General introduction

Infection with the Human Immunodeficiency Virus (HIV) is currently a chronic disease and, with successful treatment, the Acquired Immune Deficiency Syndrome, better known as AIDS, has become rare (1, 2). In the mid-1990s, combination Antiretroviral Therapy (cART) was introduced by combining antiretroviral agents that were previously given as monotherapy. cART proved to be a highly effective treatment for HIV and one of the most important successes in the history of the epidemic. Treatment with cART has resulted in a greatly improved life expectancy for people living with HIV (PLWH) and, if started early after diagnosis, PLWH can have a normal life expectancy (1, 2). On a population level, cART has resulted in more people with a suppressed viral load. This is important because PLWH with an undetectable viral load do not transmit HIV to others via sexual contact (3, 4).

According to estimations of the Joint United Nations Program on HIV/AIDS (UNAIDS), in 2018 nearly 38 million people worldwide were living with HIV and yearly about 1.7 million people became newly infected (5). Although people living in Africa account for the majority of the people affected by HIV (5), it is still very present in Europe, where the HIV epidemic continues with 25.353 people newly diagnosed within the European Union and European Economic Area (EU/EEA) in 2017 (6, 7). Continuing efforts need to be made to tackle HIV worldwide. Therefore, in 2014, UNAIDS proposed three HIV treatment targets to be reached by 2020: namely that 90% of all PLWH know their HIV status, 90% of these PLWH receive sustained ART, and 90% of these PLWH on ART are virally suppressed (8). In order to reach these targets, a focus on the multiple components of HIV care is required. This can be illustrated by in the so called ‘continuum of care’ that moves from individuals becoming aware of their HIV positive status via testing (‘diagnosed’) to being linked to care (‘linked to care’), kept in care (‘retained in care’), on treatment with ART (‘on ART’), and, at the end of continuum, having undetectable HIV RNA (‘viral suppression’) (Figure 1) (9).

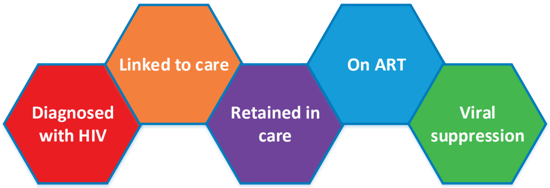

Figure 1. Continuum of care

MIGRANTS AND THE CONTINUUM OF HIV CARE

In Western Europe, several ‘key populations’ have been identified as disproportionally affected by HIV and as having a high risk of not following through all steps on the continuum of care. One key population is individuals with a migration background: people who are born outside of the country they reside in and people for whom one or both parents were born outside the country they reside in (hereafter referred to as ‘migrants’). In a recent review by Ross et al., HIV outcomes in migrants living with HIV (MLWH) originating from low- and middle income countries living in high-income countries were reported (10). Compared to PLWH originating from high income countries, MLWH from low- and middle income countries were more likely to present relatively late for testing (as evidenced by lower CD4-cell counts at time of diagnoses), have lower retention in clinical care rates, were more frequently lost to follow up, initiated ART less frequently, and experienced more virologic failure. In the Netherlands, this is also evident with MLWH doing poorer on every step on the continuum of HIV care compared to PLWH who were born in the Netherlands (Figure 2) (11).

