

<http://hdl.handle.net/1765/125515>



General discussion



The introduction of combination Antiretroviral Therapy (cART) in the mid-1990s has made infection with the Human Immunodeficiency Virus (HIV) a treatable chronic disease with a greatly improved life expectancy (1, 2). Also, the latest report of the United Nations Programme on HIV/AIDS (UNAIDS) showed that the number of people newly infected is declining, strongly in Sub Saharan Africa and more gradually in other parts of the world (3). However, that same report also showed that the burden of the epidemic continues to be substantial with nearly 38 million people worldwide living with HIV in 2018 and, in the same year, about 1.7 million people became newly infected. In order to tackle HIV worldwide, we need effective interventions that improve outcomes for people living with HIV (PLWH) on all steps of the 'continuum of HIV care', which 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')(4).

In Europe, people with a migration background (migrants) are identified as a population disproportionately affected by HIV. Migrants living with HIV (MLWH) have a higher risk of not following through all steps on the continuum of care when compared to PLWH born in the country in which they reside (5, 6). The studies presented in this dissertation were performed in HIV treatment centers in the Netherlands and therefore focused on MLWH who were already in clinical care. However, it is important to briefly consider challenges in reaching undiagnosed MLWH. A study performed in the Netherlands showed that the estimated proportion of undiagnosed PLWH among migrant populations compared to the general PLWH population (34%) was considered to be excessively high: 44% among MLWH originating from the Caribbean and 48% among MLWH from Sub Saharan Africa (7). Previous studies have identified multiple barriers and a few facilitators of HIV testing uptake among MLWH living in high-income countries (**Chapter 1**) (8-12). Blondell et al. concluded that HIV testing in this population is complex and highlighted the need for culturally sensitive approaches that take into account additional barriers unique to migrants (12). It is clear that there is still work to be done to ensure that all PLWH, and MLWH in particular, reach the first steps in the continuum of care.

Promoting treatment adherence is fundamental to tackling HIV as treatment adherence results in good clinical outcomes among PLWH and prevents transmission to others (1, 13, 14). The general aim of this dissertation was to: investigate treatment adherence among MLWH with a specific focus on adherence to cART, explore factors associated with adherence, and assess the feasibility of interventions that may improve cART adherence in MLWH. In the following section, the most important findings of this dissertation are summarized. Furthermore, critical reflections on adherence research among MLWH within and outside of this dissertation are given. Lastly, the implications for clinical care and future research are discussed.

MAIN FINDINGS

Chapter 2 investigated two methods to measure adherence to cART: pharmacy refill data and self-reported adherence data. The findings support the use of self-reported adherence questions among MLWH. It seems to be a relatively easy and effective method when compared to measuring adherence via pharmacy refill data. In the Netherlands, where there is no closed pharmacy system, measuring treatment adherence via pharmacy refill data is laborious and in many cases not possible. In addition, the findings of **Chapters 3 and 4** that investigated risk factors for non-adherence to cART among MLWH confirm the following risk factors: a low educational attainment, experiencing a lack of social support, experiencing low treatment adherence self-efficacy, being at risk for symptoms of psychological distress, and experiencing internalized HIV-related stigma (marginal association). Furthermore, **Chapter 5** investigated the feasibility and, if feasible, the possible efficacy of directly administered antiretroviral therapy (DAART), group medical appointments (GMA), screening and treatment of psychological distress, and peer support as interventions to improve treatment adherence. The findings suggest that DAART and GMA are not feasible interventions to improve adherence among MLWH. While screening of psychological distress was feasible, follow-up diagnostic screening and linkage to psychiatric services were not. Peer support by trained MLWH appeared to be a feasible intervention, and the results on HIV RNA and outpatient clinic visit attendance were promising. Also, the findings from a qualitative evaluation of the impact of peer support by trained MLWH in **Chapter 6** suggest that support for and by MLWH can enable positive changes in attitudes towards living with HIV and the development of coping strategies that affect HIV treatment management. Lastly, in **Chapter 7**, which investigated the availability of support services (in addition to medical care) for MLWH in the Netherlands among HIV care providers from the 27 Dutch HIV treatment centers, the findings indicated a need for additional care in the form of peer support, psychosocial care, and care specifically for refugees and undocumented MLWH in rural areas of the Netherlands.

