Reducing Tuberculosis Incidence by Tuberculin Skin Testing, Preventive Treatment, and Antiretroviral Therapy in an Area of Low Tuberculosis Transmission

Luigia Elzi,[1] Matthias Schlegel,[2] Rainer Weber,[3] Bernard Hirschel,[4] Matthias Cavassini,[5] Patrick Schmid,[7] Enos Bernasconi,[8] Martin Rickenbach,[6] and Hansjakob Furrer,[2] and the Swiss HIV Cohort Study[a]

[1]University Hospital Basel, Basel, [2]University Hospital Berne, Berne, [3]University Hospital Zurich, Zurich, [4]University Hospital Geneva, Geneva, [5]University Hospital Lausanne and [6]Swiss HIV Cohort Study Data Center, Lausanne, [7]Cantonal Hospital St. Gall, St. Gall, and [8]Ospedale Regionale di Lugano, Lugano, Switzerland

(See the editorial commentary by Reider on pages 103–4)

Background. Tuberculin skin testing (TST) and preventive treatment of tuberculosis (TB) are recommended for all persons with human immunodeficiency virus (HIV) infection. We aimed to assess the effect of TST and preventive treatment of TB on the incidence of TB in the era of combination antiretroviral therapy in an area with low rates of TB transmission.

Methods. We calculated the incidence of TB among participants who entered the Swiss HIV Cohort Study after 1995, and we studied the associations of TST results, epidemiological and laboratory markers, preventive TB treatment, and combination antiretroviral therapy with TB incidence.

Results. Of 6160 participants, 142 (2.3%) had a history of TB at study entry, and 56 (0.91%) developed TB during a total follow-up period of 25,462 person-years, corresponding to an incidence of 0.22 cases per 100 person-years. TST was performed for 69% of patients; 9.4% of patients tested had positive results (induration $\geqslant$5 mm in diameter). Among patients with positive TST results, TB incidence was 1.6 cases per 100 person-years if preventive treatment was withheld, but none of the 193 patients who received preventive treatment developed TB. Positive TST results (adjusted hazard ratio [HR], 25; 95% confidence interval [CI], 11–57), missing TST results (HR, 12; 95% CI, 4.8–20), origin from sub-Saharan Africa (HR, 5.8; 95% CI, 2.7–12.5), low $CD4^+$ cell counts, and high plasma HIV RNA levels were associated with an increased risk of TB, whereas the risk was reduced among persons receiving combination antiretroviral therapy (HR, 0.44; 95% CI, 0.2–0.8).

Conclusion. Screening for latent TB using TST and administering preventive treatment for patients with positive TST results is an efficacious strategy to reduce TB incidence in areas with low rates of TB transmission. Combination antiretroviral therapy reduces the incidence of TB.

Coinfection with tuberculosis (TB) and HIV is one of the world's biggest health problems [1]. HIV infection facilitates reactivation of latent TB. On the other hand, TB-induced immune activation may lead to faster progression of HIV infection [2, 3]. In resource-poor countries, TB is among the most frequent and devastating opportunistic infections among HIV-infected individuals. Migrants from these regions contribute to the burden of TB in Switzerland before and during the era of combination antiretroviral therapy (cART) [4, 5].

Tuberculin skin testing (TST) is considered to be part of routine care for HIV-infected persons [6, 7], despite the limited sensitivity and specificity of the test [8–11]. A PPD test with an induration of $\geqslant$5 mm is an indication for preventive treatment of latent TB [6]. This recommendation is based mainly on studies conducted before the cART era that were performed in areas with a high prevalence of latent TB [12–15]. Sensitivity of TST may be markedly reduced among HIV-infected

Received 1 August 2006; accepted 11 September 2006; electronically published 28 November 2006.

[a] Members of the Swiss HIV Cohort Study are listed at the end of the text.

Reprints or correspondence: Dr. Hansjakob Furrer, Klinik und Poliklinik für Infektiologie, University Hospital Berne, Inselspital PKT2 B, CH-3010 Bern (hansjakob.furrer@insel.ch).

Clinical Infectious Diseases 2007; 44:94–102

1058-4838/2007/4401-0017$15.00

Table 1. Demographic and clinical characteristics of study patients.

