistically, that the joint effect of isoniazid and ARVs is to eliminate the risk of TB the impact on the long term transmission of TB would be greater (Fig. 3B). Under these circumstances, and assuming 85% coverage, starting ARV therapy at 500/µl would reduce the number of TB cases among those who are HIV positive by 70%; starting at 200/µl would only reduce the number of cases by 25% (Fig. 3B).

The conditions under which ARVs could prevent a significant fraction of TB cases are therefore demanding,

requiring treatment early in the course of HIV infection, plus high coverage and high compliance. As yet, no low- or middle-income country comes close to satisfying these requirements, with the possible exception of Brazil (*31*).

For countries that are attempting to manage interacting epidemics of TB and HIV/AIDS, one way to proceed would be to strengthen national TB control programmes and use them as a point of entry for ARV therapy. A strong reason for doing so is that HIV infection is concentrated among TB patients; in parts of southern Africa more than 60% of TB patients are HIV positive and in the WHO African Region 31% of TB cases and 40% of TB deaths are directly attributable to HIV (*1*). Furthermore, as shown above, TB patients who are infected with HIV generally present to health services with $CD4^+$ count in the range 150 to 300/μl, the currently recommended level at which ARV therapy should start in non-industrialized countries (*29*). Taking this approach, the immediate role for ARV drugs in TB control would be in supporting curative treatment and ensuring long term survival, rather than as a mechanism of prevention. For an HIV-infected TB patient, neither anti-TB drugs nor antiretroviral drugs alone will significantly extend life expectancy, but the two kinds of therapy should be powerful in combination.

References

1. E. L. Corbett *et al.*, *Archives of Internal Medicine* **163**, 1009 (2003).
2. World Health Organization, "Global Tuberculosis Control: Surveillance, planning financing (World Health Report 2003)" *Tech. Report No. WHO/CDS/TB/2001.287* (World Health Organization, 2003).
3. UNAIDS, "Report on the global HIV/AIDS epidemic" *Tech. Report No. UNAIDS/02.26E* (UNAIDS, 2003).
4. M. C. Raviglione, A. Pio, *Lancet* **359**, 775 (2002).
5. K. M. De Cock, R. E. Chaisson, *International Journal of Tuberculosis and Lung Disease* **3**, 457 (1999).
6. J. Cohen, *Science* **296**, 2320 (2002).
7. Médicins Sans Frontières (2002).
8. D. Tan, R. E. Upshur, N. Ford, *BMC International Health and Human Rights* **3**, 2 (Apr 1, 2003).
9. Y. Yazdanpanah *et al.*, *International Journal of Epidemiology* **30**, 864 (Aug, 2001).
10. M. Dorrucci *et al.*, *European Journal of Epidemiology* **15**, 317 (Apr, 1999).
11. G. S. Gottlieb *et al.*, *Journal of Infectious Diseases* **185**, 905 (Apr 1, 2002).
12. R. Salamon *et al.*, *Journal of Acquired Immune Deficiency Syndromes* **29**, 149 (Feb 1, 2002).
13. T. E. Yamashita *et al.*, *AIDS* **15**, 735 (Apr 13, 2001).
14. R. Detels *et al.*, *Journal of the American Medical Association* **280**, 1497 (Nov 4, 1998).
15. P. T. Schellekens *et al.*, *AIDS* **6**, 665 (Jul, 1992).
16. P. J. Easterbrook, J. Emami, B. Gazzard, *AIDS* **7**, 959 (Oct, 1993).
17. A. Cozzi-Lepri *et al.*, *Journal of Infectious Diseases* **175**, 775 (Apr, 1997).
18. W. Lang *et al.*, *Journal of Acquired Immune Deficiency Syndromes* **2**, 63 (1989).
19. A. J. McNeil, S. M. Gore, *Statistics in Medicine* **15**, 75 (Jan 15, 1996).
20. J. J. Drabick, W. J. Williams, D. B. Tang, W. Sun, R. C. Chung, *AIDS Research and Human Retroviruses* **8**, 2039 (Dec, 1992).
21. CASCADE Collaboration, *Lancet* **355**, 1131 (2000).
22. D. Morgan *et al.*, *AIDS* **16**, 597 (Mar 8, 2002).
23. G. Antonucci, E. Girardi, M. C. Raviglione, G. Ippolito, *JAMA* **274**, 143 (Jul 12, 1995).
24. M. Badri, D. Wilson, R. Wood, *Lancet* **359**, 2059 (2002).
25. N. Markowitz *et al.*, *Annals of Internal Medicine* **126**, 123 (Jan 15, 1997).
26. J. A. Pilheu *et al.*, *International Journal of Tuberculosis and Lung Disease* **1**, 422 (1997).
27. B. G. Williams, A. Kochi, C. Dye, Submitted for publication (2002).
28. C. S. M. Currie, B. G. Williams, R. C. Cheng, C. Dye, *AIDS*, in press (2003).
29. World Health Organization, *Scaling up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach* (World Health Organization, Geneva, 2002).
30. A. D. Harries, N. J. Hargreaves, F. M. Salaniponi, *International Journal of Tuberculosis and Lung Disease* **5**, 1109 (2001, 2001).
31. G. C. Levi, M. A. A. Vitoria, *AIDS* **16**, 2373 (2002).