CONTINUUM OF CARE AND MIGRANT POPULATIONS

As shown in **Chapter 1**, MLWH perform poorer on the continuum of care than PLWH born in the country in which they reside and are therefore considered a 'key population' among PLWH (5, 6). The studies presented in this dissertation report on research conducted with a large sample of MLWH originating from outside of Western Europe who visit the outpatient clinics of the two HIV treatment centers in Rotterdam, the Netherlands. However, selecting MLWH for research on treatment adherence based to their migrant status alone might not be specific enough. There may be additional considerations because MLWH are not a homogenous group and the experiences and backgrounds of MLWH in the Netherlands may be diverse. As such, their performance on the continuum of care may not be related only to their migrant status. It is possible that

various subpopulations can be delineated based on factors such as region of origin, gender, and the means by which HIV was acquired. Future research on adherence to cART among MLWH may benefit from taking these factors into account.

Region of origin

When considering region of origin, Figure 3 in **Chapter 1** showed that most MLWH living in the Netherlands originate from Sub Saharan Africa, Latin America, and the Caribbean, and indeed results from previous studies conducted with MLWH living in Western Europe have shown that poorer outcomes on the continuum of care are mainly seen in MLWH originating from these three regions (6, 15-17). Similar trends have been shown in the Netherlands (**Chapter 1**, Figure 2) and, therefore, the studies presented in this dissertation had a specific focus on MLWH originating from outside of Western Europe. However, migrants are a heterogeneous group with social, economic, and cultural diversity among subpopulations that might lead to different outcomes. Previous literature suggests that events before departure from the country of origin, during the migratory trajectory, or after arrival in the residence country may contribute to health outcomes (18). Future studies should therefore investigate the factors that cause specific migrant populations to perform poorer on the continuum of care and, although this dissertation has mostly focused on MLWH originating from Sub Saharan Africa, Latin America, and the Caribbean, PLWH originating from other regions should be taken into account as well. For example, in the Netherlands, PLWH originating from Central Europe represent a smaller group within the total PLWH population, but, in recent years, evidence has shown that they too perform poorer on the continuum of care (6).

Gender differences

Another way to differentiate within a population is by gender. Previous studies on gender differences in adherence and HIV treatment outcomes have shown inconsistent results. Several studies have shown that, compared to men, women were more at risk for becoming non-adherent to cART or experiencing poorer clinical outcomes (15, 19, 20). Other studies have reported poorer clinical outcomes in men (21, 22), and still others have reported similar outcomes for men and women (21). Another important subpopulation to consider is people who identify as transgender, non-binary, or gender queer. Research among PLWH of transgender experience have shown mixed evidence with regard to their performance on the continuum of care when compared to cisgender men and women living with HIV, with studies showing both poorer outcomes for PLWH of transgender experience and similar outcomes for transgender and cis-gender PLWH (23-26).

Previous studies on gender differences in adherence tend to have been conducted in the general PLWH population and not specifically in MLWH populations. This is a significant shortcoming because, in Europe, the proportion of women in MLWH populations usually is high compared to the PLWH population born in the country in which they reside (27-29). One study comparing HIV treatment outcomes of PLWH born in the country in which they reside to MLWH showed poorer outcomes among MLWH, but the virological responses differed for men and women from

different regions of origin (15). In fact, all groups showed virological responses of $\geq 85\%$ except for women originating from the Caribbean (77.7%). Additionally, the same study showed that, when compared to PLWH originating from the country in which they reside, lower virological response rates were found in men originating from Sub-Saharan Africa, North Africa, and the Middle East, and women originating from the Caribbean. A sub analysis performed on data from the studies described in **Chapters 2, 3, 4, and 5** showed no differences in detectable viral load and adherence to cART between MLWH men and women (30). However, risk factors for non-adherence did differ between men (low educational attainment and low social support) and women (high internalized HIV-related stigma and being at risk for symptoms of psychological distress). When considering MLWH of transgender experience living in Europe, it is not possible to discuss outcomes within this population compared to cisgender MLWH as there does not seem to be any literature available on outcomes for MLWH of transgender experience living in European countries. Studies performed in the United States with bi-cultural PLWH of transgender experience showed mixed evidence on adherence to cART and viral suppression (23, 25, 31). It is plausible that this subpopulation has specific barriers that contribute to poorer performance on the continuum of care, such as intersectional stigma. Therefore, future studies should investigate HIV outcomes, and barriers and facilitators on the continuum of care, specifically for MLWH of transgender experience and for cis-gender migrant women with HIV living in Europe.

