Outpatient HIV care in the Netherlands

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General introduction
One of the most important events in the history of the HIV/AIDS epidemic was the introduction of combination antiretroviral therapy (cART) in the mid-1990s. What was once a fatal diagnosis turned into a chronic, increasingly manageable condition. Moreover, with the capacity of cART to reduce HIV in the blood to undetectable levels, thereby reducing the risk of transmission, came the hope that the end of the epidemic was in sight. Unfortunately, it soon became evident that far more than the discovery of cART was needed in the battle against HIV/AIDS. Although expanding access to cART has led to undeniable gains, in terms of declines in the number of new infections and AIDS-related deaths, HIV continues to be a major public health problem. Currently, an estimated 37 million people are infected with HIV and the virus claims at least 1 million lives every year (Figure 1). With the estimated annual number of new infections among adults remaining nearly stable at about 1.9 million in 2015, the HIV/AIDS epidemic is nowhere near an end.

Figure 1: The number of AIDS-related deaths and new HIV infections per year worldwide: 2010-2015

Clearly there remains a considerable gap between what we know is attainable, namely fewer new HIV infections and markedly reduced HIV-related morbidity and mortality, and the ongoing, far-reaching global epidemic. The challenges in combating the epidemic exist on many levels, including political, social, economic, health-facility related and individual factors. To identify and overcome the barriers to an effective response to HIV/AIDS, it is important to understand what the prerequisites for a successful treatment are. To put it simply, successful treatment of HIV requires that the amount of HIV in the blood of an infected individual reaches a stable, undetectable level (“viral suppression”), as a result of taking cART. This can only be achieved once an infected individual is aware of his/her HIV-positive status (“diagnosis”), enters care (“linkage to care”), stays in care (“retention in care”), receives cART and adheres to cART. This course of events is also referred to as the HIV care continuum, and is often presented as the cascade of HIV care (Figure 2). Laying out a cascade of care can provide insight into the extent to which patients are lost along the HIV care continuum (“attrition”).
Unfortunately, attrition is a widespread problem, consequently compromising the impact of cART at both the individual and population levels. In this context, the World Health Organisation (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) proposed the ‘90–90–90’ treatment targets, where by 2020, 90% of HIV-infected individuals worldwide should know their diagnosis, 90% of these people should be on cART and 90% of those on cART should be virally suppressed.

Figure 2: The cascade of HIV care

In this thesis, we focus on the events that take place after an HIV-infected individual has been linked to care. The goal of the studies was to gain more knowledge on how the organisation of outpatient HIV care can be improved, in order to fully realize the benefits of cART. Using the results from these studies, we aim to provide healthcare workers and policy makers with more evidence based recommendations for designing outpatient HIV care.

Before reporting our study methods and results in detail (chapters 2–7), we provide background information in this introductory chapter. We start off by introducing the essential components of outpatient HIV care (chapter 1.1). We then give a brief overview of the HIV/AIDS epidemic in the Netherlands (chapter 1.2). After that, we outline the unique history of HIV treatment in the Netherlands and how it is currently organized (chapter 1.3). Subsequently, we explain how we studied the outcomes of HIV care in this thesis (chapter 1.4). This chapter ends with an outline of the rest of the thesis (chapter 1.5).

1.1. Outpatient HIV care

A brief history

The first international reports of what later became known as the AIDS syndrome were published in 1981. Within three years of the initial reports, HIV was identified as the cause of AIDS. Since effective drugs against HIV were absent at that time, the management of HIV infection was limited to relieving symptoms, preventing and treating opportunistic infections, monitoring disease progression (with CD4 cell counts) and offering counselling. The first drug shown to slow disease progression and reduce deaths in patients with AIDS, zidovudine, became available in 1987. Several drugs from the same class (i.e. that act on the same stage of the HIV life cycle), the nucleoside reverse-transcriptase inhibitors (NRTIs), followed after 1991.
Chapter 1. General introduction