Supporting Online Material

www.sciencemag.org/cgi/content/full/1086845/DC1
SOM Text
Figs. S1 to S3
Tables S1 to S3
References

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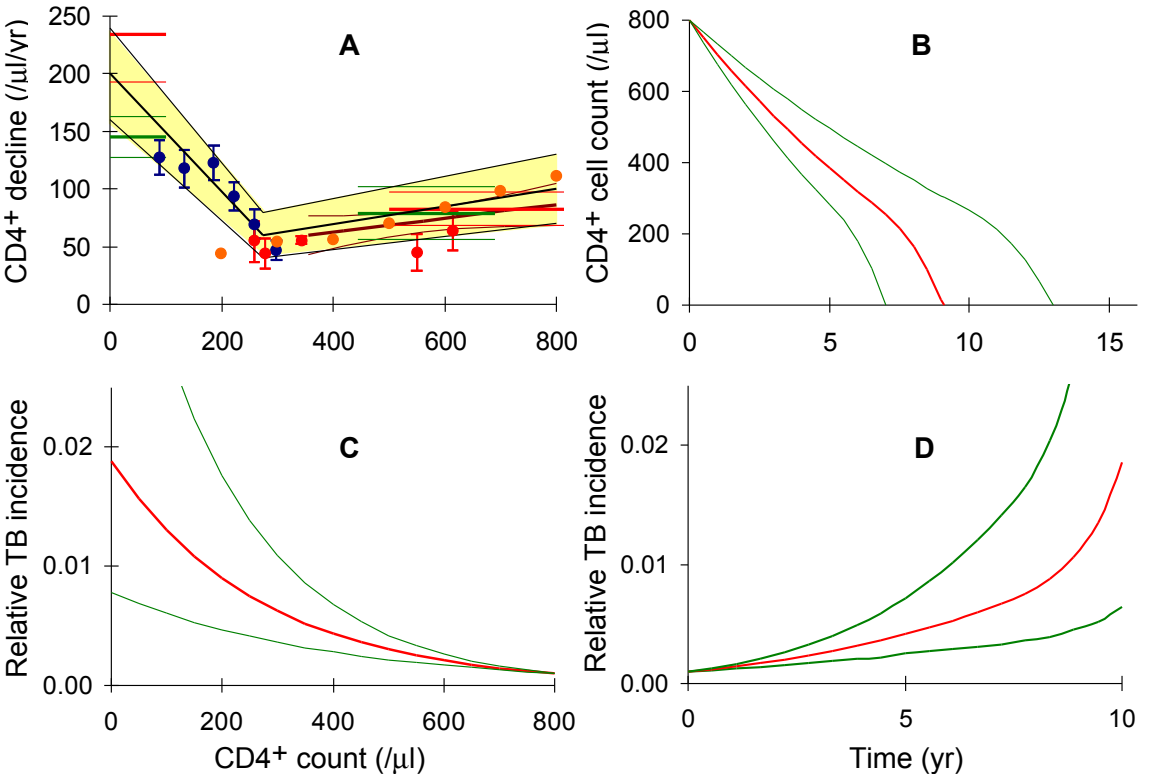
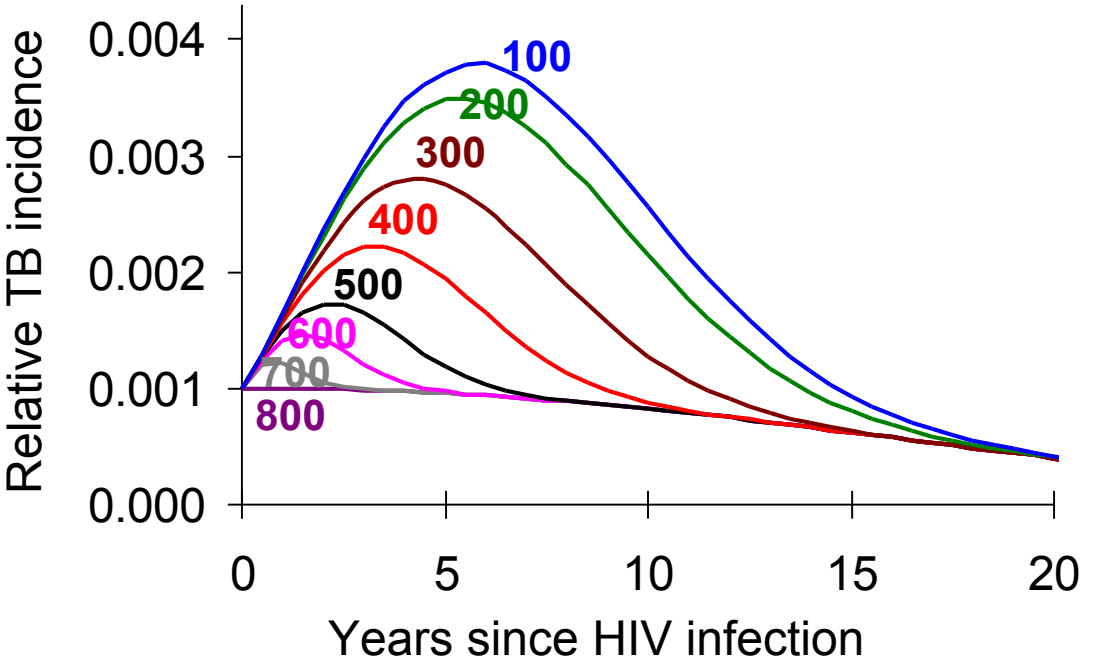
Fig. 1. Data used to estimate the incidence of TB in a cohort of people infected with HIV. (**A**) Estimated rates of decline of $CD4^+$ count as a function of $CD4^+$ count with 95% confidence limits. Brown lines (*14*); red lines (*15*); green lines (*18*); blue dots (*16*); orange dots (*17*); red dots point estimates (*9–13*). The horizontal lines indicate results for studies in which the rate of decline was constant over the given range of $CD4^+$ cell count. For the red and green lines running from 0 to 100 $CD4^+$ cells/μl, time was measured to the onset of AIDS.

