Supporting online material

Anti-retroviral drugs for tuberculosis control in the era of HIV/AIDS

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Decline of $CD4^+$ cell counts with time since infection

The concentration of $CD4^+$ cells in the plasma is a good marker of disease progression in people infected with HIV and several studies consider the rate of decline of $CD4^+$ counts as people infected with HIV progress to AIDS.

In the study most directly concerned with the decline in $CD4^+$ cell counts over the course of an infection Schellekens *et al.* (*S1*) followed-up 187 initially asymptomatic men every three months for five years. Their mean $CD4^+$ cell count was measured as a function of time since sero-conversion and as a function of time to the diagnosis of AIDS for 45 men who progressed to AIDS (Fig. S1 and Table S1). The estimated median time from sero-conversion to entry into the study was 18 months. The data suggest that the median $CD4^+$ cell count soon after sero-conversion is $910 \pm 41/\mu l$ and declines linearly at a rate of $82.5 \pm 14.5/\mu l/yr$ for the first four to five years (here and elsewhere errors are 95% confidence limits). For the sub-set of men who progressed to AIDS during the study their $CD4^+$ cell counts fell over a period of two years from about 560 to about $500/\mu l$ at a rate of $41.5 \pm 33.0/\mu l/yr$ which is not significantly different from the rate of decline measured as time since sero-conversion ($p = 0.108$). However, the rate of decline increased to $233.5 \pm 12.8/\mu l/yr$ fifteen months before the onset of AIDS. A similar effect was observed in a study by Lang *et al.* (*S2*) (Table S1) in which the $CD4^+$ cell counts declined at a rate of $79 \pm 23/\mu l/yr$ when measured as time since sero-conversion but at a rate of $145 \pm 18/\mu l/yr$ when measured against time before the onset of AIDS.

Detels *et al.* (*S3*) used data from men enrolled in the Multi-Centre AIDS Cohort Study (MACS) in four urban areas of the USA and determined the rate of decline of $CD4^+$ cell counts as a function of both calendar time and time since infection. Before July 1995 the mean rate of decline of $CD4^+$ cells was 75.1 ± 5.0 cells/$\mu l/yr$ and this did not vary significantly with time since infection (the slope of a regression of the rate of decline against time since infection is $3.3 \pm 4.3/\mu l/yr^2$). After July 1995, $CD4^+$ cell counts increased at a rate of $23 \pm 58/\mu l/yr$ and the

authors attribute this change to the use of protease inhibitors or non-nucleoside reverse transcriptase inhibitors (comparing rates, $p = 0.0009$).