Until the mid-1990s, the standard antiviral therapy for patients with HIV was treatment with initially, a single drug ("monotherapy") and, later, two drugs ("dual therapy"). Unfortunately, the efficacy of antiviral therapy was often short-lived, due to the ease with which the virus becomes drug resistant. It was not until 1996, when new classes of antiretroviral drugs were combined with two NRTIs (i.e. combination antiretroviral therapy, cART), that long-term suppression of HIV replication was achieved. To this day, this viral suppression with cART is the cornerstone of HIV treatment. By achieving and sustaining viral suppression, the damage that the virus causes to the immune system can be limited and remarkable decreases in HIV-related morbidity and mortality can be achieved.

The complexity of the treatment of HIV

Along with the great advances in antiretroviral therapy came new challenges in the treatment of HIV. In the current era, several important factors complicate the management of HIV:

- Patients face a lifelong treatment with complex cART regimens, in which strict adherence is vital. Adhering to cART can be challenging and may be further complicated by factors including side effects, mental illness and substance abuse. Difficulty adhering to cART can lead to treatment failure, disease progression and the development of resistance to antiretroviral drugs.

- The ageing HIV-infected population is increasingly affected by age-related comorbidities, which may be experienced at younger ages than in the general population. For instance, increased rates of cardiovascular disease, non-AIDS malignancies, kidney disease, osteoporosis and diabetes have been reported, with multiple factors (e.g. HIV-induced inflammation and cART) accounting for these findings. Treatment of these comorbidities requires multidisciplinary collaboration. Furthermore, adequate measures are necessary to prevent and manage problems related to polypharmacy, such as drug-drug interactions and side effects.

- Ever since the first cases of AIDS, people infected with HIV have been burdened by stigma. Unfortunately, stigma surrounding HIV/AIDS continues to be a widespread problem, with major consequences. In addition to negatively impacting psychological well-being and social relationships, stigma may discourage people with HIV from seeking early treatment and adhering to treatment, thereby jeopardizing their treatment outcomes. Moreover, it is an important barrier to testing for HIV status. These effects of stigma, in turn, result in missed opportunities to reduce infectivity of HIV-positive individuals, and thereby to reduce transmission of HIV at the population level.

For the abovementioned reasons, it is generally accepted that the care for patients with HIV infection should be provided at healthcare facilities and by care providers with experience in HIV medicine. Given the complexity of cART and its central role in the management of HIV infection, HIV care has conventionally been hospital-based and doctor-led. In low resource settings, adaptations to this traditional model are often made, with the aim of improving access to care and reducing staff burden.
These interventions include the decentralization of care (i.e. relocating services from hospitals to peripheral health facilities), and task shifting (cART provision by nurses and other non-physician providers).

Essential components of HIV care
Regardless of the setting, a number of essential components of HIV care have been recognized. These include:

- Counselling (education, coping and disclosure), adherence support and psychosocial support (e.g. linkage to support groups or treatment buddies).
- Laboratory support (HIV-specific testing, such as viral load and CD4 count; general tests such as complete blood cell count and blood biochemistry tests).
- Prevention and management of opportunistic infections and other HIV-related diseases.
- Prevention and management of non-HIV comorbidities.
- Mental healthcare (screening, referral, treatment).
- Prevention of mother-to-child transmission of HIV (PMTCT: HIV testing during pregnancy; appropriate cART for pregnant women with HIV; safe childbirth and appropriate infant feeding practices).
- Sexual and reproductive health support (e.g. screening and treatment for sexually transmitted infections; family planning advice and services).

In the Netherlands, as further mentioned in chapter 1.3, the HIV specialist and HIV nurse consultant (specialised nurse) form the core of the HIV treatment team. They are responsible for providing or coordinating the services listed above.