Variable	No TB (n = 5962)	Prevalent TB (n = 142)	Incident TB (n = 56)	Total (n = 6160)	P
Percentage of total patients	96.8	2.3	0.91	100	
Female sex	31	40	50	32	.001
Age, median years (IQR)	36 (30–43)	34.5 (28–42)	31.5 (28–39)	36 (30–43)	<.001
Median CD4$^+$ cell count at registration (IQR)	330 (174–528)	167 (83–295)	248 (118–348)	326 (170–518)	.001
CD4$^+$ cell count <200 cells/μL at registration	28.8	58.5	39.3	29.6	.001
Median $\log_{10}$ plasma HIV RNA level at registration (IQR)	4.3 (3.1–5.0)	4.2 (2.6–5.3)	4.7 (4.1–5.3)	4.3 (3.0–5.0)	.04
Region					<.001
Low-risk region	81.0	44.4	37.5	79.7	
Medium-risk region	7.2	7.8	14.3	7.3	
Sub-Saharan Africa	11.8	47.9	48.2	13.0	
Transmission					<.001
HET	42.0	71.1	73.2	43.0	
IDU	20.3	16.9	14.3	20.2	
MSM	33.5	5.6	8.9	32.6	
Other or unknown	4.2	6.3	3.6	4.2	
Health care provider					<.001
Main centers	73.4	76.8	89.0	73.6	
HIV clinics in smaller hospitals	5.9	14.1	1.8	6.0	
Private physicians	20.73	9.2	8.9	20.4	
Receipt of ART at registration	40.5	57.0	28.6	40.83	<.001
Receipt of cART at registration	33.4	52.1	19.6	33.7	<.001

NOTE. Data are % of patients, unless otherwise indicated. ART, antiretroviral therapy; cART, combination antiretroviral therapy; HET, heterosexual transmission; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men; TB, tuberculosis.

patients with low CD4$^+$ cell counts [16, 17]. An evaluation within the Swiss HIV Cohort Study (SHCS) prior to the introduction of cART has shown a significantly increased adjusted relative risk of 5.5 for persons with a positive TST result and CD4$^+$ cell counts >200 cells/μL [4]. We aimed to assess the effect of TST and preventive therapy on the incidence of TB in the cART era in a geographic area with a low rate of TB transmission.

METHODS

The SHCS

The SHCS (http://www.shcs.ch) is a prospective observational study of HIV-infected individuals performed at HIV outpatient clinics at 5 university hospitals and 2 large district hospitals [18]. At study enrollment and every 6 months thereafter, sociodemographic, clinical, and laboratory information is collected. Treatment of HIV infection and of opportunistic infections is documented.

Guidelines recommend performing TST for all patients within 1 year after registration by injecting 0.1 mL of tuberculin (2 U of PPD RT-23) intradermally on the forearm. Documented TSTs performed before registration are also entered into the database. An induration diameter of $\geqslant$5 mm defines a positive TST result according to the recommendations of the American Thoracic Society [19].

Study Participants and Definitions

For the present analysis, all participants entering the SHCS after 1 January 1996 were considered. We used the database updated in February 2006. Three groups of patients were defined: (1) the "no TB" group, which included patients without a history of TB and who did not develop TB during follow-up; (2) the "prevalent TB" group, which included patients with a history of TB before entering the SHCS; and (3) the "incident TB" group, which included patients with incident active TB during follow-up within the SHCS.

Regions of origin were regrouped according the prevalence of TB into (1) sub-Sahara Africa; (2) medium-risk regions, including Eastern Europe, Central Asia, North Africa and the Middle East, South Asia, East Asia, and the Caribbean; and (3) low-risk regions. Preventive treatment of latent TB infection was defined as treatment with isoniazid for at least 24 weeks, rifampicin or rifabutin for at least 16 weeks, or a combination of rifampicin or rifubutin together with pyrazinamide for at least 8 weeks. cART was defined as antiretroviral treatment with at least 3 antiretroviral drugs.

Study Design and Statistical Analysis

Prevalence of TB. Associations of prevalent TB with sociodemographic factors were evaluated with multivariable logistic regression.