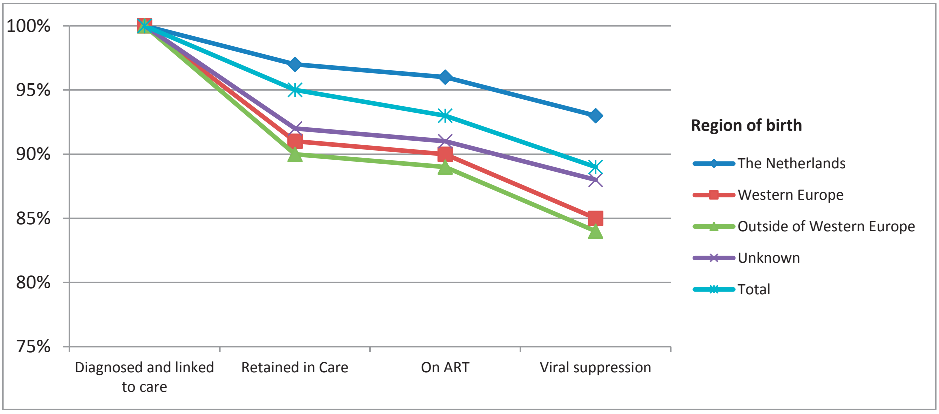

Figure 2. Continuum of care in the Netherlands, Stichting HIV Monitoring, 2019

Diagnosis

Migrants affected by HIV

In Europe, migrants comprise a substantial proportion of the people newly diagnosed with HIV (first step on the continuum of care). In fact, nearly 40% of the people diagnosed with HIV between 2008 and 2017 were born outside of the country they reside in (6). Most of the newly diagnosed MLWH originate from a country with a high HIV endemicity outside of Western Europe, like countries in the region of Sub Saharan Africa (6). Similar trends are seen in the Netherlands as 38% of the people newly diagnosed between 2015 and 2017 originated from outside of Western Europe (Stichting HIV Monitoring, unpublished data). When looking at the total number of PLWH in clinical care in the Netherlands in 2017, 35% originated from outside of Western Europe (Figure 3) (11).

Remarkably, emerging evidence shows that a significant proportion of migrants, even when originating from countries with high HIV endemicity, most likely acquire HIV after arrival in Europe (12-14). One study performed in nine European countries showed an average postmigration HIV acquisition percentage of 63%, varying between 45% for people originating from Sub Saharan Africa to 71% for people originating from Latin America and the Caribbean (13). In the Netherlands, the proportion of postmigration HIV acquisition increased from 39% before 2015 to 55% in 2015 or later, predominantly shown in people originating from Sub Saharan Africa (6). These findings suggest that current HIV prevention efforts towards MLWH in Europe are likely inadequate. They further suggest that HIV prevention interventions targeted on MLWH should not only focus on reaching MLWH directly after arrival in Europe, but also in the years following their arrival. In addition, adequate access to HIV services needs to be in place in order to ensure early testing in at risk individuals and access to treatment after HIV is acquired.

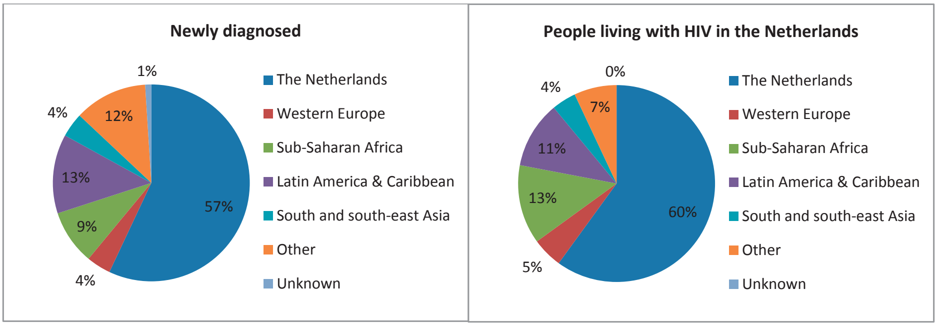

Figure 3. Region of birth of newly diagnosed PLWH and PLWH in clinical care in the Netherlands, Stichting HIV Monitoring, 2018 (unpublished data) (11).

