

# How does tuberculosis relate to HIV positive and HIV negative drug users?

Sytze T Keizer, Miranda M W Langendam, Henk van Deutekom, Roel A Coutinho, Erik J C van Ameijden

## Abstract

**Objectives**—(1) To compare the incidence of active tuberculosis in HIV positive and HIV negative drug users. (2) To describe the main characteristics of the tuberculosis cases.

**Design**—A prospective study was performed from 1986 to 1996 as part of an ongoing cohort study of HIV infection in Amsterdam drug users.

**Methods**—Data from the cohort study, including HIV serostatus and CD4-cell numbers, were completed with data from the tuberculosis registration of the tuberculosis department of the Amsterdam Municipal Health Service. Analyses were carried out with person time and survival methods.

**Results**—Of 872 participants, 24 persons developed culture confirmed tuberculosis during a total follow up period of 4000 person years (0.60 per 100 py, 95% CI: 0.40, 0.90). Nineteen cases were HIV positive (1.54 per 100 py, 95% CI: 0.86, 2.11) and five HIV negative (0.18 per 100 py, 95% CI: 0.08, 0.43). Multivariately HIV infection (relative risk: 12.9; 95% CI: 3.4, 48.8) and age above 33 years (RR: 6.8; 95% CI: 1.3, 35.0, as compared with age below 27) increased the risk for tuberculosis substantially. Additional findings were: (1) 13 of 22 pulmonary tuberculosis cases (59%) were detected by half yearly radiographic screening of the chest; (2) tuberculosis occurred relatively early in the course of HIV infection at a mean CD4 cell number of 390/ $\mu$ l; (3) an estimated two thirds of the incidence of tuberculosis observed among HIV positive cases was caused by reactivation; (4) all but one patient completed the tuberculosis treatment.

**Conclusion**—HIV infection increases the risk for active tuberculosis in Amsterdam drug users 13-fold. The incidence of tuberculosis in HIV negative drug users is still six times higher than in the overall Amsterdam population. In the absence of contact tracing and screening with tuberculin skin tests, periodic chest radiographic screening contributes substantially to early casefinding of active tuberculosis in Amsterdam drug users.

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that time the interaction between both agents has been disastrous, especially in Third World countries.<sup>2,3</sup> In the Netherlands an increase of the tuberculosis incidence since 1987, after decennia of decrease, could not be explained by the HIV epidemic.<sup>4</sup> In Amsterdam where half of all AIDS cases and a quarter of all smear positive tuberculosis cases in the Netherlands are diagnosed, some 6000 opioid addicts reside, a group already associated with an increased risk for tuberculosis before the HIV epidemic.<sup>5</sup> The approximately 2500 injecting drug users in Amsterdam of whom 30% became infected with HIV<sup>6-8</sup> might, like in other cities,<sup>9</sup> illustrate the connection between HIV and tuberculosis most evidently. Tuberculosis infection and active tuberculosis already proved more incident in Amsterdam drug users than in the general Dutch population<sup>10,11</sup> and drug users elsewhere in the Netherlands.<sup>12</sup> A recent study using molecular epidemiological methods showed a high degree of active transmission of *M tuberculosis* among Amsterdam drug users.<sup>13</sup> Because we experienced problems with contact investigation and a poor compliance with isoniazid prophylaxis in this population, chest radiographic screening for pulmonary tuberculosis twice a year was started in 1988 for drug users attending methadone programmes as an alternative control strategy, yielding four cases per 1000 chest radiographs.<sup>14,15</sup> Screening as well as compliance to tuberculosis treatment are required for participation in the methadone programme.

We studied the influence of HIV infection on the incidence of tuberculosis as part of a comprehensive study among HIV positive and HIV negative drug users in Amsterdam. Besides contributing to general knowledge, our study also provides data of interest to evaluate our efforts to control tuberculosis in this particular population.

## Methods

Amsterdam adopted the concept of harm reduction to minimise the negative consequences of drug use. Among the contributing programmes, methadone distribution has a coverage of 60% of all 6000 opioid addicts. Chest radiographic screening for tuberculosis in six monthly intervals has been performed since 1988 among some 3000 methadone clients of the Municipal Health Service.