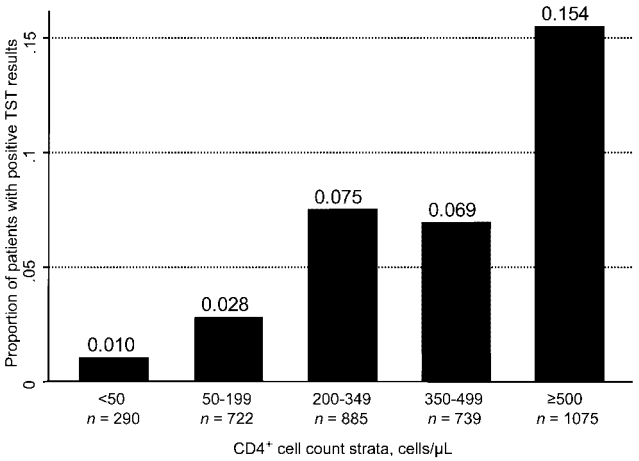

Figure 1. Proportion of patients with positive tuberculin skin test (TST) results according to $CD4^+$ cell count stratum at the time of TST ($P <$ .001 for trend statistics).

Prevalence of positive TST results. Data about TST results were analyzed with regard to epidemiological parameters, including history of TB, region of origin, $CD4^+$ cell count, and receipt of concurrent cART.

Incidence of TB. The incidence of TB in the SHCS was evaluated assuming a Poisson distribution of events. Association of incidence with epidemiological parameters and TST results and history of treatment of latent TB were analyzed using Kaplan Meier curves, log-rank statistics, and multivariable Cox proportional hazards models, including start of antiretroviral therapy with at least 3 drugs as a time-dependent covariate, splitting follow-up time accordingly. The proportional hazards assumptions in Cox models were tested on the basis of Schoenfeld residuals, and they had to be fulfilled for each covariate.

RESULTS

Patient Characteristics

Among 6160 SHCS participants who entered the SHCS after 1 January 1996, 142 (2.3%) had a history of TB, and 56 (0.91%) developed new active TB during follow-up. Three patients with history of TB before registration received a diagnosis of recurrent TB during follow-up. These patients were excluded from the analyses of TB incidence. The patient characteristics are shown in table 1. The differences in baseline characteristics are because of the predominant presumed heterosexual HIV transmission mode, younger age, and higher number of female subjects among patients from regions of higher TB endemicity.

History of TB at Registration

A history of TB at registration was found in 142 (2.3%) of the patients. HIV infection was documented in 65 (46%) of these 142 patients after the diagnosis of TB and in 53 (37%) within 1 year after TB diagnosis. Forty-four (68%) of the participants with a diagnosis of TB before documented HIV infection were from sub-Sahara Africa.

Patients with a history of TB at registration had lower $CD4^+$ cell counts and were more likely to be receiving cART when entering the SHCS (table 1). This paradoxical finding can be explained by the lower nadir $CD4^+$ cell counts in patients who started cART and had a history of TB (median $CD4^+$ cell count, 88 cells/μL), compared with the TB-free patients (median $CD4^+$

Table 2. Logistic regression models of associations with positive tuberculin skin test (TST) results.

	Univariate analysis (n = 3681)	Mulitvariate model (n = 3681)		Multivariate model (n = 1056)	
Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Sub-Saharan Africa vs. low-risk region	4.68 (3.68–5.95)	5.58 (3.88–8.01)	<.001	4.76 (2.40–9.45)	<.001
Medium-risk region vs. low-risk region	2.05 (1.43–2.95)	2.36 (1.54–3.62)	<.001	1.91 (0.828–4.42)	.1
Female sex	1.17 (0.94–1.46)	0.59 (0.44–0.80)	<.001	0.52 (0.29–0.92)	.3
Heterosexual HIV transmission vs. MSM	2.07 (1.59–2.69)	1.48 (1.03–2.12)	.04	2.18 (1.06–4.48)	.03
IDU HIV transmission vs. MSM	1.29 (0.92–1.81)	1.63 (1.10–2.42)	.01	2.74 (1.22–6.14)	.01
Other/unknown HIV transmission vs. MSM	3.03 (1.93–4.74)	2.23 (1.27–3.91)	.005	3.68 (1.35–10.0)	.01
Age per 10-year increase	0.80 (0.71–0.89)	1.02 (0.89–1.17)	.8	1.15 (0.89–1.49)	.3
$CD4^+$ cell count at TST per 100-cell/μL increase	1.21 (1.17–1.26)	1.23 (1.17–1.28)	<.001	1.02 (0.88–1.18)	.8
Plasma HIV RNA level at TST per $\log_{10}$ copies/mL increase	0.87 (0.82–.092)	0.84 (0.77–0.92)	<.001	0.91 (0.78–1.07)	.3
Triple ART at TST	0.66 (0.52–0.84)	0.42 (0.29–0.60)	<.001	0.65 (0.33–1.27)	.2
Nadir $CD4^+$ cell count before TST per 100-cell/μL increase	1.30 (1.18–1.43)	…		1.30 (1.08–1.56)	.006