Sexual orientation

A final way in which subpopulations can be defined is based on their sexual orientation. In the Netherlands, MSM and non-MSM PLWH have shown different results on the continuum of care. A recent report showed that, in 2017, in general, MSM PLWH had better outcomes on the continuum of care compared to non-MSM men and women, especially among those who originated from outside of the Netherlands (6). Results from another Dutch study on migrant and non-migrant PLWH support these findings (32). The results from that study showed that, although all groups reported high self-reported adherence (94% and higher), migrant non-MSM men and women found it more difficult to adhere to their cART regimen than migrant MSM, and MSM and non-MSM who were born in the Netherlands. This 'non-MSM men and women' subpopulation among MLWH may have specific barriers on the steps of the continuum of care that need to be investigated.

In short, it is important to consider MLWH as a diverse population and to recognize that their performance on the continuum of care may be related to factors other than their migrant status. Future research and the development of adherence improving interventions should consider that risk factors for non-adherence, as well as HIV outcomes, may vary between MLWH subpopulations that can be delineated based on region of origin, gender, and means of HIV acquisition.

TREATMENT ADHERENCE IMPROVING INTERVENTIONS

In **Chapter 5**, the feasibility and, if feasible, the possible efficacy of directly administered antiretroviral therapy (DAART), group medical appointments (GMA), screening and treatment of psychological distress, and peer support by trained MLWH to improve treatment adherence were assessed. Participants who experienced substantial difficulty in living with HIV, had problems with HIV treatment adherence, or were at risk for non-adherence based on the outcomes from the first questionnaire, were offered one or more intervention(s). A multidisciplinary HIV care team determined which intervention (DAART, GMA and/or peer support) or combination of interventions would be most appropriate for each given patient, and participants with a HADS score ≥ 15 were allocated to early screening and treatment of psychological distress.

Feasible interventions in MLWH

The results from **Chapter 5** suggest that the following interventions were feasible: screening for psychological distress and peer support by trained MLWH. However, as follow-up diagnostic screening with the CIDI was not feasible, it was not possible to determine the possible efficacy of the screening and treatment of psychological distress intervention. It was possible to collect data on psychosocial and clinical outcomes within a small sample receiving peer support (**Chapters 5 and 6**). These results contributed to a better understanding of the feasibility of adherence-improving interventions among MLWH. Peer support for and by MLWH is promising, but a more extensive evaluation is needed. The results of the peer support intervention are important as current research on the effect of peer support on treatment adherence is minimal, inconclusive, and usually does not specifically target MLWH living in Europe (33). The results of the pilot project (**Chapters 5 and 6**) are thus important first steps in addressing these gaps in the literature. However, these results are based on a pilot project with a sample that was too small to determine a significant effect. In order to ascertain the effectiveness of peer support by MLWH on MLWH, a full trial is recommended with an intervention and control cohort and both quantitative and qualitative research components. In addition, the included sample should have sufficient power and, because we can expect challenges with regard to patient inclusion, it is recommended that more than two HIV treatment centers participate in this trial. Lastly, the research team should take factors like longer time since HIV diagnosis, and having additional mental or personal problems into account when screening participants for eligibility as the results from **Chapter 6** showed that participants with these characteristics were more likely to have unsuccessful matches. A full trial would provide stronger evidence for whether or not peer support for and by MLWH projects should be expanded to other parts of the Netherlands, including, as indicated in **Chapter 7**, rural areas where HIV care providers feel the need for peer support is even greater.

Other adherence improving interventions

In the past decades, many interventions aiming to improve adherence to cART have been tested (34). For the studies presented in this dissertation (**Chapters 4, 5, and 6**), DAART, GMA, screening and treatment of psychological distress, and peer support by trained MLWH were assessed. However, there may also be other options.

One intervention that has been tested in the Netherlands is a nurse-delivered intervention that incorporates adherence feedback from electronic drug monitoring with an electronic pill bottle cap that registers date and time of bottle opening (35). The results of this study showed that PLWH in the intervention group had better virological outcomes compared to PLWH receiving standard care, and the intervention was also shown to be cost-effective. However, there are concerns about the acceptability of this intervention as almost 60% of eligible participants refused to participate due to, e.g., the size and look of the non-discrete bottles (36). Especially within the MLWH population, where fear of (third) party disclosure and stigmatization are substantial concerns, this intervention may not be feasible.