Access to HIV services

Although the linkage of PLWH to HIV services (early testing and early treatment) has improved significantly in the last few decades, recent estimates from Western European countries have shown that still between 10 and 15% of the PLWH may be undiagnosed (15). In the Netherlands, the estimated number of undiagnosed PLWH in 2017 was 2.300 (10%) (11). Estimations in several European countries also have shown that the proportion of undiagnosed MLWH is higher compared to the general PLWH population (16, 17). These findings suggest that HIV services are not able to sufficiently reach this key population. Several factors may contribute to lower access to HIV services (e.g., HIV testing, linkage to HIV care, and treatment) among MLWH, and particularly among undocumented migrants living in the EU/EEA (18). These include: availability of health services and rights for (undocumented) migrants in the country they reside in, low socio-economic status, language barriers, cultural differences, lack of knowledge about HIV, self-stigma, fear of being stigmatized by others (e.g. one's own community) and the consequences of disclosure, and health care workers' attitudes towards migrants and PLWH in general (19-23). These factors may contribute to the relatively high number of 'late' diagnoses among MLWH.

More 'late' diagnoses

An early HIV diagnosis and subsequent (access to) treatment are vital to ensure good clinical outcomes and prevent transmission (24-26). However, the European Centre for Disease Prevention and Control has reported that nearly half (47%) of all MLWH in Europe are diagnosed 'late', defined by having a CD4 cell count <350/mm^3 (Figure 4) (27). Other studies have confirmed that MLWH have a higher risk of late presentation compared to PLWH who were born in the country they reside in (11, 28-31). Specifically in the Netherlands, between 2015 and 2017, a late diagnosis was reported among people originating from Sub Saharan Africa (57%), followed by South and South-East Asia (56%), the Netherlands (46%), Latin America (41%), and the Caribbean (42%) (11).

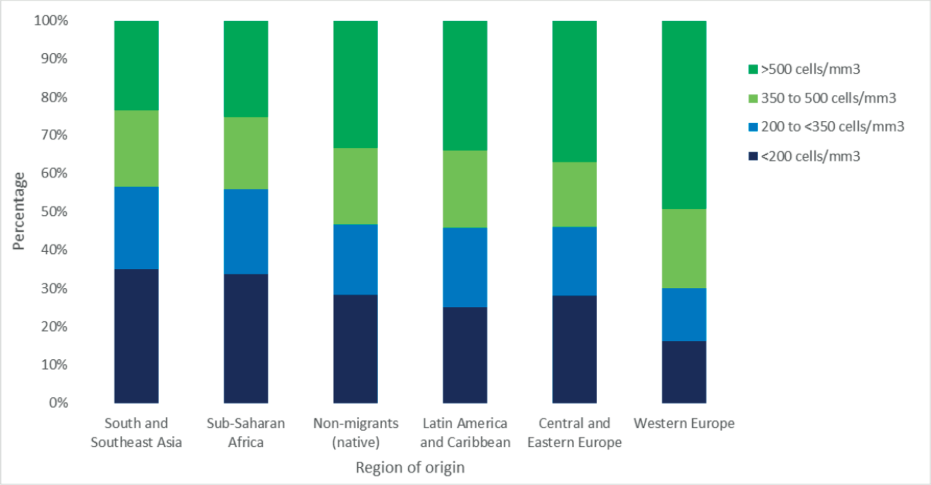

Figure 4. Late diagnosis of HIV among migrants in the EU/EEA, ECDC 2015 (27)

Retention in care

MLWH's retention in care rates compared to the general PLWH populations living in Western countries have shown mixed results in different parts of the world. In fact, two studies in the United States showed worse retention in care among MLWH compared to PLWH born in the United States (32, 33), and one study performed in Australia showed no differences in loss to follow-up rates (34). Better retention in care results were shown among (undocumented) MLWH in another United States study (35), and among MLWH who had recently (<10 years ago) immigrated to Canada (36). Studies performed in Europe showed more consistent results. In the Netherlands, Belgium, and Spain, MLWH were less likely to be retained in care compared to PLWH originating from the country they reside in (Figure 2) (21, 37, 38). Results from a study performed in Italy, showed that undocumented MLWH were more likely to become lost to follow up compared to PLWH born in Italy (39).