NOTE. The multivariate models included only patients with all parameters available and included all parameters in the table. The multivariate model with 1056 participants included all patients with a documented nadir $CD4^+$ cell count before TST and before initiation of antiretroviral therapy. ART, antiretroviral therapy; IDU, injection drug use; MSM, men who have sex with men.

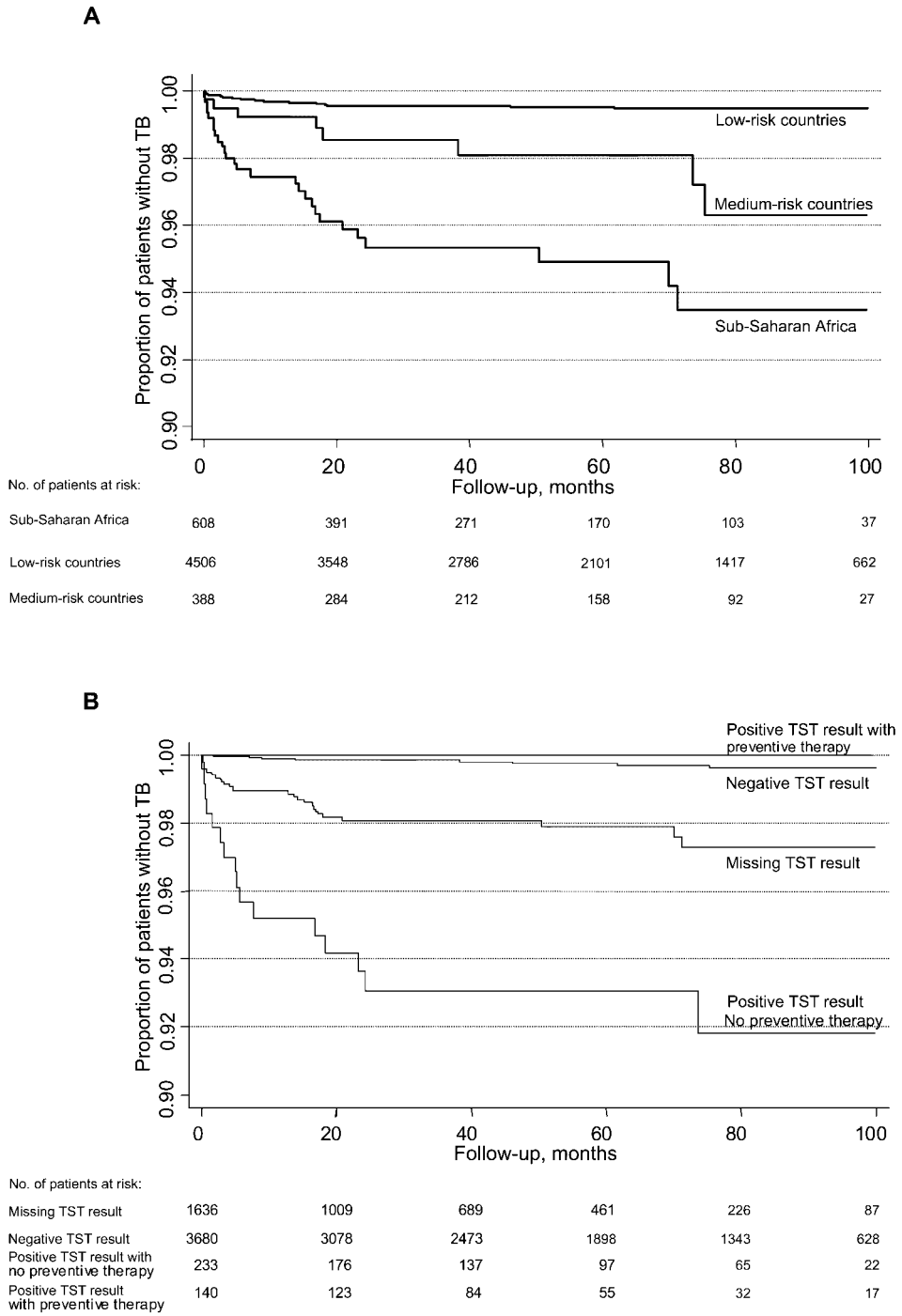

Figure 2. *A,* Kaplan Meier curve of the proportion of participants remaining free of tuberculosis (TB) according their region of origin ($P < .001$, by log rank test). *B,* Kaplan Meier curves according to whether a tuberculin skin test (TST) had been performed and according to the results of the TST. The participants with a positive TST result were grouped according to whether they had received a full course of preventive therapy against latent TB infection ($P < .001$, by log rank test).

cell count, 216 cells/μL; $P < .001$), whereas duration of cART or plasma viral load were not significantly different between these 2 groups. In a logistic model, the adjusted OR (aOR) for the association of epidemiological factors with a history of TB at registration were female sex (aOR, 0.58; 95% CI, 0.40–0.84; $P = .004$), age per 10-year increase (aOR, 1.0; 95% CI, 0.85–1.20; $P = .8$), and sub-Saharan African origin, compared with origin from a low-risk region (aOR, 5.7; 95% CI, 3.6–8.9;

Table 3. Incidence of tuberculosis (TB) according to tuberculin skin test (TST) results and region of origin among patients who did not receive preventive treatment.

Variable	No. of incident TB cases	No. of persons at risk	No. of person-years of follow-up	Incidence per 100 person-years (95% CI)
Low-incidence countries				
All results	21	4756	20,929	0.10 (0.06–0.15)
Positive TST result	5	158	726	0.69 (0.22–1.61)
Negative TST result	5	3098	15,791	0.03 (0.01–0.07)
