Chapter 7

General discussion
The aim of this thesis was to better understand epidemiological developments in the field of tuberculosis (TB), with special attention to the effect of HIV-infection and drug resistance in a low-prevalence country with a – as assumed- sound TB control system.

This chapter provides answers to the research questions posed in this thesis, it discusses implications for future TB control in the Netherlands and lists the main conclusions and recommendations:

- What proportion of TB patients are infected with HIV – and what are their characteristics?

Over the period 1993-2001, 4.1% of all TB patients notified in the Netherlands were reported to have HIV-infection. (Chapter 2). The HIV prevalence did not change over time.

There is a strong and independent association of HIV infection with origin from western industrialized countries (HIV prevalence 23.1%; aOR 3.05), this may well reflect a relatively high proportion of Men having Sex with Man (MSM), as may in part the higher HIV-prevalence (7.0%) among patients living in major towns. Over time, HIV prevalence among patients coming from these industrialized countries as well as among patients living in major towns decreased. This may indicate a decreased incidence of TB in this population, probably due to a decreased HIV-prevalence and/or improved immunity as a result of cART.

Over the study period a decrease in HIV-prevalence among drug using patients, but an increase among patients coming from Africa was observed. The distinct decrease among illicit drug using patients (28% in 1993-1995 to 13% in 1999-2001) occurred despite stable numbers of illicit drug using TB patients over time. Apart from an impact of cART, this probably reflects the decline in HIV-incidence that has been observed among intravenous drug users in the Netherlands. This decline has been attributed to effective prevention of HIV-transmission by means of needle-exchange programs and a shift from intravenous use to inhalation, smoking or methadone maintenance treatment.

The increase over time in prevalence of HIV-infection among TB patients from Africa (24% in 1993-1995 to 52% in 1999-2001) primarily reflects an increasing
proportion of TB patients from Sub-Saharan Africa, where HIV prevalence are relatively high. The HIV-prevalence among these patients did not increase, although it did among patients from the Horn of Africa and the Northern regions of this continent. Apart from a true increase in HIV-prevalence, the latter could also be explained by increased HIV-testing, as a two-fold increase in HIV-testing among patients from the Horn and Northern Africa in the period 1995-2001 was observed.

- What proportion – and which TB patients are tested for HIV-infection?

Only a minority of TB patients are tested for HIV (16% in 1995 and 21% in 2001, Chapter 3). If tested, the TB patients mainly belong to known HIV risk groups. Determinants of performing an HIV-test were: notification in one of the four major towns, localisation of disease (pulmonary in combination with extrapulmonary TB) and coming from sub-Saharan Africa. Only part of all patients coming from known HIV risk groups, such as illicit drug users (56.3%) and patients coming from sub-Saharan Africa (30.6%) were tested for HIV-infection. The expected increase in HIV-testing as a consequence of the introduction of cART was not seen. Mainly TB patients coming from risk groups were tested for HIV-infection, in accordance with the national HIV-testing policy from 1992. On top of that, reluctance in testing patients from these risk groups could still be seen in 2001.

An HIV-test was more frequently performed by patients notified in a major town. This may reflect a larger proportion of drug users and home-less patients in these towns, possibly also a larger number of MSM. TB in HIV-infected patients more often has an extrapulmonary presentation. Possibly the spreading of this knowledge among physicians has led to more HIV-testing among this presentation.
· What is the impact of HIV-infection in TB patients on mortality?

Chapter 3 shows that HIV-infected TB patients have an increased risk of death (16.8% vs 7.1%; aOR 4.71) during 1993-2001. Age- and sex-standardised mortality rates among HIV-infected patients decreased significantly over time, from 22.9% in 1993-1995 to 14.8% in 1996-1998 and 11.8% in 1999-2001. A similar pattern was observed for multivariable adjusted relative risks of death for the three time periods. As no such change was observed for HIV-negative patients, a likely explanation is that, by 1999, cART was being widely used in the Netherlands. Even in the period 1999-2001, the death rate among HIV-infected patients remained higher than among non-HIV infected TB patients. This reflects the incomplete reduction of mortality by cART, which is probably due to incomplete restoration of immunity and the associated risk of other opportunistic infections. In addition, not all HIV-infected patients will have been on cART, for example because their HIV-infection only became apparent when they were diagnosed with TB.

In addition, the risk of death increased significantly with age, probably reflecting the increased mortality with age seen in HIV-infected and non HIV-infected TB patients 5.