1.2. The HIV epidemic in the Netherlands
The number of HIV-infected individuals living in the Netherlands by the end of 2015 has been estimated to be 22,900 (95% confidence interval (CI) 22,300–23,500). As in many European countries, the epidemic in the Netherlands is concentrated, with a low prevalence of HIV infection in the general population and higher prevalence in certain subpopulations. In the Netherlands, the high-risk groups are men who have sex with men (MSM) and migrants from countries with a high prevalence of HIV. In contrast to many other settings (including Eastern Europe), injecting drug use is rarely reported as the mode of transmission in the Netherlands.

Of the 18,866 HIV-positive patients in clinical care as of May 2016, 60% were from the Netherlands and 14% from sub-Saharan Africa (SSA). With regard to the route of transmission, 62% of those in clinical care were MSM and 29% acquired their infection through heterosexual contact. The distribution of region of origin differs substantially according to route of transmission. In the MSM population, 71% originated from the Netherlands, 11% from other countries in Europe, 7% from South America, and 4% from the Caribbean. In contrast, in the heterosexual population, only 37% originated from the Netherlands, while 34% originated from SSA, 10% from South America, 5% from the Caribbean, and 4% from South/South-East Asia.
The median age of the population in clinical care has been increasing since 1996 and is currently 49 years. This increase in age is mainly due to the improved life expectancy of HIV-infected patients, owing to cART. In addition, the age at which patients are diagnosed with HIV has been increasing over time.\textsuperscript{25,26}

Since 2008, there has been a steady decline in the annual number of new HIV diagnoses to approximately 900 new diagnoses in recent years.\textsuperscript{26} In addition, there are indications that people are being diagnosed at an increasingly earlier stage of infection. These include an increase in CD4 counts at diagnosis and a decreasing proportion of late presenters with AIDS or a CD4 count less than 350 cells/mm\textsuperscript{3}, primarily among MSM. Nonetheless, the proportion of patients that present late remains troublingly high. In 2015, 45% of newly-diagnosed patients presented late for care (CD4 count <350/mm\textsuperscript{3} or AIDS), and 29% presented with advanced HIV disease (CD4 count <200 cells/mm\textsuperscript{3} or AIDS). The risk groups for presenting late for care or with advanced HIV disease were men with heterosexually acquired infection, people from South/ South-East Asia, South America and sub-Saharan Africa, and individuals aged 45 years or older.

Figure 3: Region of origin and transmission route of people with HIV in clinical care in the Netherlands.

<table>
<thead>
<tr>
<th>Region of origin</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>60%</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>14%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>7%</td>
</tr>
<tr>
<td>South America</td>
<td>5%</td>
</tr>
<tr>
<td>Caribbean</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transmission</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>62%</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>29%</td>
</tr>
<tr>
<td>IDU</td>
<td>2%</td>
</tr>
<tr>
<td>Blood or blood products</td>
<td>6%</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1%</td>
</tr>
</tbody>
</table>

source: HIV Monitoring Report 2016, Stichting HIV Monitoring
Abbreviations: MSM, men who have sex with men; IDU, injecting drug use

1.3. HIV care in the Netherlands

Healthcare coverage

All residents of the Netherlands are insured under the Healthcare Insurance Act (ZWV). This legislation obligates insurance companies to accept anyone who applies for a standard healthcare package.\textsuperscript{26} Individuals with an ongoing asylum application are collectively insured through the Asylum Seekers Care Regulation (RZA) and are entitled to nearly all services included in the basic package of the Health Insurance Act. Illegal immigrants cannot apply for insurance under the Healthcare Insurance Act, but are entitled to receive essential medical care, including the treatment of HIV infection, which they are to pay themselves. If uninsured individuals are unable to pay for delivered services, the care provider can apply for reimbursement of the unpaid bill via the care funding regulations of the National Health Care Institute.\textsuperscript{28} Given these conditions, access to HIV treatment is available to all people residing in the Netherlands.
Regulation of HIV Care