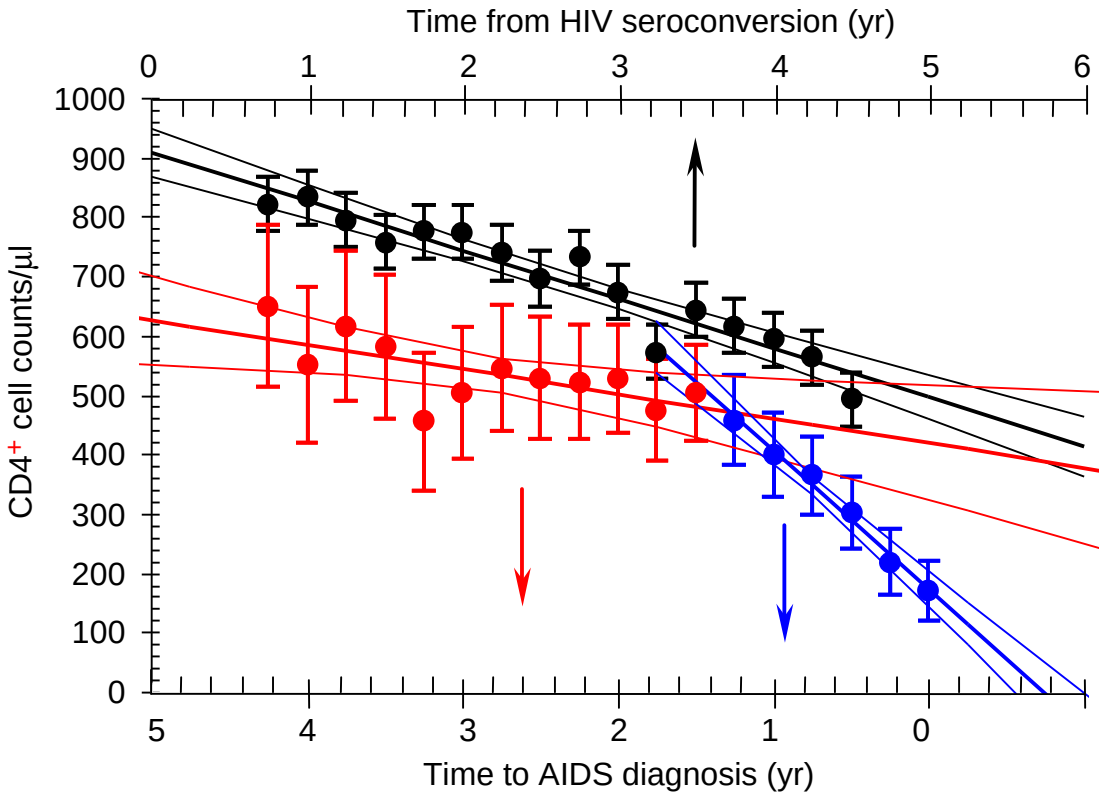

Fig. S1. CD4$^+$ cell counts as a function of time from HIV seroconversion (black; *x*-axis at the top) and time to AIDS (red and blue; *x*-axis at the bottom) from Schellekens *et al.* (*S1*). The red and blue data points are a subset of the black points but measured as the time before the onset of AIDS. The equations of the lines are (intercept = *a*; slope = *b*): black: $a = 910 \pm 41$/µl, $b = -82.5 \pm 14.5$/µl/yr; red: $a = 784 \pm 193$/µl, $b = -41.5 \pm 33.0$/µl/yr, blue: $a = 2217 \pm 290$/µl, $b = -233.5 \pm 40.9$/µl/yr. The slopes of the red and the black lines are not significantly different.

Dorucci *et al.* (*S4*) studied people taking part in the Italian Seroconverter Study (ISS) who became infected with HIV between 1983 and 1995. The median cell count at serum collection was 614 and the rate of decline was 64 (49–83)/µl/yr.

Drabick *et al.* (*S5*) analysed data for six patients receiving only zidovudine and/or PCP prophylaxis at the Walter Reed Army Medical Research Centre. CD4$^+$ cell counts declined exponentially with time from four to five hundred per microlitre down to less than one hundred per microlitre. However, their data suggest that with an initial CD4$^+$ cell count of 363/µl and a half life of 3.3 ± 0.6 months the rate of CD4$^+$ cell count decline (at 363/µl) is about 1,400 per year which seems unrealistically fast. Although their evidence for an exponential decline is convincing on the two patients for which they present data the fact that data are only available for six people led us to omit this study from further analysis.

Table S1. Studies of the decline in $CD4^+$ cell counts as a function of $CD4^+$ cell count.

Author	Location	Period	$CD4^+$ counts (/μl) Median	Decl./yr	95% CL
Dorrucci 1999 (*S4*)	Italy*	1983–1985	614	64	49–83
Gottlieb 2002 (*S6*)	Senegal, Dakar	1994–1998	259	55	36–72
Salomon 2002 (*S7*)	Ivory Coast, Abidjan	1997–2000	550	45	29–61
Yamashita 2001 (*S8*)	USA§	1995–1999	278	44	31–57
Yazdanpanah 2001	France†	1987–1995	343	55	53–58
Detels 1998 (*S3*)	USA §	1990–1997	800	93	69–105
			355	63	43–77
Schellekens 1992 (*S1*)	Netherlands, ‡		900 to 500	83	68–98
			560 to 500	24	11–37
			500 to 100	234	220–246
Easterbrook 1993	UK, London	1986–1991	89	127	112–142
			134	118	101–134
			186	122	107–137
			222	94	81–106
			260	70	57–82
			298	47	38–55
Cozzi-Lepri 1997	Italy #	1980–1993	200	44	•
			300	54	•
			400	56	•
			500	70	•
			600	84	•
			700	98	•
			800	111	•
Lang 1989 (*S2*)	USA ¶		689 to 445	78.9	23.0
			550 to 200	145.0	25.6

* Italian Sero-converter Study.

§ Multi-Centre AIDS Cohort Study.

† Tourcoing AIDS Reference Centre and the Groupe d'Epidémiologie Clinique du SIDA.

‡ The Netherlands Red Cross Blood Transfusion Service, Amsterdam. See also Fig. S1.

