Proactive HIV testing strategies in primary care
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CHAPTER 1

General introduction and outline of the thesis
A BRIEF HISTORY

In 1981, a case report was published concerning five patients with an unknown syndrome that was soon to be known as ‘acquired immunodeficiency syndrome’ (AIDS). At that time, the cause of the immunodeficiency was unknown; however, the major transmission routes were described soon after the discovery of the illness. The causative agent was found in 1983. Human Immunodeficiency Virus (HIV) is a retrovirus that affects CD4+ T-cells. These cells protect the body from infection and their count indicates the stage of disease progression among HIV-infected patients. HIV is considered a global health problem, with more than 70 million people infected since the early 1980s, and more than 35 million people dying of HIV/AIDS. However, after the introduction of therapy, HIV changed from a deadly disease to a chronic treatable infection, with those infected – if treated in time – having almost the same life expectancy as those not infected.

CLINICAL COURSE OF INFECTION

HIV infection is characterized by three phases: the acute or primary infection, the asymptomatic, and the symptomatic phase. Primary HIV infection is characterized by high levels of the virus and a temporary decrease in the number of CD4+ T-cells, returning to a normal level within 3-4 months after infection. The majority of those infected with HIV in the acute phase (50-90%) present with symptoms of acute retroviral syndrome which is often mistaken for flu or acute Epstein Barr virus infection. These symptoms include fever, and/or nausea, vomiting, weight loss, arthralgia or myalgia, pharyngitis, oral ulcers, rash and or lymphadenopathy. The risk of transmission is much higher during this phase due to the high viral load. During the asymptomatic phase, the number of CD4+ T-cells gradually declines over time. If no therapy is started, most, if not all, of those infected with HIV will develop AIDS. At this stage of the illness, the immune system of a person infected with HIV is severely impaired and is no longer able to fight against opportunistic infections or AIDS-related cancers.

The three main transmission routes of HIV are: 1) sexual transmission, 2) sharing of injecting equipment among people who inject drugs and 3) mother-to-child transmission.

In 1985, the first antibody HIV test became available. The latest HIV antibody tests are able to shorten the test-negative window, but false positive results occur, making an additional confirmatory procedure necessary. There are also other HIV tests which are able to detect both antibodies and antigens. The Centres for Disease Control and Prevention (CDC) HIV screening algorithm recommends that these antibody/antigen tests are administered first, but also that an additional confirmatory procedure is needed.
Rapid HIV antibody tests have been developed over the years. These tests produce quick results – within 30 minutes or less – and are performed on blood or oral fluid. Several studies have shown that HIV rapid antibody tests are well accepted and received by patients and healthcare providers. The major advantage of these tests is that they can be used in nonclinical settings, for example, in the community or at home. However, the misinterpretation of test results and the complexity of quality control are mentioned as major disadvantages. Moreover, these tests require an additional confirmatory procedure. Interestingly, the updated World Health Organization (WHO) guidelines recommend that lay providers who are trained and supervised should be permitted to perform rapid HIV testing.

WHO recommends starting treatment in all individuals with HIV, regardless of clinical stage or CD4+ T-cell count. Recent studies have shown that immediate therapy after diagnosis regardless of CD4+ T-cell count improves the health prospects of the individual being treated. Other studies have reported that early initiation of therapy also greatly reduces the risk of transmission of HIV to sexual partners. These findings were reported by studies among HIV discordant couples, and support the need for early detection.

THE HIV EPIDEMIC IN THE NETHERLANDS

By the end of 2015, 88% of people estimated to be living with HIV in the Netherlands had been diagnosed, linked to care and registered by Stichting HIV Monitoring. In total, 88% of individuals linked to care had started treatment, and of this group, 93% have suppressed viremia. (personal communication from A. van Sighem)

The Joint United Nations Programme for HIV/AIDS (UNAIDS) has set the goal of ending the AIDS epidemic by 2030. They have stated that worldwide by 2020, 90% of all people living with HIV should be aware of their HIV status, 90% of all those diagnosed with HIV should receive therapy, and of that group, 90% should achieve viral suppression. While the Netherlands is within reach of achieving the UNAIDS '90-90-90' target, 28% (88% x 88% x 93%) would still be undiagnosed or not virally suppressed.

In the Netherlands, there is a concentrated HIV epidemic among men who have sex with men (MSM) and heterosexuals originating from HIV endemic countries. However, there has been a decreasing trend in the annual number of new HIV diagnoses in recent years, with approximately 1,000 new cases annually. Unfortunately, a high percentage of newly diagnosed HIV-infected patients still present late for care (44%). This means that when a person is diagnosed they have a CD4+ T-cell count < 350/mm³ or present with an AIDS-defining illness regardless of CD4+ T-cell count. The percentage of late presenters was highest among females and heterosexual males from HIV endemic countries (53%; 66%), while in the MSM group, this percentage was lower (36%). Despite clear guidelines, reducing late presenters in groups other than MSM has not been successful.
THE ORGANIZATION OF HIV CARE IN THE NETHERLANDS

In the Netherlands, HIV testing is mainly provided by general practitioners (GPs) and specialized sexually transmitted infection (STI) centres. About two-thirds of STI care is provided by GPs and one-third by STI clinics. The costs of STI tests and medication from the GP are covered by mandatory health insurance, with the patient only having to cover their insurance excess. Specialized STI centres provide additional low-threshold and free of charge STI care to certain groups at risk of STI/HIV.