Missing TST result	11	1500	4543	0.24 (0.12–0.43)
Medium-incidence countries				
All results	8	420	1581	0.51 (0.22–1.00)
Positive TST result	2	23	75	2.67 (0.32–9.64)
Negative TST result	2	267	1185	0.17 (0.02–0.61)
Missing TST result	4	130	322	1.24 (0.34–3.17)
Sub-Saharan Africa				
All results	27	651	2084	1.30 (0.85–1.89)
Positive TST result	9	65	203	4.42 (2.02–8.40)
Negative TST result	3	379	1540	0.19 (0.04–0.57)
Missing TST result	15	207	407	3.69 (2.06–6.08)
All patients				
All results	56	5827	24,593	0.23 (0.17–0.30)
Positive TST result	16	246	1005	1.59 (0.91–2.59)
Negative TST result	10	3744	18,516	0.05 (0.03–0.10)
Missing TST result	30	1837	5273	0.57 (0.38–0.81)

$P < .001$). HIV transmission modes by heterosexual sex (aOR, 6.1; 95% CI, 2.8–13.3; $P < .001$) and injection drug use (aOR, 5.9; 95% CI, 2.6–13.2; $P < .001$) were associated with a history of TB, compared with transmission associated with men who have sex with men.

TST

A TST was performed for 4168 (69%) of the 6018 patients without a history of TB at entry, and 390 (9.4%) of those who were tested had positive results. TST had been performed for only 26 (46%) of the 56 patients who developed TB during follow-up, and 16 (62%) had positive results.

Adherence to recommendation of TST. The percentage of participants tested in the different centers was 32.5%–87.8% ($P < .001$). There was no difference in adherence to TST for patients of different origin (68.9% of patients from low-risk regions, 70.2% of patients from medium-risk regions, and 71.3% of patients from sub-Saharan Africa were tested). TST was performed more frequently among patients with $CD4^+$ cell counts at registration of <200 cells/μL (72.2%) than among patients with $CD4^+$ cell counts $\geq$200 cells/μL (68.1%; $P = .002$) and less frequently among patients receiving cART at registration than among those not receiving cART (63.6% vs. 72.1%; $P < .001$).