Italian Sero-converter Study. Only fitted values given, no error estimates.

¶ San Francisco Men's Health Study.

Gottlieb *et al.* (*S6*) studied patients at the University of Dakar Infectious Disease Clinic, Fann Hospital, in Dakar, Senegal and commercial sex workers who presented to the sexually transmitted disease (STD) clinics in Dakar and M'Bour between October 1994 and November 1998. The purpose of the study was to compare the rate of decline in people infected with HIV-1

and HIV-2. For those infected with HIV-1 the median $CD4^+$ cell count was 259/μl and the rate of decline was 52 (36–72)/μl/yr.

Salomon *et al.* (*S7*) studied blood donors in Abidjan, with known dates of seroconversion, for 24 months (median time of follow up). The median $CD4^+$ cell count on entry was 550/μl. The authors suggest that the rate of decline is 20 to 25/μl per year. Fitting a straight line to their data (an exponential fit is indistinguishable) gives a rate of decline of 45 (± 16)/μl/yr.

The study by Yamashita *et al.* (*S8*) used data from the MACS cohort between 1995 and 2001. The $CD4^+$ cell counts declined at a rate of 44 (31–57)/μl/year for up to 4 years before starting HAART. Some participants may have been on mono-therapy or double therapy.

In the study carried out in France by Yazdanpanah *et al.* (*S9*) the decline in $CD4^+$ cell count was reported to be 55 (53–58)/μl/yr. Data were collected on people whose $CD4^+$ cell counts ranged from over 500/μl to zero with a median of 343/μl. The paper only gives fitted values with estimated errors at each of the fitted points so that the confidence limits on the slope have to be inferred indirectly from the stated confidence limits.

Easterbrook *et al.* (*S10*) studied the rate of $CD4^+$ cell decline before, and for one year after, initiation of zidovudine (ZDV) therapy in people attending hospital based clinics in London between 1986 and 1991. As the median $CD4^+$ cell count declined from 300/μl to 90/μl the rate of decline increased from 47/μl/yr to 127/μl per year.

Cozzi-Lepri *et al.* (*S11*) analysed data from the Italian Seroconverters Study between 1980 to 1993 and give the rate of decline for $CD4^+$ cell counts from 800/μl down to zero. However, the rates in their table give a life expectancy of three years at most (from a starting value of 800/μl) and the data in their table do not agree with the plot of the decline of $CD4^+$ cell counts over time obtained by fitting these data. The first author suggests (Cozzi-Lepri, personal communication) that the table should be ignored and the data read from the figure. We have read values off their figure and calculated the corresponding rate of decline.

McNeil *et al. (S12)* carried out a sophisticated statistical analysis of $CD4^+$ counts in 164 individuals from the Edinburgh City Hospital cohort with known dates of seroconversion and at least 10 $CD4^+$ cell counts each. They concluded that the decline in $CD4^+$ cell counts with time is best described as linear in the square root of the counts. Without access to the data that they used in their fitting it is not possible to confirm or further investigate their conclusions and we have not included their estimates.

Lang *et al.*(*S2*) used data from the San Francisco Men's Health Study (SFMHS) for 37 men who seroconverted while under observation, 304 prevalent seroconverters, positive on entry but AIDS free three years later, and 69 who developed AIDS while under observation. The $CD4^+$ cell counts before seroconversion were 1119 ± 91/μl but fell rapidly to 716 ± 50/μl within one month of seroconversion (this initial drop is 403 ± 100/μl.) Among the AIDS free prevalent HIV seropositives the $CD4^+$ cell count fell linearly from about 700/μl to about 450/μl at a rate of 79

± 23/μl and more rapidly among the incident AIDS cases from 550/μl to 200/μl at a rate of 130 ± 26/μl.

The data are summarized in Table 1 and plotted in Fig. 1A in the paper. When the $CD4^+$ cell counts are between about 350 and 800/μl there are two point estimates and three estimates which run over time (green, red and brown lines) which suggest that the rate of decline drops from about 100 to 50/μl/yr. In the range 100 to 300/μl there are eight point estimates which suggest that the rate of decline increases from about 50 to 150/μl/yr. At $CD4^+$ cell counts below this, two studies (*S1*, *2*) suggest that the rate of decline as $CD4^+$ cell counts approach zero is between 150 and 250/μl/yr.