Since December 1985, injecting drug users and non-injecting drug users without AIDS are recruited via methadone programmes, an STD clinic for prostitutes, and word of mouth to participate on a voluntary basis in an open

Departments for Tuberculosis-control and AIDS-research, Division of Public Health and Environment, Amsterdam Municipal Health Service, PO Box 2200, 1000 CE Amsterdam, the Netherlands  
S T Keizer  
M W Langendam  
H van Deutekom  
R A Coutinho  
E J C van Ameijden

Department of Retrovirology of the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands  
R A Coutinho

Correspondence to:  
Dr S T Keizer.

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Epidemiological studies in the United States during the mid-eighties showed for the first time a relation between an increased incidence of tuberculosis and the HIV epidemic.<sup>1</sup> Since

Table 1 General characteristics of 872 drug users at entry in the study

Patient characteristics	Total (n=872) (%)	HIV positive (n=872) (%)	HIV negative (n=872) (%)	$\chi^2$ p value
Gender				>0.05 (NS)
female	358 (41.1)	91 (40.4)	267 (41.3)	
male	514 (58.9)	134 (59.6)	380 (58.7)	
Age				>0.05 (NS)
$\leq 27$	292 (33.5)	60 (26.7)	232 (35.9)	
28–32	276 (31.7)	83 (36.9)	193 (29.8)	
$\geq 33$	304 (34.9)	82 (36.4)	222 (34.3)	
Nationality				0.0005
Dutch	634 (72.7)	140 (62.2)	494 (76.4)	
German	126 (14.4)	51 (22.7)	75 (11.6)	
other	112 (12.8)	34 (15.1)	78 (12.1)	
Ethnicity*				0.002
western European	672 (77.1)	174 (77.3)	498 (76.2)	
Surinamese or Antillean	76 (8.7)	7 (3.1)	69 (10.7)	
other	57 (6.5)	19 (8.4)	38 (5.9)	
Intravenous drug use				<0.0001
ever injected	710 (81.4)	217 (96.4)	493 (76.2)	
never injected	162 (18.6)	8 (3.6)	154 (23.8)	
Duration of residence in Amsterdam*				0.02
$\leq 4$ years	232 (26.6)	48 (21.3)	184 (28.4)	
5–14 years	259 (29.7)	81 (36.0)	178 (27.5)	
$\geq 15$ years	293 (33.6)	70 (31.0)	223 (34.5)	
Other characteristics				
mean follow up period in years (SD)	4.2 (3.0)	4.2 (2.8)	4.3 (3.1)	>0.05 (NS)
mean number of cohort visits (SD)	10.9 (7.4)	11.6 (7.2)	10.7 (7.4)	>0.05 (NS)

\*Because of missings these variables do not add up to the total.

cohort to study the prevalence, incidence, and natural course of HIV infection. The study is carried out independently from any medical care facility and investigators are not involved in methadone distribution.

Participants are asked to return every four months to answer standardised questions, including medical history, treatment, and hospital admissions. At every cohort visit blood is drawn. Blood specimens are tested for HIV by two enzyme linked immunosorbent assays (ELISA; Abbott, North Chicago, Illinois, USA and Vironostica tecknika, Organon, Oss, the Netherlands) and positive specimens are confirmed by western blot test (Department of Human Retrovirology, Amsterdam Academic Medical Centre). To determine CD4 cell counts (systematically done since 1989), peripheral blood mononuclear cells are isolated from heparinised venous blood by using density gradient centrifugation on ficoll hypaque. Lymphocyte immunophenotyping is determined by flow cytometry (Department of Clinical Viro-immunology, Central Laboratory of the Bloodtransfusion Service).

To study the incidence of tuberculosis, 872 participants with at least one follow up visit, who were free of active tuberculosis at entry, were included. The diagnosis of active tuberculosis was only accepted if confirmed by a positive culture for *M tuberculosis*. For the overall analysis follow up was censored after a first episode of tuberculosis, after the last cohort visit, or on 31 December 1995, the date of the final cross linkage with the tuberculosis register (see below). For CD4+ counts follow up was censored one year after the last cohort visit to limit measurement error. The average number of cohort visits was 11 (SD 7; range 2–33), the average duration of follow up was 4.2 year (see table 1).

When active tuberculosis was diagnosed, the patient register of the tuberculosis department of the Amsterdam Municipal Health Service was used to complete the cohort data. These

included the mode of detection (classified as passive detection—that is, when a person sought help for symptoms and active casefinding—that is, when a person was called or sent for screening), clinical presentation, drug resistance (after 1991 determined routinely), results of IS6110-based restriction fragment length polymorphism (RFLP) analysis using standard methodology<sup>16</sup> (systematically available since 1 January 1993, National Institute of Public Health and Environment) and treatment results.