The risk of death among HIV-infected TB patients diagnosed by active case finding was 20-fold lower than among those who were diagnosed by passive case finding, such as among those who presented with symptoms. This may be related to less advanced TB disease among patients identified by screening, and suggests that early TB case finding could reduce mortality among HIV-infected patients in this low-prevalence setting as it does in high TB-HIV prevalence countries.

The average level of immune competence of HIV-infected TB patients may have increased over time, resulting in decreased mortality unrelated to cART treatment 4, although adjusted for expected determinants of such a shift, such bias cannot be excluded.
- **What is the effect of HIV-infection in TB patients, regarding resistance patterns?**

Among new TB patients, multidrug resistance was significantly associated with HIV infection (aOR 3.43). In addition, near-significant associations with HIV infection were observed for resistance to isoniazid (OR 1.50) and resistance to rifampin (OR 2.35)

Among previously treated patients, HIV infection was significantly associated with any rifampin resistance (OR 4.12)

Only 7 cases of MDR TB occurred among 329 TB patients with HIV during the 9-year period (2.1%). Despite this small number, MDR TB was significantly more frequent among previously untreated patients with TB and HIV infection than among those without HIV infection. Non-Dutch origin appears to play an important role in this association. Transmission in the Netherlands could be ruled out in 4 of 5 new TB cases infected with HIV, therefore most if not all of these infections were acquired abroad. The MDR-TB infections in these patients may have been acquired in institutional settings such as hospitals, but data on the pre-immigration history were lacking.

Four (19%) of 21 case-patients with previously treated TB and HIV infection had rifampin-resistant isolates, including 2 (10%) that were rifampin monoresistant. Acquisition of monoresistance to rifampin is associated with HIV infection and may be related to intestinal malabsorption, intermittent treatment with rifabutin, and drug interactions. 7,8

- **What TB patients have MDR-TB and which factors predict MDR-TB treatment outcomes?**

Of all notified and treated for MDR-TB patients in the Netherlands, 38% were previously treated for TB, and 92% were immigrants from different regions of the world, with a variety of co-morbidities, including HIV-infection, drug and/or alcohol addiction, mental and mood disorders, hepatitis B or C infection, and diabetes. These MDR-TB patients were infected with heavily resistant strains, resistant to 5 drugs on average. An overall treatment success rate of 84% could be achieved.
Factors predicting a favourable treatment outcome were a negative HIV status and no previous/and or current illicit drug and/or alcohol addiction. Alcohol and/or substance abuse are known risk factors for default in MDR-TB patients \(^9,10\). Almost 56% of the alcohol and/or drug using MDR-TB patients were nonetheless cured or completed treatment. When restricted to HIV-negative MDR-TB, the treatment success rate was 92.4%.

**Main methodological issues**

Limitations were partially inherent to using routine data, e.g. incomplete records on risk groups, unidentified errors or validity. Not all TB diagnoses were culture-confirmed. Nevertheless analysis restricted to culture-confirmed cases showed that no relevant bias was introduced.

In the Netherlands, HIV testing of TB patients is not routine. The observed HIV-prevalence may therefore underestimate the true prevalence. Our data on HIV-testing among a random sample of TB patients showed a non-significant increase in the proportion tested between 1995 and 2001, and little change across risk groups. Therefore, underestimation of HIV-prevalence is likely to have remained of similar extent, and not to affect our conclusion of a stable trend over time. On the other hand, since mainly patients with known risk factors for HIV groups were tested, we may have overestimated the relative risk of HIV-infection among these groups.

The NTR does not contain data on sexual risk factors such as sexual behaviour (e.g., MSM).

Selection bias may have occurred, as not all TB patients were tested for HIV. It is possible that patients with severe disease, responding poorly to treatment or coming from a risk group have been tested for HIV more frequently than other patients. As these patients are also likely to have increased mortality, the relative risk of death among HIV-infected compared to non-infected patients may have been overestimated. It is expected that this overestimation has been the same over time, as the proportion of TB patients tested for HIV did not increase when cART became available.
HIV prevalence among our MDR-TB patients might have been underestimated, since HIV status was unknown in six patients and considered negative.

CONCLUSIONS

HIV infection has had no impact on TB prevalence in the Netherlands (probably because of the low incidences of both infections)

In contrast, MDR TB is more prevalent among HIV-infected TB patients, most likely because MDR TB is an imported disease and because of the HIV-infection itself.