Treatment with cART and viral suppression

cART initiation

Over the past few decades, significant improvements in access to cART have been made worldwide (40). A special report on MLWH by the World Health Organization (WHO) has shown that documented MLWH living in Western European countries should have adequate access to cART (27). However, also in this step on the continuum of care, MLWH do poorer as they are less likely to initiate cART compared to PLWH born in the country they reside in. This was shown in high income countries in general (35), and specifically in the Netherlands as well (11).

With the increase of evidence to support earlier initiation of cART, recommendations on when to initiate cART have evolved. In the Netherlands, HIV treatment guidelines from the United States are followed which are based on the results from two large randomized controlled trials comparing outcomes of PLWH initiating cART at different CD4 cell counts (24, 26). These studies showed a 50% reduction in morbidity and mortality when cART is initiated immediately, even with CD4 cell counts >500 cells/mm^3, when compared to deferred cART initiation until CD4 cell counts drop below 350 cells/mm^3. Therefore, it is recommended that cART is initiated immediately upon diagnosis in all PLWH, regardless of CD4 cell count (41). At the same time, the same Unites States guidelines also state that the decision to initiate cART should always be made on a case-by-case basis. Clinical and/or psychosocial factors might influence a persons' readiness or willingness to start treatment as there may be reasons to (temporarily) defer cART initiation or indicate additional interventions to support adherence.

Lifelong adherence to cART

Since the introduction of cART in the mid-1990s, treatment regimens have become more effective, with less side effects, and a lower pill burden with current regimens containing only one pill per day (42). In addition, further treatment simplifications with infrequent dosing like long-acting injectables are being developed (43). However, with no available cure for HIV found yet, lifelong treatment with cART is required to achieve good HIV outcomes on an individual level (43), and high levels of adherence to treatment are a condition to achieve these outcomes (1, 44).

The literature on adherence among MLWH is limited to a few studies that have researched differences in cART adherence between MLWH and PLWH born in the country they reside in. Two studies, conducted in the Netherlands and Switzerland, showed lower cART adherence rates among MLWH (45, 46). Another Dutch study showed no differences in adherence measures, but did find poorer treatment outcomes in MLWH compared to PLWH born in the Netherlands (47). These differences in treatment outcomes were attributed to more unstructured treatment interruptions among MLWH. Most other studies reported their outcomes based on the steps of the continuum of care (from HIV diagnosis, to being linked to care, retained in care, on ART, and reaching viral suppression) (9), and although adherence to cART has not been defined as one of these steps, it is a precondition for viral suppression.

Viral suppression

The effect of cART is measured by viral load (HIV RNA in copies/ml) monitoring and viral suppression is established when HIV RNA levels fall below the lower limits of detection (41). In the Netherlands, 'viral suppression' refers to a HIV RNA <20 copies/ml for HIV-1 infection and <50 copies/ml for HIV-2 infection. Sometimes during treatment with cART, a 'blip' or viral rebound occurs which is defined as a confirmed HIV RNA of ≥200 copies/ml after viral suppression, but this usually is not associated with virologic failure (41, 48). However, persistent levels of HIV RNA ≥200 copies/ml are considered as virologic failure (41).

In the Netherlands, 97% of the people who originate from the Netherlands and on cART have a suppressed viral load (Stichting HIV Monitoring, unpublished data). However, with the exception of MLWH who originate from South and South-East Asia, all MLWH populations in the Netherlands have a higher risk of suboptimal viral suppression. This is especially the case in MLWH originating from the Caribbean (91%), Sub Saharan Africa (94%) and Latin America (94%).