The registration includes all tuberculosis patients residing in Amsterdam. Pulmonary localisation of tuberculosis was distinguished in “typical” and “atypical” radiological appearance. Typical radiological appearance was defined as focal infiltration in the upper segments of the upper or lower lobes, with or without cavitation. Pulmonary infiltrates in other sites, miliary pattern, pleurisy, intrathoracic lymphadenitis or absence of abnormalities were considered atypical.<sup>17 18</sup>

Statistical comparison of general characteristics of the study population was done by  $\chi^2$  and Student's *t* tests. The cumulative incidences of tuberculosis among HIV negative and HIV positive participants were estimated with the Kaplan-Meijer survival method. HIV status was analysed as a time dependent variable: from entry to seroconversion seroconverters counted as HIV negative, from seroconversion to end point as HIV positive.

The relative hazard for tuberculosis among HIV positive participants as compared with HIV negatives was calculated with Cox proportional hazard analysis. We adjusted for the following potential confounders: sex, age, duration since first intravenous drug use, nationality, ethnicity, duration of residence in Amsterdam and year of entry in the study.

To study the relation between CD4+ cell numbers and tuberculosis incidence, poisson regression analysis was used. Because CD4+ cell numbers are routinely measured after

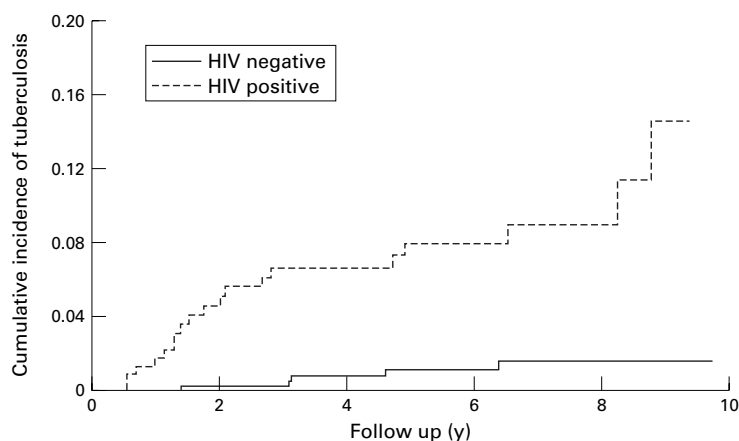


Figure 1 Cumulative incidences of active tuberculosis in HIV positive and HIV negative drug users, estimated with the Kaplan-Meier survival method.

Table 2 Cox's regression analysis: variables independently and significantly related to incidence of tuberculosis in a cohort of 872 Amsterdam drug users

Variable	Relative risk	95% confidence intervals
HIV infection*	12.85	3.38, 48.81
Age at entry (y)		
≤27	1.00	
28–32	3.4	0.66, 17.56
≥33	6.78	1.31, 35.04

\*Time dependent variable.

1988, the calculated number of person years was reduced to 975, with 14 tuberculosis cases. p Values lower than 0.05 were considered statistically significant (two sided). Analyses were performed with SPSS<sup>19</sup> and EGRET.<sup>20</sup>

## Results

At entry in the cohort study, 225 of a total of 872 participants (26%) were HIV positive and 647 HIV negative (74%). Apart from a strong relation between HIV infection and history of intravenous drug use, the HIV positive and HIV negative participants differed significantly with regard to nationality, ethnicity, and duration of residence in Amsterdam (table 1). During the study period 72 persons (11%) seroconverted from HIV negative to HIV positive.

The total follow up period was 4000 person years (py): 1235 py for HIV positive people (including follow up of seroconverters after seroconversion) and 2765 py for HIV negative people (including follow up of seroconverters until time of seroconversion).

Table 3 Main characteristics of 24 tuberculosis patients

Characteristics	HIV positive (n=19)	HIV negative (n=5)
Mode of detection		
passive case finding	10	1
6 monthly chest radiography	9	4
Type of tuberculosis		
only pulmonary (typical presentation*)	12 (8)	5 (5)
pulmonary+extra-pulmonary (typical presentation*)	5 (1)	0
extra-pulmonary	2	0
Mean CD4 cell number per µl (SD)†	390 (220)	800 (180)
TB diagnosis after 1 January 1993‡	9	2
Occurrence in RFLP cluster	5 (55%)	2 (100%)

\*Focal infiltration with or without cavitation in apical segments of upper or lower lobes. †Data from 14 HIV positive and 2 HIV negative patients. ‡Date after which RFLP became systematically available.