The role of GPs in HIV prevention is different in every European country. In the Netherlands, GPs are an important point of referral to specialized hospitalized HIV care. Every person living in the Netherlands is required to register with a GP and 75% contact their GP at least once per year. Nonetheless, limited information is available on the HIV testing behaviour of Dutch GPs, and while a Dutch study showed an increase in the number of HIV tests between 2007 and 2009, the number of HIV tests was only 1 (95% CI of 8-13) per 10,000 patients registered in general practices in 2009. These results were not based on laboratory-documented HIV testing results but on questionnaires filled out by GPs who had one or more STI-related consultation in their practice. To date, no national or regional monitoring data is available on Dutch GP laboratory-documented HIV testing trends over time.

PROACTIVE RISK-BASED HIV TESTING IN PRIMARY CARE

Since 2002, provider-initiated HIV testing has been recommended in regional and global guidelines. At the end of 2013, the updated Dutch STI guidelines for GPs were released, which promote a more proactive role for GPs. The populations at higher risk for STIs, including HIV risk groups, are defined in this guideline as MSM, commercial sex workers (CSW), clients of CSW, people from countries where STIs are endemic, people who have had three or more partners in the last six months, and people with a partner in one of these risk groups. It is recommended that patients in these risk groups be tested for all five major STIs: chlamydia, gonorrhoea, hepatitis B, syphilis and HIV. Low risk patients who are diagnosed with an STI are required to be evaluated relative to their history and symptoms in order to determine whether they should be tested for other STIs. STI endemic countries are described on the website of the National Institute for Public Health and the Environment, which provides a pragmatic list of countries that are known to have a higher prevalence of STIs, including HIV, among the population, compared to countries with a lower STI prevalence. It is also recommended that GPs proactively discuss HIV testing, regardless of the reason for the consultation, among MSM and patients who originate from HIV endemic regions.
A Dutch study has shown that 75% of HIV-infected patients presenting late for care had one or more risk factors for HIV (according to the national STI guidelines for GPs). Provider-initiated testing places the responsibility for the test more in the hands of the provider rather than the patient. In the Netherlands, discussion of an HIV test initiated by the GP during a consultation has slowly increased in the period from 1988 (11%) to 2009 (23%). However, this strategy may not be that easy to operationalize in daily practice.

**HIV INDICATOR CONDITION-GUIDED TESTING IN PRIMARY CARE**

The WHO guidelines recommend that provider-initiated testing should be offered to clients in clinical settings who present with symptoms or medical conditions that indicate a possible HIV infection. European guidelines recommend offering a routine HIV test to patients who present with HIV indicator conditions (ICs). These findings were based on the fact that studies from the United States and France suggested that HIV testing is cost-effective as long as the undiagnosed HIV prevalence is above 0.1%. The Dutch STI guidelines for GPs briefly mentioned this strategy using a few examples of ICs (hepatitis B or C, mononucleosis-like illness, recurrent pneumonia) from the European Centre for Disease Prevention and Control (ECDC) guideline. The ECDC defines ICs as: “1) conditions which are AIDS-defining among people living with HIV; 2) conditions associated with an undiagnosed HIV infection, with a prevalence of > 0.1%, for example, herpes zoster, STI, hepatitis B and C; and 3) conditions in which failing to diagnose an HIV infection may have significant adverse implications for the individual’s clinical management, despite the fact that the estimated prevalence of HIV is most likely lower than 0.1% (for example, when aggressive immune-suppressive therapy is considered – organ transplantation or cancer).” A British study on primary care found multiple preselected ICs were associated with an HIV diagnosis. ICs occur more frequently in people living with HIV, either because they share a common mode of transmission or because they occur as a result of the characteristic immunodeficiency associated with an HIV infection.

**GEOGRAPHIC MAPPING OF THE HIV EPIDEMIC**

UNAIDS concludes that an accelerated and more focused public health response is needed to fight the HIV epidemic and to localize sites of the epidemic by using data to map areas with a higher HIV prevalence and populations at higher risk of HIV. Also, initiatives by municipalities and primary care facilities in the Netherlands recommend a more focused public health approach to tackle healthcare issues in municipalities or neighbourhoods. A public health approach was established in Amsterdam in 2014 to end the HIV epidemic,
known as the Dutch HIV Transmission Elimination Amsterdam (H-team). The H-team has developed and implemented a combination of interventions to prevent the spread of the virus and to expand HIV testing and immediate linkage to care. GPs play an important role in this initiative and are stimulated to expand their HIV testing behaviour in their practice.