Another approach to promoting treatment adherence is ‘mHealth’, which refers to interventions that use mobile and wireless technology to achieve health objectives and facilitate HIV self-management. Two recent systematic reviews showed that, in recent years, an increasing number of studies have investigated the impact of applying mHealth in HIV care (e.g., mobile reminders for taking medication, medical appointments, or HIV education) for adherence to treatment, and these interventions have shown to be effective, feasible, and acceptable (37). However, both reviews argued for more comprehensive mHealth interventions that target more barriers to adherence and that incorporate not only mobile text messages, but also aspects like interactivity, links to contact health care professionals, and HIV education.

Looking at evidence from studies worldwide on adherence-improving interventions, mHealth and peer support seem to show the most promise. In fact, KanTERS et al. performed a systematic review and network analysis on 85 studies that investigated interventions to improve adherence to antiretroviral therapy, and found evidence for the effectiveness of mHealth interventions, cognitive behavioral therapy, and supporter interventions (34). In addition, they found that the use of multiple interventions showed better results on treatment adherence compared to single interventions, indicating an additive effect of adherence interventions.

There are also other examples of mHealth that might have a positive influence on treatment adherence. One example is a 10-weeks guided internet-based intervention with telephone coaching for PLWH who experience symptoms of psychological distress (38). This intervention consisted of cognitive behavioral therapy with exercises that focused on activation, relaxation, identifying and changing negative thoughts, and goal setting with the aim to increase confidence to attain goals. Although the intervention did not specifically seek to improve adherence, it did focus on improving resilience in participants by reducing psychological distress which is a risk factor for non-adherence to cART (39-41). The study results showed that symptoms of psychological distress decreased, and that the reduction was significantly larger in the intervention group compared

to the control group. Although this study did not specifically focus on MLWH and the intervention was only available in Dutch and English, it has potential for MLWH. Specifically, because the intervention does not entail face-to-face contact and does not require travel, fear of (third) party disclosure and HIV-related stigma may be lessened. Additionally, the intervention could be easily translated into other languages. These intervention characteristics might make it an intervention that is more accessible for MLWH compared to, for instance, the follow-up diagnostic screening with the CIDI that was tested in **Chapters 4 and 5**.

Challenges in implementation

While there are a number of interventions that show promise and the use of multiple interventions is considered best, the implementation of interventions is not always ideal. The results from **Chapters 4, 5 and 6** showed that it was challenging to find MLWH willing to participate in several of the interventions for various reasons, such as not being willing to make the necessary time investment, having a language barrier, fearing (third party) disclosure, and fearing stigmatization. In addition, multiple eligible participants could not be reached or did not show up for their appointment(s).

The interventions that were tested in this dissertation were chosen based on theory about the determinants of HIV (treatment) outcomes among PLWH, and were based on their performance in previous studies among PLWH populations or other people living with a chronic disease (**Chapter 5**). Professionals in formal and informal HIV care for, and HIV research with, MLWH, and a program officer on MLWH from Soa Aids Nederland were consulted in the development and execution of this research project and in the selection of the interventions that were tested. The development of effective behaviour change interventions requires consultation, or better yet, co-creation of intervention programs with representatives of the target community or population, and that collaboration is also key to implementation (42-46). Including community representatives enables the project team to, among other, better address the issues that are unique to the target population, choose and/or customize interventions to ensure their acceptance, and improve implementation strategies. This is also termed the 'meaningful involvement of people with HIV/AIDS' (MIPA), and, in this research project, perhaps more opportunities for MIPA of MLWH could have been explored. It is possible that DAART and follow-up diagnostic screening with the CIDI would have been excluded from the list of interventions if representatives from the MLWH population would have been included more in the project team's decision making processes. On the other hand, it is possible that these representatives would have been on board with the interventions that were chosen, and their input could have resulted in better acceptance of DAART, GMA, and follow-up diagnostic screening with the CIDI among the study participants.

While it is clear that MIPA is essential in HIV research, it is not always feasible. HIV care providers report that, for a considerable proportion of the MLWH, participation of MLWH in a project team is a challenge, particularly in light of reports that MLWH already struggle to comply with outpatient clinical appointments that take place only a few times per year. This may especially be

the case when MLWH have to deal with what they likely perceive to be more issues surrounding them such as legal status, unemployment, or other challenges that were described in **Chapter 1**. Nevertheless, it is important to continue to seek how to engage MLWH and find a way how to involve them in the development and implementation of new interventions, and such involvement might also serve to empower MLWH as their opinions as ‘experts by experience’ are highly valued. Evidently, MLWH representatives in project teams should be reimbursed for their time spend in the project team.