KEY FACTORS INFLUENCING ADHERENCE TO CART AMONG MLWH

In general, medication adherence is considered to be complex behavior that can be influenced by multiple factors. These factors can be divided into sociodemographic, patient-related, condition-related, treatment-related, and interpersonal characteristics (49). Several studies have identified factors that impact cART adherence and subsequent health outcomes. These include: low adherence self-efficacy, concerns and beliefs about cART, (symptoms of) psychological distress, lack of social support, (fear of) HIV-related stigma, disclosure concerns, poorer quality of life, substance use, high pill burden, cART side effects, financial constraints, and relationship with the healthcare provider (45, 50-59).

Relevant psychosocial factors

A number psychosocial factors that influence adherence to cART are more prevalent in MLWH than in PLWH living in the country they reside in. Previous research in the Netherlands has shown that MLWH tend to experience more HIV-related stigma, more disclosure concerns, less social support, more symptoms of psychological distress, and less quality of life compared to PLWH born in the Netherlands (45, 60).

HIV-related stigma is one of the most important psychosocial aspects of living with HIV and it has clearly been shown to impede adherence to cART. Pescosolido and Martin defined stigmatization as "a social process embedded in social relationships that devalues through conferring labels and stereotyping" (61). HIV is highly stigmatized because it is often associated with behaviors perceived to be immoral or norm-violating (such as same sex relations, promiscuity, sex work, and drug use), and seen as highly contagiousness with potentially devastating outcomes (62-65). Stigmatization has significant consequences. Results from a meta-analyses showed associations between HIV-related stigma and depression, low social support, lower levels of adherence, and lower access to and usage of health and social services (66). Also in Europe, HIV-related stigma is prevalent. This is especially the case in migrant communities (65). Consequences of HIV-related stigma include emotional pain, sadness, internalized stigma, limited social support, social isolation, and poor treatment adherence (65). Additionally, MLWH are likely to experience 'intersectional stigma' related to having HIV and being a migrant, that might impede them from disclosing their HIV status to others (67). Whembolau et al., in their systematic review on MLWH from Sub Saharan Africa living in Western Europe, reported that migrants not only face a foreign country with new cultures and languages, but also uncertainty in legal status, discrimination, and socio-economic difficulties (68). They also reported that MLWH often have to deal with these challenges without support from family and friends, and that they have to navigate HIV care in a new healthcare system.

There is mixed evidence on the association between HIV status disclosure and adherence to cART in general. Although Daskalopoulou, in a cohort of 3258 PLWH living in the United Kingdom, found no association between disclosure and adherence (69), a review of literature on HIV-status disclosure in Ethiopia showed a positive effect of disclosure on adherence to cART (70). European studies have shown lower rates of disclosure and more disclosure concerns among MLWH compared to PLWH born in the country they reside in (45, 69). Disclosure, while perceived to be beneficial for social support (71), is often impeded by a (fear of) stigmatization and its possible consequences (e.g. exclusion), particularly among MLWH originating from Sub Saharan Africa and the Caribbean (64, 68).

Social support is indeed another important psychosocial factor that can impact treatment adherence. Previous studies have shown that social support can be a contributing factor to adherence to cART, and lack of social support negatively impacts adherence (51, 54, 72, 73). Taylor defined social support as "the perception of experience that one is cared for, esteemed, and part of a mutually supportive social network" (74). There are different types of support: emotional support (expression of affection, empathy, and caring), informational support (provision of recommendations, advice, and other helpful information), tangible support (financial, material or physical assistance), and network support (the presence or availability of others for social engagement) (75). Social support can be given by, e.g., family, friends, partners or support groups. Especially in migrant populations, social support is important as migration may result in limited close relationships with family and friends, and people are dependent on support from new social networks.