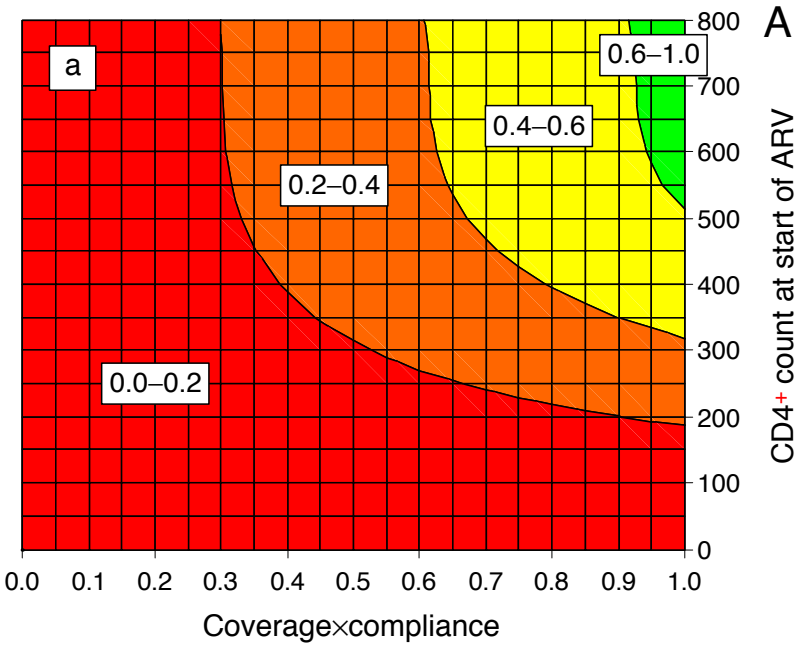
These represent selected groups of rapid sero-converters and may be regarded as an estimate of the maximum rate of decline among people who have advanced HIV infection. Heavy black line gives the expected rate of decline of $CD4^+$ count from the aggregate data, the yellow polygon indicates the range. (**B**) $CD4^+$ count plotted against time for the expected rate of decline in (A) (red line) with confidence limits corresponding to the yellow polygon in (A) (green lines). (**C**) Estimated TB incidence as a function of $CD4^+$ count (red line; confidence limits, green lines) for a population in which the $CD4^+$ count, immediately after seroconversion, is 800/μl and the annual incidence of TB is 100 cases per 100,000 people per year. (**D**) Incidence of TB as a function of time estimated from (B) and (C) assuming a nominal incidence of TB immediately after seroconversion of 100 cases per 100,000 people per year.