The research project described in this dissertation was a pilot project that sought to address adherence and test adherence improving interventions in MLWH in the Netherlands. It is recommended that future research projects among MLWH make use of Intervention Mapping and Implementation Science in adherence-improving intervention development, implementation, and evaluation. Fernandez et al. recently proposed combining Intervention Mapping and Implementation Science, and termed this Implementation Mapping (46), which is defined as: “a systematic approach for developing strategies to improve the adoption, implementation, and maintenance of evidence-based interventions in real-world settings”. Implementation Mapping is based on the six steps Intervention Mapping and specifically focusses on the fifth step: Program Implementation Plan (44). Implementation Mapping consists of five tasks: (1) conduct an implementation needs assessment and identify program adopters and implementers; (2) state adoption and implementation outcomes and performance objectives, identify determinants, and create matrices of change objectives; (3) choose theoretical methods (mechanisms of change) and select or design implementation strategies; (4) produce implementation protocols and materials; and (5) evaluate implementation outcomes (46). Including these tasks in future adherence improving interventions is highly recommended and will likely help to alleviate expected challenges in implementation.

OUTCOME MEASURES IN HIV CARE

In the studies presented in this dissertation (**Chapters 2, 3, 4, 5 and 6**), treatment adherence was measured using several commonly used methods including effectiveness of cART (viral load monitoring), self-reported adherence to cART, pharmacy refill adherence, and outpatient clinic appointment attendance (in the peer support intervention group only). However, there are other valuable outcomes in HIV research that are worth consideration as living with HIV entails more than focusing on treatment.

With the shift towards HIV being a chronic condition that can be managed with improved cART regimens that have fewer pills, less side effects, and viral suppression with adherence levels of <100% (47), the focus of HIV disease management has increasingly shifted to living with HIV beyond viral suppression. This suggests a need for a more holistic approach (48) such as the value-based healthcare (VBHC) model suggested by Porter. VBHC focusses on maximising the value

for the patient and reducing healthcare costs (49). HIV care providers at the Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam are one of the first to have explored the possibilities of VBHC for their HIV patients (50). They do this by not only structurally measuring outcome indicators that focus on process (retention in care), and treatment outcomes, as well as the sustainability of health (therapy tolerance, therapy effectiveness, cardiovascular disease, and mortality); they also invest in measuring and adding patient value (health-related quality of life, HRQoL) as an outcome. In this context, a questionnaire was designed that included items on quality of life, symptoms of psychological distress, HIV-related stigma, social support, sexuality problems, self-esteem, sleeping difficulties, and treatment tolerance (51).

HRQoL has been suggested as the fourth “90” following the testing and treatment targets suggested by UNAIDS: 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 (52, 53). **Chapter 1** demonstrated the relevance of a number of themes that fall under HRQoL, such as HIV-related stigma, social support, mental health, and quality of life in relation to treatment adherence and subsequent clinical outcomes, especially in the MLWH population. It is advisable to take steps towards structurally measuring HRQoL in clinical care. This would entail collecting data via questionnaires. However, the feasibility and practical implementation of this among MLWH needs to be carefully explored together with (representatives of) MLWH. Here, the development team should consider possible challenges such as language barriers, illiteracy, and the cultural appropriateness of the survey research and questionnaire items.

IMPLICATIONS AND RECOMMENDATIONS

The findings of the studies reported in this dissertation and the general discussion have implications for clinical care and provide input for future research.

For clinical care

The first implication for clinical care is that, in the Netherlands, HIV care providers can use self-reported adherence questions to measure adherence to cART in MLWH. This method seems to be superior compared to using pharmacy refill data in determining adherence to cART. As shown in **Chapter 2**, both methods can predict viral load but, because there is no closed pharmacy system, measuring treatment adherence via pharmacy refill data is laborious and in many cases not possible.