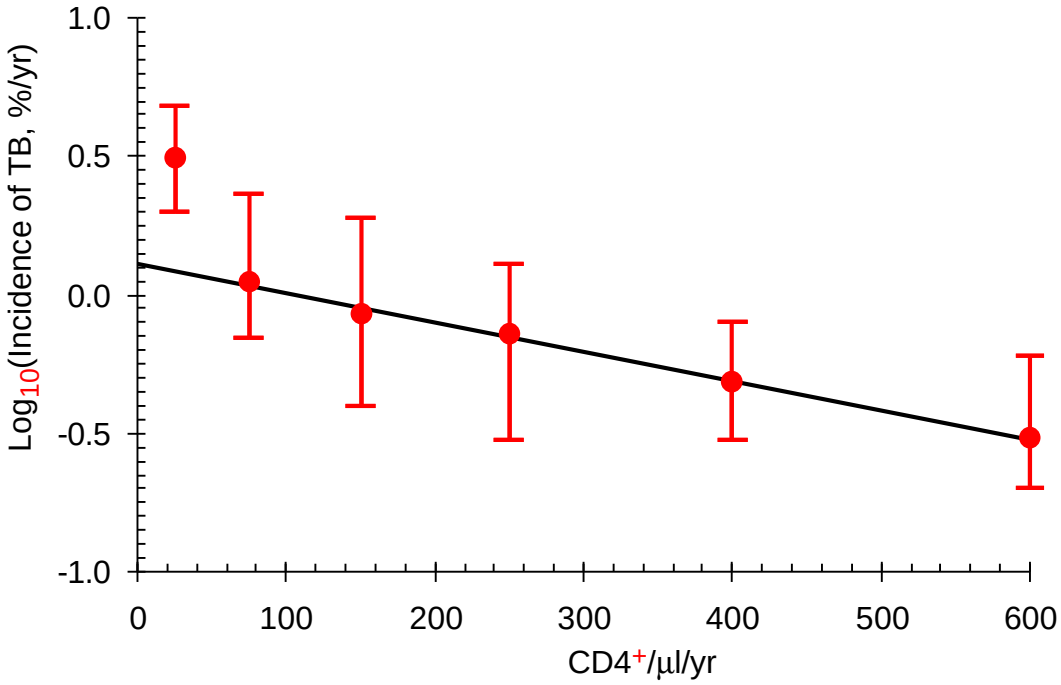

Fig. S2. Incidence of tuberculosis as a function of $CD4^+$ cell count (*S9*). The intercept is 0.114, the slope is 1.06 (–2.02 to –0.09)×10^{-3}/yr.

Incidence of tuberculosis and $CD4^+$ cell counts

In order to estimate the incidence of tuberculosis from HIV-seroconversion to the development of AIDS, we need to know how the incidence of tuberculosis increases as $CD4^+$ cell counts decrease.

Table S2. The incidence of tuberculosis as a function of $CD4^+$ cell counts. In the French study* some of the patients were treated with zidovudine mono-therapy. In the Italian study† the incidence is further broken down by PPD status. In the Cape Town study¶ data are also given for a similar group of patients receiving triple therapy.

		$CD4^+/\mu l$	TB inc. (%/yr)	95% CI
France (*S9*)		> 500	0.30	0.17–2.34
		301–500	0.49	0.30–2.67
		201–300	0.72	0.34–4.23
		101–200	0.86	0.41–5.38
		51–100	1.12	0.60–5.36
		0–50	3.13	0.79–5.27
Italy (*S13*)	PPD Negative	> 350	0.4	0.1–1.1
		200–350	0.3	0.0–1.5
		< 200	1.3	0.2–4.7
	Anergic	> 350	0.7	0.2–1.7
		200–350	2.2	1.1–3.9
		< 200	4.9	3.6–6.5
	PPD Positive	> 350	2.6	0.7–6.6
		200–350	6.5	2.1–15.3
		< 200	13.3	4.9–29.0
Cape Town, South Africa (*S14*)		> 350	3.6	2.0–6.0
		200–350	12.0	7.9–17.5
		< 200	17.5	10.1–23.7
	With triple therapy	> 350	2.0	0.2–7.2
		200–350	1.7	0.2–6.1
		< 200	3.4	1.1–7.9

* Data for 2664 HIV-infected patients from the Tourcoing AIDS Reference Centre and the hospital based information system of the Groupe d'Epidémiologie Clinique du SIDA en Aquitaine, enrolled January 1987 to September 1995. The data are fitted, not observed values.