The Netherlands has a long history of regulated HIV/AIDS care. In the 1980’s, well before the advent of cART, the care for patients with AIDS was provided in a number of clinics. In 1990, with the aim of concentrating expertise, twelve clinics were formally designated as HIV/AIDS treating clinics. These clinics received financial support from the government. In 2001, the provision of HIV treatment came to fall under the Special Medical Procedures Act (WBMV). Under this legislation, costs for HIV outpatient care could only be covered when delivered in officially designated treatment centres. These treatment centres were required to meet a number of criteria. Amongst these were criteria regarding the experience and training of the staff, the number of patients in care and the continuity of care. In addition, the treatment centres were required to collaborate with the collection of data for a national registry, maintained by the Stichting HIV Monitoring. The criteria were based on expert opinion, and were set up and approved by the Dutch association of HIV-treating physicians (NVHB) and the ministry of Health, Welfare and Sport.

In 2012, the Dutch Minister of Health, Welfare and Sport announced plans to remove HIV outpatient care from the WBMV Act. In practice, this would mean that clinics lacking experience in HIV care could start treating patients with HIV. In reaction to this, and with the aim of maintaining high quality of HIV care, the NVHB took the initiative to set up a new quality assurance system for HIV care in the Netherlands. In this system, clinics would be able to apply for formal certification as an HIV treatment centre. With financial support of the Ministry of Health, and in collaboration with the institute for harmonisation of quality standards in clinical care (Stichting HKZ), a set of standards of care was developed. The NVHB, The Dutch association Nurse Consultants HIV (V&VN VCH) and patient representatives (Dutch HIV Association) took part in the development process. Other stakeholders, including health insurers (ZN), the National Institute for Public Health and the Environment (RIVM), the public health service (GGD) and general practitioners were also consulted.

Currently, there are 26 acknowledged HIV treatment centres for adults, and four paediatric HIV centres in the Netherlands (figure 4). The HIV care is generally provided and coordinated by specialised clinicians and specialised nurses. To gain certification, clinics must meet criteria regarding staff and number of patients in care (Table 1). Other requirements include (but are not limited to) having a policy plan, clearly stating the responsibilities of the members of the HIV treatment team and a close collaboration with other disciplines (i.e. pulmonary medicine, dermatology, neurology, medical microbiology and gynaecology). Furthermore, there must be access to mental health services, either within the health facility or through external referral.
Chapter 1. General introduction

Figure 4: The 26 HIV treatment centres for adults (1-26) and children (A-D) in the Netherlands.

Table 1: The criteria for HIV treatment centres, HIV-treating physicians and specialised HIV/AIDS nurses.

<table>
<thead>
<tr>
<th>Treatment centre</th>
<th>HIV medical specialist</th>
<th>Specialised HIV/AIDS nurse</th>
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<tbody>
<tr>
<td>≥ 2 HIV treating physicians</td>
<td>Infectious disease specialist</td>
<td>HIV/AIDS experience</td>
</tr>
<tr>
<td>≥ 1 specialised nurse</td>
<td>HIV/AIDS experience</td>
<td>HIV/AIDS masterclass</td>
</tr>
<tr>
<td>≥ 160 patients</td>
<td>≥ 80 patients in care</td>
<td>Registration as a specialised</td>
</tr>
<tr>
<td>≥ 20 new patients per year</td>
<td>≥ 10 new patients per year</td>
<td>HIV/AIDS nurse</td>
</tr>
<tr>
<td>Continuity of care (24/7 access to medical specialist)</td>
<td>Training</td>
<td></td>
</tr>
<tr>
<td>Multidisciplinary team meetings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National surveillance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access to scientific literature</td>
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</tbody>
</table>
1.4. Measuring quality of HIV care