The second implication for clinical care is that MLWH with low educational attainment, low social support, low treatment adherence self-efficacy, or risk for symptoms of psychological distress should be closely monitored by HIV care providers as they are at risk for treatment non-adherence (**Chapters 3 and 4**). Also, given the important role of HIV-related stigma among MLWH and its effects on adherence, it is recommended that MLWH are screened for enacted,

anticipated, and internalized HIV-related stigma as well. If MLWH are found to be (at risk) for non-adherence based on the results of these screenings, in addition to the clinical assessment of the HIV care provider, a multidisciplinary team should discuss the available options that might support the patient in HIV treatment.

The third implication for clinical care is that DAART, GMA, and diagnostic screening with the CIDI are not feasible interventions within a MLWH population. As shown by the findings in **Chapters 4 and 5**, DAART was found to be intrusive and impractical by study participants. Fear for HIV-related stigma and third-party disclosure among MLWH appeared to be key barriers to participation in GMAs. Diagnostic screening with the CIDI was impeded by, among others, language barriers. Additionally, the results from **Chapters 4, 5 and 6** showed that peer support is a feasible intervention and that the HADS is a suitable screening tool for MLWH from different cultural and lingual backgrounds.

The fourth implication for clinical care is that support for and by MLWH can enable positive changes in attitudes towards living with HIV and the development of coping strategies that affect HIV treatment management (**Chapters 5 and 6**). In addition, the results within a small intervention group on viral load and outpatient clinical appointment attendance were promising. Therefore, as an addition to standard care and as part of a more holistic approach to care for MLWH, peer support by trained MLWH is recommended as an intervention to improve HIV treatment adherence in MLWH who are (at risk for becoming) non-adherent. The findings in **Chapter 7** showed that, besides a need for additional care in the form of psychosocial care, and care specifically for refugees and undocumented MLWH, there is a need for additional care in the form of peer support. This is especially the case in rural areas of the Netherlands.

For future research

The first recommendation for future research is that future studies provide a comprehensive analysis of risk factors in the different MLWH subpopulations based on region of origin, gender, or the means by which HIV was acquired. Specifically, this should be performed among MLWH originating from low- and middle income countries and living in high income countries. The results from these studies could help develop targeted interventions that adequately respond to the relevant risk factors for non-adherence in the different subpopulations.

The second recommendation for future research is that, in general, continuing efforts to assess interventions that aim to improve HIV treatment adherence among MLWH are recommended. In doing so, key figures from migrant (living with HIV) communities should be included to ensure that the research design and interventions are sufficiently culturally sensitive and thereby more likely to be accepted by MLWH (42, 43). As previously discussed in this chapter, evidence from studies worldwide on adherence-improving interventions show that interventions including mHealth, cognitive behavioral therapy, and/or peer support seem to show the most promise (34). Interventions seeking to improve adherence should subsequently be evaluated for effect, while controlling for variability in the standard of care provided to control groups as this can influence

the effect sizes of behavior change interventions (54, 55). Also, the possible additive effects of multiple interventions should be considered (34). It is recommended that the tasks of Intervention Mapping and Implementation Mapping are included in these research projects.

The third recommendation for future research is that peer support by trained MLWH should be evaluated more extensively, and in a larger sample, to further determine the effect on psychosocial and clinical outcomes. This future evaluation could take the form of an intervention study with an intervention cohort (peer support by MLWH) and a control cohort (standard HIV care), and should include: (1) a research team that includes key figures from the target population(s) to, among other, specify criteria for eligible participants and design the intervention(s) in a way that increases acceptability by the target population, (2) possibly multiple supporter interventions, like peer support and interventions that include aspects of mHealth as well, (3) more than two HIV treatment centers to ensure a sample of MLWH with sufficient power, (4) outcomes in the form of process indicators, treatment outcomes, sustainability of health, and patient value, and (5) both quantitative and a qualitative components.

CONCLUDING REMARKS

In this dissertation, treatment adherence among non-Western European MLWH living in the Netherlands was investigated, with a particular focus on adherence to cART. This dissertation contains studies that explored different ways to measure adherence, and factors associated with adherence in MLWH. Furthermore, 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 was investigated. Further, the availability of support services (in addition to medical care) for MLWH in the Netherlands, from the perspective of HIV care providers, was explored.

Addressing risk factors for treatment non-adherence in MLWH is important as high levels of adherence to cART ensure good clinical outcomes on an individual level and prevents transmission to others (1, 13, 15). Continuing efforts to assess interventions that aim to improve HIV treatment adherence among MLWH should be prioritized. In the development of such interventions, it is imperative that key figures from migrant (living with HIV) communities are included. Peer support by MLWH seems to be a feasible and promising intervention to positively influence treatment adherence among MLWH and should be evaluated more extensively to determine its effect on psychosocial and clinical outcomes.