† Data for 2695 HIV-infected subjects followed up for at least four weeks in 23 infectious disease units in public hospitals in Italy.

¶ Incidence of tuberculosis in a prospective cohort of 770 non-HAART patients who were attending Somerset Hospital Adult HIV Clinic, University of Cape Town, and 264 patients who received HAART (triple ARV therapy) in phase III clinical trials, between 1992 and 2001.

The results of a French study, reported by Yazdanpanah *et al.* (*S9*), are given in Fig. 2S and Table 2S. Tuberculosis was determined by culture from pulmonary, blood or other tissue

samples. The authors only provide fitted values with error estimates rather than actual data points and, when approached, were unable to provide the raw data. We therefore fitted a straight line to the logarithm of their published data, excluding the first point which differs significantly from the trend suggested by the remaining points. To estimate the errors in the slope of the line we used the (experimental) error estimates provided by the authors to determine upper and lower 95% confidence limits for the fitted line. This suggests that the incidence of tuberculosis increases by a factor of 1.6 (1.0–2.8) for a decline of 200 $CD4^+$ cells/μl.

The data from an Italian study (*S13*) and a South African study (*S14*) given in Table 2S are plotted in Fig. S3. An ANOVA was used to fit the log-transformed incidences for the Italian data to the three $CD4^+$ categories and the PPD (purified protein derivative) tuberculin status (negative, anergic or positive). The interaction term was not significant and the incidence of tuberculosis increases by a factor of 3.2 (1.3–8.1) from each PPD category to the next (negative to anergic to positive); and 2.4 (1.2–4.7) from each $CD4^+$ category to the next (< 200 to 200–350 to > 350/μl). For the South African study (*S14*) the incidence of tuberculosis increases by a factor of 2.1 (1.6–2.8) from each $CD4^+$ category to the next (< 200 to 200–350 to > 350/μl).

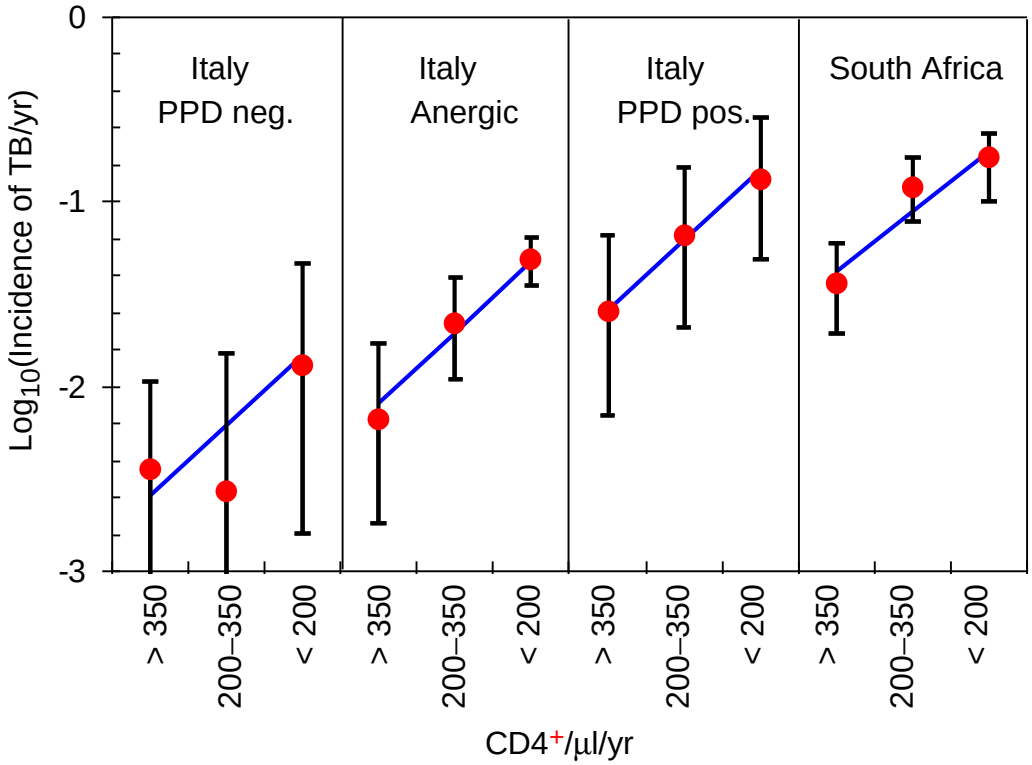

Fig. S3. Incidence of tuberculosis as a function of $CD4^+$ cell count from the Italian study (*S13*) for those who are PPD negative, anergic and PPD positive and the South African study (*S14*).