In contrast to the United States and the United Kingdom, maps of areas with a higher HIV prevalence in the Netherlands are rarely integrated into current interventions. Mapping areas with a higher HIV prevalence is the first step in developing a better public health approach in municipalities or neighbourhoods.

**THE ROUTINE OFFER OF HIV TESTING**

The CDC recommends a routine offer of HIV testing for all patients aged 13-64 years in all healthcare settings in the United States (threshold of cost effectiveness > 0.1%). However, a routine offer of HIV testing across the whole population is not advised in the United Kingdom if overall HIV prevalence is lower than 0.1%. Nonetheless, British guidelines recommend routinely offering an HIV test to patients aged 15-59 in areas where HIV prevalence is above 0.2%. These guidelines make the assumption that a high HIV prevalence in an area is a predictor of undiagnosed HIV infections. The routine offer of an HIV test is operationalized by offering HIV testing to new patients during registration in primary care, and to anyone undergoing a laboratory blood test, regardless of the indication. The French government recommends routinely offering HIV screening for 15-70 year olds across the general population. In Spain, the government recommends extending HIV testing in healthcare settings beyond risk-based or IC-guided testing. The Dutch STI and hepatitis guidelines for GPs recommend proactively discussing HIV and hepatitis among risk groups only, regardless of the reason for a consultation.

**OUTLINE OF THIS THESIS**

The studies in this thesis were initiated with the goal of increasing our understanding of proactive HIV testing strategies in primary care and other healthcare settings. The results of these studies may contribute in particular to improve HIV testing programmes and assist in the implementation of these strategies in daily practice. In Chapter 2 we present additional information collected from a primary care database (NIVEL) to gain a better understanding of HIV testing by GPs in relation to risk groups during STI-related consultations. We further investigate the frequency and reasons for testing or not testing for HIV. This database includes 42-45 practices and 59 GPs, and covers about 0.8% of the total Dutch population, representative for age, gender, geographical distribution and population density. We also aimed
to investigate the contribution of GPs to the diagnosis of HIV infections in the Netherlands by using the ATHENA national observational HIV cohort, which monitors all registered HIV-infected individuals from the 31 HIV treatment centres, including four paediatric centres.26

Chapter 3 reports on a survey conducted among recently diagnosed HIV-infected patients attending two HIV outpatient clinics in Amsterdam. We collected information by using patient questionnaires, and GPs were approached for additional information. We determined the proportion of those who had consultations in primary care and other healthcare settings in the five years prior to HIV diagnosis. We also investigated patient and GP perspectives on the primary healthcare providers’ awareness and registration of sexual orientation and ethnicity in the electronic medical record (EMR).

Chapter 4 reports on data obtained from a primary care database (HAG-net-AMC), which collects medical records from six general practices located in southeast Amsterdam.69 We aimed to investigate the incidence of patient consultations and the number of ICs reported in the medical files five years prior to diagnosis. We also determined HIV prevalence rates between 2002 and 2012, with the aim of determining whether this area qualifies as a high prevalence area according to the British guidelines.60, 61, 62 This pilot study was conducted in six general practices in a multicultural area of Amsterdam, which cannot be extrapolated to a national level.

In Chapter 5 we describe a study performed using a primary care database (IPCI).70 This database contains the electronic medical records of 747 Dutch GPs. The database incorporates a considerable proportion (about 10%) of the total Dutch population, making it representative of the general population. The aim of this study was to investigate the incidence of ICs reported in medical records up to five years prior to HIV diagnosis among HIV cases, compared to matched controls. We also wanted to explore the association between HIV diagnosis and ICs when comparing gender, age group or urbanization level.

In Chapter 6 we describe the areas with a higher HIV prevalence in the Netherlands using Geographic Information System (GIS) techniques to identify regions suitable for expanded HIV testing at GP practices. In Chapter 7 we report on a qualitative study performed among GPs to investigate the barriers to and facilitators of both strategies (IC-guided testing and the routine offer of HIV testing in higher HIV prevalence areas). We undertook semi-structured in-depth interviews of key informants in HIV prevention in primary care and group discussions.

In Chapter 8 we investigate whether a blended educational programme for GPs to stimulate proactive HIV testing would be effective in changing their HIV testing behaviour, while in Chapter 9 we investigate the HIV prevalence at three emergency departments to determine whether the routine offer of HIV testing should be implemented in this setting in the Netherlands.

In Chapter 10 we evaluated the HIV test week 2015 in Amsterdam, and Chapter 11 concludes with a general discussion, which discusses the main findings of this thesis. Recommendations and suggestions for future research and clinical practice are also presented.
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