In a multivariable logistic model including the region of origin, individual SHCS center, $CD4^+$ cell count stratum, cART at registration, sex, presumed HIV transmission mode, and age, TST was performed significantly less often at certain individual centers, for patients with an HIV transmission mode of injection drug use, and for patients receiving cART at registration.

Associations with positive TST results. Positive TST results were highly associated with $CD4^+$ cell count at the time of TST (figure 1). Results of a logistic regression model of associations with positive TST results are shown in table 2. In the multivariate model, a positive TST result was associated with origin from a region with higher TB prevalence, male sex, HIV transmission mode other than men who have sex with men, higher $CD4^+$ cell counts, and lower plasma HIV RNA levels. Receiving cART was associated with a lower rate of positive TST results if analyzed for all patients with available TST results.

In a subset of 1051 patients for whom nadir $CD4^+$ cell counts before TST were available, lower nadir $CD4^+$ cell counts were strongly associated with negative TST results. In this model with less power, the point estimate of the adjusted ORs for plasma HIV RNA level, $CD4^+$ cell count, and receipt of cART at the time of TST moved towards 1, and the respective associations did not reach statistical significance.

Preventive Treatment of TB Infection

Preventive treatment of latent TB infection was administered to 193 participants and consisted of isoniazid in 149 (77%), rifabutin combined with pyrazinamide in 30 (16%), rifabutin in 7

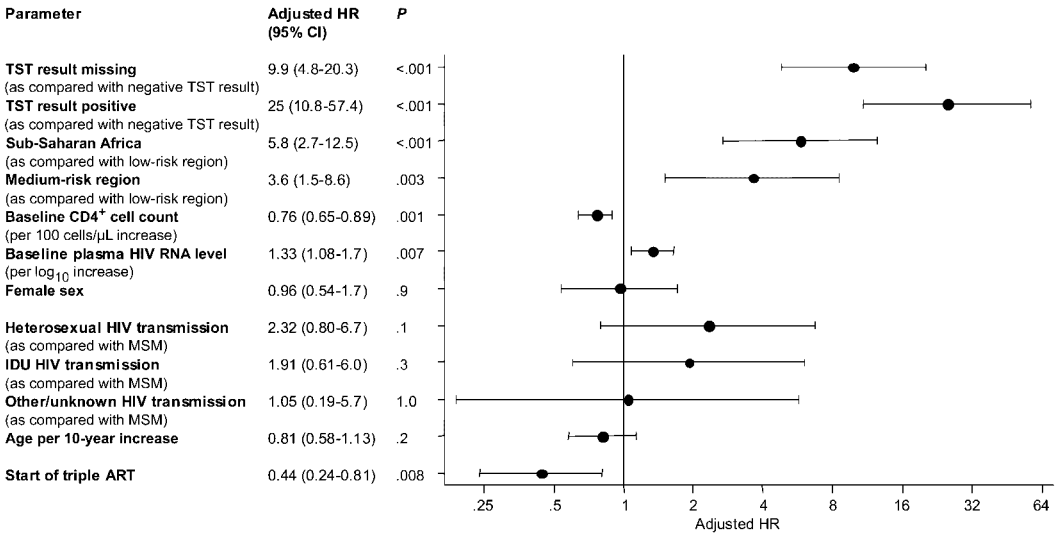

Figure 3. Results of a Cox proportional hazards model of developing tuberculosis during follow-up. The model included all of the variables shown. *Bars,* 95% CI. ART, antiretroviral therapy; HR, hazard ratio; IDU, injection drug use; TST, tuberculin skin test.

(4%), rifampicin combined with pyrazinamide in 4 (2%), and rifampicin alone in 3 (1.5%). Two of these participants had a history of active and treated TB. Among 390 patients with a positive TST results, 144 (37%) received a full course of treatment, as did 13 with missing TST data and 34 with negative TST results. No participant who started a full course of preventive treatment developed TB during follow-up. Among the 246 participants with a positive TST result who did not receive preventive treatment, 16 (6.5%) developed active TB.