The Italian and South African studies cannot be compared precisely with the French study (*S9*) without knowing the mean $CD4^+$ cell counts in each category but if we assume that in the

lowest category (< 200/μl) the mean is about 100/μl and in the highest category (> 350/μl) about 500/μl then the difference between categories is 200/μl so that the three studies are consistent although the confidence limits are wide. The weighted average of these estimates suggests that the incidence of tuberculosis increases by a factor of 2.1 (1.4–3.0) for each decline of 200 $CD4^+$ cells/μl.

The Italian study (*S13*) shows that the incidence of tuberculosis varies with PPD status as well as with $CD4^+$ cell counts. A similar result was obtained in a study of HIV-positive patients in the United States (*S15*) where the incidence of tuberculosis was 11.3 (3.8–33.7) times greater among those who were PPD negative than among those who were PPD positive which may be compared with 10.2 (1.7–65.6) times in the Italian study (*S13*). Crucially, the interaction term is not significant.

$CD4^+$ cell counts as a function of time

We start from measurements of $R(t)$, the rate of decline of $CD4^+$ cell counts with time since seroconversion (Fig. 1A). To determine $C(t)$, the actual $CD4^+$ cell count at a given time since seroconversion, we integrate from time zero so that

$$C(t) = C(0) + \int_0^t R(t)dt \qquad \text{S1}$$

and this gives the curve shown in Fig. 1B. To determine confidence limits on $C(t)$ we apply Eqn. S1 to the upper and lower bounds in Fig. 1A and this gives the confidence limits in Fig. 1B.

TB incidence as a function of $CD4^+$ cell counts

In the text we show that the incidence of tuberculosis increases by a factor of 2.1 (1.4–3.0) for each decline of 200 $CD4^+$ cells/μl and in Fig. 1C we plot the corresponding exponential curves to show how $J(C)$ the incidence of TB varies with $CD4^+$ cell counts assuming that the $CD4^+$ cell count starts at 800/μl at which value the incidence of TB is a nominal 100 cases per 100,000 people per year.

Incidence of TB as a function of time

$I(t)$, the incidence of TB as a function of time (Fig. 1D), is obtained directly from $J(C)$ and $C(t)$ as $I(t) = J[C(t)]$.

Incidence of TB in a cohort

To determine the incidence of TB in a cohort we need to combine the probability of surviving for a given time with the incidence as a function of time since seroconversion. Suppose that $S(t)$ is the Weibull survivorship at time t. Then, $P(t)$, the probability density function for dying at time t, is

$$P(t) = \frac{dS(t)}{dt} \qquad \text{S2}$$

In Fig. 1B $C(t)$, the curve describing the decline of $CD4^+$ cell counts over time, gives a life expectancy of 9 years. For people who live for live for t years the $CD4^+$ cell counts at time t will be $C(9t/t)$. In a cohort of people all of whom are infected at time 0, $R(t)$, the incidence of TB at time t is

$$R(t) = \int_{t=t}^{\infty} I(9t/t)P(t)dt \qquad \text{S3}$$

If people are started on anti-retroviral therapy immediately after sero-conversion and if, under these conditions, the incidence of tuberculosis is constant, then the term $I(9t/t)$ can be taken out of the integral sign and with Eqn. S2 the incidence is then proportional to $S(t)$, the number who are still alive at time t.

$CD4^+$ cell counts at tuberculosis diagnosis

A useful check on the validity of the calculations is to compare the $CD4^+$ cell counts when people present with TB from our analysis with measured values. Table 3S gives the $CD4^+$ cell counts from a variety of studies for different categories of tuberculosis patients (*S16-22*). Although there is considerable variation in the observed $CD4^+$ cell counts in HIV-positive people with tuberculosis, the average value of the medians, 202 (136–269)/μl, is consistent with estimate based on the analysis in the paper of 256/μl (207–310)/μl.

Table 3S. Median $CD4^+$ cell count in HIV-positive tuberculosis patients. EP: extrapulmonary; P: pulmonary; C+: culture positive; SS+: smear positive, tuberculosis.