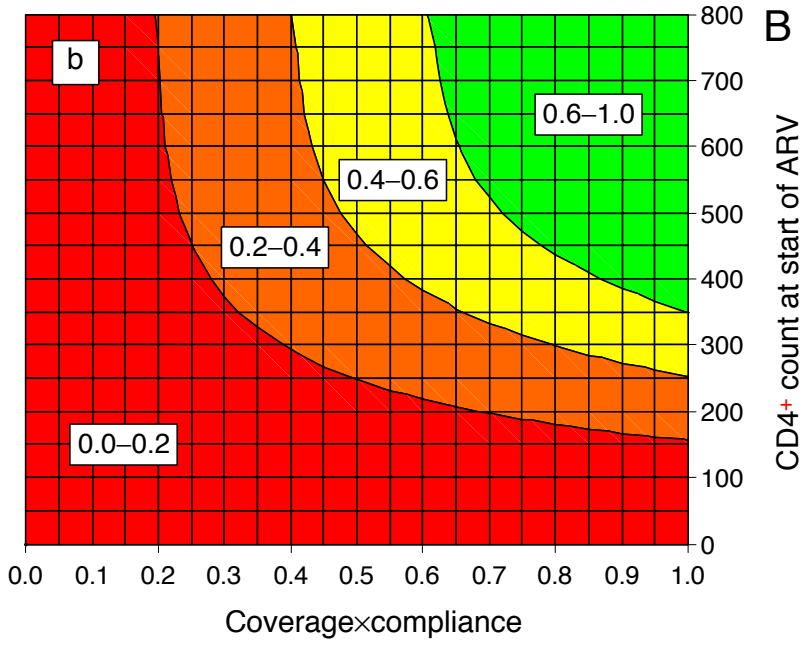
Fig. 2. Relative incidence of TB in a cohort of newly infected people as a function of time and of the $CD4^+$ count below which people are given triple therapy (inset numbers $CD4^+$ cell count/μl). The nominal incidence of TB immediately after seroconversion is 100 cases per 100,000 people per year; if the background incidence were higher or lower the curves would be scaled up or down accordingly.

Fig. 3. Proportional reduction in the incidence of TB over 20 years among HIV-positive people (inset boxes) as a function of effective coverage (actual coverage×compliance) and the $CD4^+$ count/μl at which people start ARV therapy. (**A**) Assuming that the effect of ARV therapy is to reduce the incidence of TB to the level immediately after sero-conversion. (**B**) As (A) but assuming that TB preventive therapy is also given and that this reduces the incidence of TB in people on ARV therapy to zero.


A
B
C
D
CD4+ decline (/µl/yr)
CD4+ cell count (/µl)
Relative TB incidence
Relative TB incidence
CD4+ count (/µl)
Time (yr)
0
50
100
150
200
250
400
600
800
5
10
15
0.00
0.01
0.02


Relative TB incidence
0.004
0.003
0.002
0.001
0.000
100
200
300
400
500
600
700
800
0
5
10
15
20
Years since HIV infection


A
a
0.0–0.2
0.2–0.4
0.4–0.6
0.6–1.0
0
100
200
300
400
500
600
700
800
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Coverage×compliance
CD4+ count at start of ARV


B
b
0.0–0.2
0.2–0.4
0.4–0.6
0.6–1.0
0
100
200
300
400
500
600
700
800
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Coverage×compliance
CD4+ count at start of ARV