Performance of TST and Numbers Needed to Treat with Preventive Therapy

We evaluated the performance of TST with regard to the development of active TB in 4034 patients who did not receive any preventive therapy. Ten (0.26%) of 3778 participants with a negative TST result developed TB, compared with 6.5% of 246 participants with a positive TST result. Therefore, the sensitivity of the test was 62.5%, the specificity was 94.3%, the positive likelihood ratio was 10.7, the negative likelihood ratio was 0.41, the positive predictive value was 6.5%, and the negative predictive value was 99.7%. The corresponding area under the receiver operating characteristic curve was 0.82.

Assuming a full protection of preventive treatment, in our patient population, we would need to treat 15 patients with positive TST results (95% CI, 10–27 patients) to prevent 1 case of TB. The corresponding numbers for participants from regions with medium or high prevalence of TB were 8 patients (95% CI, 5–15 patients) and 33 patients (95% CI, 14–97 patients), respecitvely.

Incidence of TB

Fifty-six participants (0.91%) developed TB during a total follow-up of 25,462 person-years, corresponding to an overall incidence of 0.22 cases per 100 person-years (95% CI, 0.17–0.29 cases per 100 person-years). The median duration of follow-up was 52 months (interquartile range, 23–85 months).

Thirty-three patients (59%) developed pulmonary TB, 18 (32%) developed extrapulmonary TB, and 5 (9%) developed combined pulmonary and extrapulmonary disease. The median $CD4^+$ cell count at TB diagnosis was 208 cells/μL (interquartile range, 112–354 cells/μL).

The Kaplan Meier curves in figure 2*A* show the strong association between the incidence of TB and the region of origin of the participants. Data regarding the development of TB according to TST results and whether preventive treatment of latent TB was prescribed for patients with positive TST results are illustrated in figure 2*B*. No participant who received preventive treatment developed TB. The risk of TB was higher for participants with a positive TST result and participants who had not been tested, compared with participants with negative TST results.

The incidences for TB among patients who did not receive preventive treatment differed according to TST results and the region of origin. These data are shown in table 3.

In a multivariate Cox proportional hazards model, the hazard of TB was highly increased in patients originating from regions with higher TB endemicity and in participants with positive or missing TST results. Higher plasma HIV RNA levels and lower $CD4^+$ cell counts remained associated with a higher risk. Start of antiretroviral therapy with at least 3 drugs included as time-

dependent variable splitting the follow-up was associated with reduction of the risk of TB by more than one-half (figure 3).

CONCLUSION

In a country with a low endemicity of TB, and in the era of cART, the region of origin was a major predictor of a history of TB in our cohort of HIV-infected patients and was associated with the risk of developing TB. A positive TST result was also related to a considerably higher risk of TB. Preventive therapy of latent TB was highly successful. In addition, starting antiretroviral therapy was associated with a significant reduction in the risk of developing TB.

The strength of our study is its use of a large, comprehensive prospective database that is representative of the epidemiology of HIV infection and the state of HIV care in our country. This allows the analyses of TB incidence, even in the context of low rates of TB transmission in the cART era. Limitations include the potential underestimation of the TB incidence because of a short follow-up of <2 years duration for one-quarter of our patients and the delay between diagnosis of HIV infection or TB and registration in the SHCS, which results in more patients entering the cohort with a history of TB than patients developing the disease during follow-up.

TST. HIV infection is associated with a ⩾20-fold increased risk for reactivation of latent TB, both in resource-poor and resource-rich countries [20, 21]. Therefore, identifying HIV-infected persons with latent TB infection and treating them with preventive chemotherapy has been included in most treatment recommendations [2, 6] and has been found to be successful mainly in countries with high rates of TB transmission [12, 13, 22]. Until recently, TST has been the standard test to identify persons with latent TB. However, the sensitivity of this test is reduced with progressing immunodeficiency in patients with HIV infection [16], and the specificity of the test may be low, especially in countries with a high proportion of persons who have received bacille Calmette-Guérin vaccine [23]. This, and the difficulties of organizing this 2-visit procedure, may have led to the surprisingly low rate of adherence of 70% to the recommendation for TST testing. We found a high difference in adherence with regard to the different centers in which the patients received treatment, indicating the importance of local priorities in HIV care.