First author and date	Location	Population	Tuberculosis	Median $CD4^+$/μl
Ackah 1995 (*S16*)	Abidjan	TB clinic patients	EP	198
			P	257
Badri 2002 (*S17*)	Cape Town	HIV clinic patients	All forms	129
Del Amo 1996 (*S18*)	London	Africans	All forms	238
Dean 2002 (*S19*)	London	Africans	C+	90
Girardi 1994 (*S20*)	Italy	Retrospective AIDS*	All forms	82
Mukadi 1993 (*S21*)	Kinshasa	Out-patients	SS+/C+	317
Wolday 2003 (*S22*)	Ethiopia	Factory workers	Before TB†	304
			After TB¶	207
Mean (95% CL)				202 (136–269)

* Retrospective study of tuberculosis in people who developed AIDS.

† Measured between 89 and 220 days before tuberculosis was diagnosed (clinical, with X-ray).

¶ Measured between 58 and 203 days after tuberculosis was diagnosed (clinical, with X-ray).

The incidence of TB in a cohort of HIV infected people

The data discussed above and in the paper allow us to calculate the incidence of TB as a function of time for a person who lives for nine years after being infected with HIV. We now combine this with the Weibull distribution of survival times for people infected with HIV. For a given survival time we scale the incidence of TB with time so that we have the incidence of TB for all times from seroconversion to death for that survival time. We then use the Weibull survivorship to determine the probability that any person survives for that long. We then sum the result over all possible survival times to get the incidence for a cohort of people infected at the same time.

Decline in $CD4^+$ cell count immediately after seroconversion

There is evidence that $CD4^+$ cell counts decline significantly immediately after seroconversion; among a cohort of male seroconverters (*S2*) the mean $CD4^+$ cell count fell from $1119 \pm 91/\mu l$ before HIV seroconversion to $716 \pm 50/\mu l$ within one month after seroconversion. If the relationship between $CD4^+$ cell counts and the incidence of tuberculosis suggested above applies to this initial stage of infection, then the incidence of tuberculosis could increase by up to four times within the first month of seroconversion. This would be difficult to measure directly but there is indirect evidence to support an increase in the incidence of TB soon after seroconversion. Corbett (Elizabeth Corbett, personal communication) carried out a retrospective cohort study of the incidence of tuberculosis among HIV-negative and HIV-positive gold mine workers. Among HIV-negative men the incidence of tuberculosis was 1.05 ± 0.20 per 100 person years and had not changed between 1991 and 1999. Among HIV positive men the incidence of tuberculosis increased from 2.2, to 5.9 and 9.4 per 100 person years over the same period. Assuming that the increasing incidence of tuberculosis in men with and without HIV infection reflects the increasing proportion of men with more advanced HIV infection, these data suggest that the incidence of tuberculosis increases by a factor of about two soon after sero-conversion and by a factor of about ten among men who have been infected for longer.

Further indirect support for an increase soon after seroconversion may be derived from a study by Glynn (*S23*) of the risk ratios for tuberculosis in people who are HIV positive and negative from six cohort studies in developed countries and Africa. The estimates do not differ significantly and the weighted (geometric) mean risk ratio is 15.5 (7.6–31.5). Glynn (*S23*) also compares odds ratios for five case-control studies in Africa. These too do not differ significantly among each other and the weighted (geometric) mean is 6.9 (5.6–8.5). This analysis lends support to the observation that HIV infection increases the risk of tuberculosis by the same relative amount whatever the background incidence of tuberculosis. It is not clear why the cohort and case-control studies appear to give somewhat different results but together they suggest that the incidence of tuberculosis increases by a factor of about 10 (5–22) times when comparing people with and without HIV infection. Our analysis suggests that the cumulative incidence of tuberculosis over the lifetime of an infected person increases by 5.0 (2.5–11.0) times if the

comparison is with the incidence among people recently infected with HIV. If it is the case that the incidence increases by 2 to 4 times soon after seroconversion, then the lifetime risk of infection among people with HIV will increase by about 14.1 (6.2–32.0) times which is consistent with the data reported by Corbett (*S24*) and the studies reviewed by Glynn (*S23*).

Furthermore, this suggests that if the incidence of infection among HIV negative people is about 100 cases per 100,000 people per year, as in East Africa, the life time risk of infection among HIV negative people will be 12% (7–17%), while if the incidence of infection among HIV negative people is 500 cases per 100,000 people per year, as it is in parts of South Africa, the life time risk of infection will be 48% (30% to 62%).

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