Mental health is also an important aspect impacting treatment adherence as the presence of symptoms of anxiety or depression (psychological distress) impedes adherence to cART (56, 58, 76). This is particularly relevant because several studies have shown that symptoms of psychological distress are common among PLWH, with a meta-analysis showing a prevalence of 12.8-78% for symptoms of depression in low-, middle-, and high income countries (58). Previous studies have also shown that, when comparing MLWH to PLWH born in the country they reside in, MLWH are at an even greater risk for symptoms of psychological distress (45). This is possible due to their migration status as MLWH may have migrated due to armed conflicts, unemployment, or poverty. Events before departure in their country of origin, during their migratory trajectory, or after arrival in the country they reside in may be traumatic and can contribute to the mental health of MLWH (77, 78).

A final psychosocial factor is quality of life. There is mixed evidence on the association between quality of life and adherence to cART. Mills et al. found decreased quality of life to be an important barrier to cART adherence (79), but inconclusive results were reported in a review by Ammassari et al. (51), and Langebeek et al. did not identify quality of life as a predictor for adherence (56). The WHO has defined quality of life as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns” (80). Quality of life among PLWH is still substantially lower compared to the general population (81), and although evidence for differences between MLWH and PLWH born in the country they reside in is limited, one study performed in the Netherlands did find significant poorer quality of life in MLWH compared to PLWH born in the country they reside in (45).

Additional factors impacting cART adherence

There are also other specific issues within the MLWH population that may cause poorer adherence to cART. For example, MLWH might experience migration related problems that need to be overcome, such as language barriers and cultural differences. Also, high levels of mobility in migrant populations have been shown to negatively impact care engagement and treatment adherence (82, 83). Lastly, the availability of social services for MLWH is of great value as mediation for housing, work, and mental support may also influence HIV-related health outcomes (20, 84). Logically, these factors may influence cART adherence as well.

OUTLINE OF THIS DISSERTATION

Cleary, MLWH perform poorer on continuum of care than PLWH born in the country they reside in. It is therefore imperative to improve care for MLWH living in Western Europe. One strategy for improving HIV outcomes in PLWH is offering interventions that target adherence to cART. This requires paying attention to factors associated with adherence to cART in general, as well as having a specific focus on individual and structural factors that are unique to key population including migrants with HIV. To date, in high income countries, most studies of, and interventions for, improving treatment adherence and engagement in HIV care are conducted with PLWH primarily originating from that country; interventions often do not specifically target MLWH (10, 85), but they should. MLWH have specific barriers to adherence to cART that need to be addressed.

The studies presented in this dissertation focus on MLWH who are already linked to care. The general aim of this dissertation is to investigate adherence to cART, explore factors associated with adherence, and assess the feasibility of interventions that may improve cART adherence in MLWH. In **Chapter 2,** two methods to measure adherence to cART are investigated: pharmacy refill data and self-reported adherence data. Both methods are compared to determine their predictive value for undetectable viral load. Additionaly, risk factors for non-adherence based on pharmacy refill data calculation are examined. **Chapter 3** presents an assessment of several socio-demographic and psychosocial factors as risk factors for non-adherence to cART to determine the focus of future interventions to improve adherence. Using cross-sectional surveys, the Hospital Anxiety and Depression Scale is evaluated in **Chapter 4** as a screening tool to measure psychologial distress within MLWH. Additionally, the association between psychological distress and treatment adherence is determined. In **Chapter 5**, a quasi-experimental design is used to assess the feasibility and, if feasible, the possible efficacy of directly administered antiretroviral therapy, group medical appointments, screening and treatment of psychological distress, and peer support as interventions to improve treatment adherence. **Chapter 6** presents a qualitative evaluation of the impact of a pilot project of peer support for adherence to HIV treatment, and explores psychosocial factors such as HIV-related stigma, social support, and mental health. In this study, the experiences of both MLWH receiving and MLWH giving peer support are described. In **Chapter 7,** the availability of support services (in addition to medical care) for MLWH in the Netherlands according to HIV care providers from the 27 Dutch HIV treatment centers is investigated. Finally, **Chapter 8** provides an overview of the most important findings and outlines some critical reflections. The chapter concludes with implications and recommendations for practice and future research.

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