In concordance with the lower sensitivity of the TST in immunosuppressed patients, we found a lower proportion of positive TST results in patients with lower $CD4^+$ cell counts. Surprisingly, we found a lower proportion of positive TST results among patients who were receiving antiretroviral treatment at the time of TST. This could be explained by the lower nadir $CD4^+$ cell count before TST in this subset of patients. The nadir $CD4^+$ cell count seems to be an important predictor of TST reactivity, and antiretroviral treatment may partly, but not fully, reconstitute skin reactivity to tuberculin antigens [24–26]. On the other hand, the high rate of positive TST results (15%) in patients with $CD4^+$ cell counts ⩾500 cells/μL points towards a considerable number of false-positive TST results, as has been shown in Switzerland in non–HIV infected individuals [23], and this has been related to the high rate of bacille Calmette-Guérin vaccination.

Incidence of TB. The overall incidence of 0.2 cases per 100 person-years is one of the lowest reported thus far for HIV-infected adults, and it is even lower than the rates recently reported by the antiretroviral therapy cohort collaboration for patients receiving combination antiretroviral therapy [27]. However, our data tend to underestimate the real incidence of TB in HIV-infected persons in our country, because TB was diagnosed in 2.3% of the patients before they entered our cohort, and TB was the marker illness for the diagnosis of HIV infection in a high proportion of participants. This was especially the case for patients from regions associated with a high risk of TB transmission. The origin of the patients, however, remained a major predictor of development of TB.

In addition, patients with a positive TST result had a hazard ratio of 25 for the development of TB (compared with participants with negative TST results) if they were not receiving preventive therapy. Preventive treatment of latent TB was highly successful in our setting. The high success rate associated with preventive therapy points towards a good adherence to therapy once it was initiated and may have been facilitated by the low rate of drug resistance and the low rate of TB transmission in our country. Reinfections are a likely explanation for the failure of preventive therapy in areas with high rates of TB transmission [28, 29], but they are rare in Switzerland. On the other hand, nonadherence of physicians to preventive therapy was a significant risk factor for incident TB. Only 37% of patients with positive TST results received a full course of preventive treatment. Fear of adverse effects and concerns about false-positive TST results may have led physicians and their patients to this decision.

On the basis of our results, 15 persons would need to be treated to prevent 1 case of active TB in our patient population. The number of patients who would need to be treated to prevent 1 case of TB was only 8 for migrants from regions associated with a higher risk of TB, but it increased to 33 for participants from regions with low rates of TB transmission. These findings clearly favor the prescription of preventive treatment, especially for participants originating from areas associated with a high or medium risk of TB transmission. Whether the introduction of the more-specific IFN-based assays to detect latent TB infection would reduce the number of patients who would need to be treated to prevent 1 case of TB needs to be investigated [30–32].

A higher grade of immunodeficiency at registration was as-

sociated with an increased risk of TB, reflecting a higher reactivation rate [33, 34]. We analyzed the influence of cART by splitting the follow-up of participants into the phase before and after start of cART. We found a significantly reduced hazard ratio of 0.44 of incident TB among patients during the period after the start of cART. cART-associated immune reconstitution has been found to reduce TB incidence in other cohorts, even in areas with high rates of TB transmission [34], and it reinforces calculations about the importance of antiretroviral therapy for TB control [35, 36].

We conclude that screening for latent TB using TST and preventive treatment for patients with positive TST results remains an efficacious strategy to reduce TB-associated morbidity, even in the cART era, in a country with low rates of TB transmission. This is especially important for patients originating from regions with high TB-infection rates. cART reduces the incidence of TB significantly.

THE SHCS

The members of the SHCS are M. Battegay, E. Bernasconi, J. Böni, H. Bucher, Ph. Bürgisser, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), H. Furrer (Chairman of the Clinical and Laboratory Committee), M. Gorgievski, H. Günthard, B. Hirschel, I. Hösli, Ch. Kahlert, L. Kaiser, U. Karrer, O. Keiser, C. Kind, Th. Klimkait, B. Ledergerber, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother and Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza (Chairman of the Scientific Board), R. Weber, and S. Yerly.

Acknowledgments

We thank all physicians and nurses of the Swiss HIV Cohort Study. We extend a special thank you to all of the patients who agreed to participate in our cohort and whose participation helps to move forward towards a better management of HIV infection and its complications.

Financial support. This study has been financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation.

Potential conflicts of interest. All authors: no conflicts.

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