National registry
In addition to having a nationally regulated system for outpatient HIV care, the Netherlands has a unique registry of people with HIV in care. This registry has its roots in the AIDS Therapy Evaluation in the Netherlands project (ATHENA). This large research study, which took place between 1998 and 2001, was set up to examine the effects of providing early access to the then newly available drug classes of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors in 3600 HIV-infected patients. The research was later extended to include all HIV-infected persons, which led to the foundation of Stichting HIV Monitoring (SHM) in 2001. Since 2002, SHM has officially been appointed by the Dutch Minister of Health, Welfare and Sport to monitor the HIV epidemic and the outcomes of HIV care in the Netherlands. Currently, SHM collects and maintains pseudonymised data from all HIV-infected patients in care in the officially acknowledged HIV treatment centres throughout the country, with the exception of a very limited proportion of patients who opt-out of having their data collected and stored. In their annual monitoring reports, SHM reports on trends over time in the HIV epidemic and the effect of treatment. SHM also produces centre-specific reports that allow HIV treatment centres to optimise their patient care and obtain formal certification. Through these activities, SHM contributes to the quality of HIV care in the Netherlands.

1.4. Measuring quality of HIV care
In the studies that are presented in the following chapters, we explore factors that affect the quality of HIV care. The first step towards measuring the quality of HIV care, is defining what effective HIV care is. As discussed earlier (chapter 1.1), an essential goal of HIV treatment is reaching and maintaining viral suppression. Consequently, viral suppression can be used to measure the outcome of HIV care, and is used extensively to assess the quality of care in clinical practice and research. Related to this measure, are measures of engagement in care, namely linkage to care, retention in care and cART usage. Viral suppression, after all, can only be achieved once an individual has engaged in these steps along the HIV care continuum (Figure 2). In this thesis we used the measures “currently in care” (to reflect retention in care), “cART initiation” and “viral suppression” to assess the quality of HIV care. Retention in care and viral suppression are patients’ outcomes and thus referred to as ‘outcome measures’. cART initiation measures the activities of care providers, therefore making it a ‘process measure’.

In addition to the process measure and outcome measures, we used patient reported outcome measures. First, we used a survey to measure the impact of disease and treatment on daily life as perceived by the patient, also referred to as health-related quality of life (HRQOL). Good HRQOL is a goal in itself, but has also been associated with increased survival in HIV-infected patients. Second, we measured patient preferences and patient experiences. The importance of responding to patients’ needs and preferences (i.e. ‘patient-centred care’) when delivering healthcare has been widely recognized. For instance, a positive physician/patient relationship has been shown to lead to better HIV treatment adherence and improved clinical outcomes.
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A broad range of other measures of quality of care have been defined and used in clinical and research settings. Amongst these are process measures related to HIV-associated diseases (e.g. rates of Pneumocystis jiroveci prophylaxis, influenza and hepatitis B vaccination, screening for tuberculosis, hepatitis B, hepatitis C and cervical cancer), non-HIV comorbidities (e.g. measurements of blood pressure, cholesterol and glucose) and treatment adherence measures. These measures, however, are beyond the scope of this thesis. Figure 5 shows the measures that we included in our studies described in the following chapters.

1.5. Thesis outline

Chapter 2 provides an overview of existing evidence linking healthcare facility and care provider characteristics to the quality of HIV outpatient care. In chapter 3 we investigated whether characteristics of HIV treatment centres in the Netherlands were associated with quality of delivered care, as measured with the cascade of care. In chapter 4, we explored how the health-related quality of life (HRQOL) of persons with HIV infection compares to that of persons with other chronic medical conditions, and assessed which demographic and clinical factors were associated with HRQOL in HIV-infected patients. Chapter 5 provides an overview of the aspects of care that are of importance to HIV-infected patients receiving outpatient care in the Netherlands. It also evaluates to what extent the received care meets patients expectations. In chapter 6, we assessed whether patients would be willing to take multiple-tablet regimens, instead of single-tablet regimens, with the goal of reducing general healthcare costs. Chapter 7 presents an overview of the most important findings and conclusions and subsequently discusses a number of methodology-related matters. Finally, the chapter concludes with recommendations for practice and for future research.

Figure 5: Measures of HIV care outcomes, per chapter in this thesis.
References

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