Treatment outcomes are worse among HIV infected TB patients, as shown in chapter 4 concerning 'HIV-related mortality among TB patients in the Netherlands' and in chapter 6 concerning 'Treatment outcomes of multi-drug resistant TB in the Netherlands'

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<td>Prevalence MDR TB</td>
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<td>HIV pos. vs HIV neg</td>
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<td>Mortality among TB patients</td>
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<td>HIV pos. vs HIV neg</td>
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<td>Treatment outcome MDR TB</td>
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<td>HIV neg. vs HIV pos</td>
<td>27.43</td>
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Implications for policy and recommendations

HIV-testing policy. The benefits of identifying previously unrecognized HIV infection are substantial, both in terms of preventing future HIV transmission, and in terms of preventing morbidity and mortality by providing cART to affected patients. More routine HIV-testing should therefore be done by offering HIV-testing as an integral part of the TB diagnostic process. More attention should be
paid to HIV-infection in immigrants, both in terms of prevention and of HIV-testing and treatment. New national guidelines were issued in 2008 and need to be implemented.

Now that the national guidelines for HIV-testing have been changed into an opting-out policy, organisational aspects at the Municipal Health Service level still have not been addressed. Within the Municipal Health Service, there are important barriers between different disciplines. In the predominantly vertically organized Municipal Health Service an HIV-infected TB patient will be approached by either a nurse specialized in Sexually Transmitted Diseases, or a nurse/and or doctor specialized in Infectious Diseases - or a nurse and/or doctor specialized in TB, but not in HIV. Besides those logistical issues that need to be dealt with, ethical and cultural aspects also need to be taken into consideration. Nevertheless, since the benefits of knowing HIV-status are substantial all these hurdles need to be taken. Another option might be to refer patients to one of the 18 HIV-care centers in the Netherlands.

**Imported disease/risk groups**

TB and HIV are mostly imported diseases and mostly patients coming from risk groups. Asylum seekers, illicit drug and alcohol users, prisoners, illegal immigrants are predominantly affected. These groups are usually difficult to reach and also difficult to treat. The difficulty is partly the result of current administrative procedures, driven by current political commitment to prevent influx of asylum seekers with little chance to become economically independent. Yet, in order to provide optimal TB screening as well as optimal health care in accordance with internationally accepted principles of human rights, it is mandatory to enable individuals suspected with TB to stay in one place for the duration of the diagnostics process. For complicated cases, like MDR-TB and for patients co-infected with HIV, treatment and follow-up should preferably also be provided and coordinated by dedicated centres with sufficient expertise. Ongoing up-to-date education of professionals working with different risk groups who have a more direct access to difficult to reach patients (e.g. methadone maintenance programs) should continue.
**Drug resistance**

In patients with HIV infection who have previously been treated for TB the possibility of rifampin resistance should be considered. Routine surveillance of resistance to anti-TB drugs will improve timely recognition of MDR TB and XDR cases and help further reduce transmission and mortality. The latter has been implemented in January 2009.

**FUTURE PERSPECTIVES**

A multifaceted approach is needed to curb the global epidemic of MDRTB and XDR-TB. Rapid diagnostic assays to detect highly drug-resistant TB are essential in preventing delays in treatment of MDR-TB and XDR-TB and reducing transmission.

MDR-TB should be studied prospectively, with regularly updated centralized data collection for surveillance. Also, prospective randomized trials could address aspects of treatment that are now essentially only expert-opinion based and that need to be evaluated for efficacy, as well as for cost-effectiveness.

Further, only few new drugs are in the pipeline, and besides the development of new drugs, also third-line drugs and drugs of uncertain efficacy should be optimized and prospectively tested, while schedules to reduce treatment duration are also urgently needed.

In a European collaborative network (such as ECDC, TB net), different MDR-TB strategies can be compared; especially, a standardized approach should prospectively be compared with individually tailored, DST-based therapy. In such a network new drugs can also (prospectively) be compared.

The Human Immunodeficiency Virus continues to have a devastating impact on individual lives as well as societies in Sub-Sahara Africa and other low- and middle income countries and regions around the world.

A large array of drugs – now, with 5 different classes - have been developed. Most of these drugs have not yet become available in poor-resource settings.

Novel approaches to prevent HIV transmission including the development of protective vaccines, although the prospects have not yet been shown to be very
promising, are necessary. Perhaps other strategies such as male circumcision campaigns need to be further explored, as these have been shown to significantly impact on transmission. In the absence of other available strategies, widespread HIV-counseling and testing is currently the only way to fight transmission of HIV. HIV-testing should be done in each and every newly diagnosed TB patient.

To further determine the best moment to start cART in a TB patient, studies should address the optimal time to start cART after initiating TB treatment.

To understand the dynamics and interactions of both diseases better, a central database existing of HIV surveillance data as well as TB surveillance data would be extremely helpful, and regulatory barriers to achieve this goal should be tackled.
REFERENCES