Twenty four of 872 participants in the cohort study developed at least one episode of active tuberculosis, corresponding with an incidence of 0.60 per 100 py (95% CI: 0.40, 0.90). Nineteen cases occurred in HIV positive people: in 15 of the 225 participants who were already seropositive at entry and in four of the 72 participants who seroconverted, all four after seroconversion, resulting in a tuberculosis incidence among HIV positive people of 1.54 per 100 py (95% CI: 0.86, 2.11). Of 575 participants who were HIV negative at entry five persons (0.9%) developed active tuberculosis (incidence 0.18 per 100 py, (95% CI: 0.08, 0.43). Figure 1 shows the Kaplan-Meier estimates of the cumulative incidences of active tuberculosis among HIV positive and negative participants.

In the univariate Cox model the relative hazard of tuberculosis in HIV positive drug users compared with HIV negative drug users was 8.5 (95%CI: 3.2, 22.9). Age above 33 years, compared with age below 27 years, and male sex were univariate predictors for tuberculosis as well (RR: 5.5, 95%CI:1.6, 19.4 and RR 3.7, 95%CI: 1.3, 10.7 respectively). Other variables (see methods) did not show a significant association with tuberculosis incidence.

Multivariately, HIV infection increased tuberculosis risk nearly 13 times (table 2). Among the other variables only age was also independently related to tuberculosis: persons with age above 33 years carried a risk seven times higher than those with age below 27 years (table 2). There was no statistical interaction between HIV and the other variables.

Of the 19 HIV positive patients there were 14 CD4+ cell numbers available: these did not show a significant relation with tuberculosis incidence (RR for CD4+ strata 300–500/µl and <300/µl as compared with counts >500/µl were 1.25, 95%CI: 0.33, 4.64 and 1.05, 95%CI: 0.28, 3.90 respectively). The mean CD4+ cell number closest to tuberculosis diagnosis was 390/µl.

Seventeen of the 19 HIV positive participants developed tuberculosis before other AIDS defining conditions (according to the latest AIDS definition). The other two already suffered from AIDS before tuberculosis was diagnosed (for 2 and 10 months respectively).

Table 3 shows several characteristics of the 24 tuberculosis patients: 13 of 22 patients (59%) with pulmonary localisation were detected through a screening programme consisting of half yearly radiological examination of the chest performed by the Municipal Health Service.

We saw typical radiological manifestations mostly in patients with only pulmonary tuberculosis. In 12 of 14 patients with typical presentation the smear of sputum or bronchial washing was Ziehl-Neelsen positive, compared with only two positive smears in eight patients with atypical presentation (p<0.05). In the seven patients with extra-pulmonary localisations *M tuberculosis* was isolated from lymph gland (4 times); pleura (3 times); blood (2 times); bone marrow (once) and urine (once). From 11 patients *M tuberculosis* was isolated

after 1 January 1993, the date after which RFLP patterns became systematically available. Seven of these patterns (63%) were part of four different clusters consisting of identical RFLP patterns (for the whole of Amsterdam). In one HIV positive patient a strain of *M tuberculosis* resistant to isoniazid was isolated (6% of 16 sensitivity tests). Tuberculosis relapsed in one HIV positive patient six years after the first episode. Finally, 23 of the 24 tuberculosis patients in the cohort completed the full nine month course of tuberculostatic drug treatment.

### Discussion

Against a background of incidences of 0.03 and 0.006 culture confirmed cases of tuberculosis per 100 inhabitants per year in Amsterdam<sup>13</sup> and the Netherlands<sup>21, 22</sup> respectively, the incidence of 0.2 per 100 py in HIV negative drug users that was observed confirms that drug users in Amsterdam are at increased risk for tuberculosis irrespective of HIV serostatus. Whereas the incidence of 1.5 per 100 py among HIV infected drug users is extremely high for Dutch standards, it is relatively low compared with the 2.1–9.6 per 100 py among drug users elsewhere in Europe and New York.<sup>9, 23–27</sup> This is probably explained by the smaller pool of drug users who are infected with *M tuberculosis* in Amsterdam: 14% in 1986,<sup>7</sup> compared with 20–31% elsewhere.<sup>9, 26</sup> As tuberculosis is supposed to reactivate in roughly 8% annually in a HIV and tuberculosis infected population,<sup>9, 25, 26</sup> we may estimate the incidence of tuberculosis attributable to reactivation in the HIV infected fraction of our cohort to be about 14% times 8%—that is, 1% per year, which approximates to two thirds of the total incidence of tuberculosis we observed among HIV positive drug users. The association we observed between higher age and active tuberculosis further confirms the major role of reactivation in the incidence of tuberculosis. On the other hand progressive primary tuberculosis resulting from recent transmission did occur as is illustrated by the identical RFLP patterns. In a recent study a high degree of active transmission of *M tuberculosis* was found for Amsterdam as a whole, and especially for hard drug users.<sup>13</sup>

As tuberculosis infection in drug users is expected to occur independently of HIV infection, the immunodeficiency induced by HIV is likely to be responsible for the 13-fold increased risk for active tuberculosis in our cohort. A comparable risk was found in New York and Sao Paulo,<sup>28, 29</sup> whereas a higher relative hazard was observed among young women in Ruanda and Zaïre.<sup>2, 3</sup>

In our cohort, tuberculosis was nearly always diagnosed before other AIDS defining conditions. The relatively high CD4+ counts at tuberculosis diagnosis and typical radiological appearance of most pulmonary lesions further complies with a diagnosis early in the course of HIV infection.<sup>17, 18</sup> The relation observed between typical radiographic manifestations and positive sputum smears corresponds with the

#### KEY POINTS

- HIV infection increases the risk for active tuberculosis in Amsterdam drug users 13-fold.
- The incidence of tuberculosis in HIV negative drug users is still six times higher than in the overall Amsterdam population.
- In the absence of contact tracing and screening with tuberculin skin tests, periodic chest radiographic screening contributes substantially to early case finding of active tuberculosis.
- Tuberculosis is detected early in the course of HIV infection.
- The harm reduction approach offers a framework for the control of tuberculosis.

finding that pulmonary lesions may be more infectious in the relatively immunocompetent host.<sup>30</sup>

Theoretically thorough contact investigations or a massive programme consisting of tuberculin skin testing followed by isoniazid prophylaxis should profoundly reduce the incidence of reactivation tuberculosis and consequently interrupt the chain of transmission. However, in our experience most drug users provide insufficient information on contacts, do not return for skin test reading and are hard to motivate for preventive treatment. Given the absence of this preventive intervention, active case finding by chest radiographic screening, at a detection rate of 60% of all pulmonary cases in the cohort, seems to be an effective alternative in this population. Even before symptoms arise, a small infiltration visible on the chest radiograph, usually has strong positive influence on the motivation for treatment. The added support of public health nurses supervising the adequate intake of medications, including adjusted methadone doses to compensate the increased breakdown by rifampicin, provided in our patients an excellent treatment outcome. Drug resistance occurred rarely, which contrasts with a study from New York, where multiple drug resistance was frequent and associated with HIV infection.<sup>31</sup>

The representativeness of the study population is unknown, as there is no registration of those who refused participation given referral of interested participants mainly via methadone programmes. Furthermore, visitors who returned for follow up visits, compared with single visitors, were more often of Dutch nationality, male gender, HIV positive or currently injecting. As a result, the estimates of the incidence of tuberculosis may be biased. However, it is unlikely that the relation between HIV infection and tuberculosis is overestimated. Also, our findings were corroborated by previous observations—that is, an overall tuberculosis incidence of 0.60 per 100 py among 3000 clients of the Municipal Health Service's methadone clinics,<sup>11</sup> and an annual tuberculosis incidence of 1.8 per 100 HIV positive drug users, based on an annual average of 14 notified cases of TB in HIV infected drug

users<sup>14</sup> and the estimated population of 800 HIV infected drug users in Amsterdam.<sup>32</sup>

We conclude that HIV infection strongly increases the risk for tuberculosis among Amsterdam drug users. Tuberculosis is detected early in the course of HIV infection. HIV negative drug users develop tuberculosis much more often than the average inhabitant of Amsterdam. The harm reduction approach offers a framework for the control of tuberculosis in Amsterdam drug users.

The Amsterdam cohort studies HIV/AIDS represent a collaborative effort between the Department of Public Health and Environment of the Municipal Health Service of Amsterdam, the Departments of Retrovirology and Internal Medicine of the Academic Medical Center, University of Amsterdam and the Department of Clinical Viro-Immunology of the Central Laboratory of the Red Cross Bloodtransfusion Service and Laboratory for Experimental and Clinical Immunology, University of Amsterdam.

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