REFERENCES

1. May MT, Gompels M, Delphech V, Porter K, Orkin C, Kegg S, et al. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS*. 2014;28(8):1193-202.
2. Trickey A, May MT, Vehreschild J-J, Obel N, Gill MJ, Crane HM, et al. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *The Lancet HIV*. 2017;4(8):e349-e56.
3. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2019. Switzerland: UNAIDS, 2019. Available from: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf.
4. Engelhard EA, Smit C, Van Sighem A, Reiss P, Nieuwkerk PT, Kroon FP, et al. Impact of HIV care facility characteristics on the cascade of care in HIV-infected patients in the Netherlands. *AIDS*. 2016;30(2):301-10.
5. Ross J, Cunningham CO, Hanna DB. HIV outcomes among migrants from low-income and middle-income countries living in high-income countries: a review of recent evidence. *Current Opinion in Infectious Diseases*. 2018;31(1):25-32.
6. Van Sighem AI, Boender TS, Wit FWNM, Smit C, Matser A, Reiss P. Monitoring Report 2018: Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring, 2018. Available from: https://www.hiv-monitoring.nl/application/files/5815/4279/2363/2018_HIV_Monitoring_Report.pdf.
7. Op de Coul EL, Schreuder I, Conti S, Van Sighem A, Xiridou M, Van Veen MG, et al. Changing Patterns of Undiagnosed HIV Infection in the Netherlands: Who Benefits Most from Intensified HIV Test and Treat Policies? *PLoS One*. 2015;10(7):e0133232.
8. European Centre for Disease Prevention and Control (ECDC). Thematic report: Migrants. Stockholm: European Centre for Disease Prevention and Control 2014 24 June 2019. Available from: <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/dublin-declaration-migrants-2014.pdf>.
9. European Centre for Disease Prevention and Control (ECDC). Migrant health: Access to HIV prevention, treatment and care for migrant populations in EU/EEA countries. Stockholm: European Centre for Disease Prevention and Control (ECDC), 2009 24 June 2019. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0907_TER_Migrant_health_HIV_Access_to_treatment.pdf.
10. Van Beckhoven D, Florence E, Ruelle J, Deblonde J, Verhofstede C, Callens S, et al. Good continuum of HIV care in Belgium despite weaknesses in retention and linkage to care among migrants. *BMC Infectious Diseases*. 2015;15:496.
11. Vazquez ML, Vargas I, Jaramillo DL, Porthé V, Lopez-Fernandez LA, Vargas H, et al. Was access to health care easy for immigrants in Spain? The perspectives of health personnel in Catalonia and Andalusia. *Health Policy*. 2016;120(4):396-405.
12. Blondell SJ, Kitter B, Griffin MP, Durham J. Barriers and Facilitators to HIV Testing in Migrants in High-Income Countries: A Systematic Review. *AIDS Behav*. 2015;19(11):2012-24.
13. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *New England Journal of Medicine*. 2016;375(9):830-9.
14. Cohen MS, Smith MK, Muessig KE, Hallett TB, Powers KA, Kashuba AD. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? *Lancet*. 2013;382(9903):1515-24.

15. Migrant Health Working Group for the Collaboration of Observational HIV Epidemiological Research in Europe (CPHERE) in EuroCoord. Immunological and virological response to antiretroviral treatment in migrant and native men and women in Western Europe; is benefit equal for all? *HIV Medicine*. 2018;19(1):42-8.
16. Monge S, Alejos B, Dronda F, Del Romero J, Iribarren JA, Pulido F, et al. Inequalities in HIV disease management and progression in migrants from Latin America and sub-Saharan Africa living in Spain. *HIV Medicine*. 2013;14(5):273-83.
17. Staehelin C, Keiser O, Calmy A, Weber R, Elzi L, Cavassini M, et al. Longer term clinical and virological outcome of sub-Saharan African participants on antiretroviral treatment in the Swiss HIV Cohort Study. *Journal of Acquired Immune Deficiency Syndromes*. 2012;59(1):79-85.
18. World Health Organization (WHO). Health of refugees and migrants: Regional situation analysis, practices, experiences, lessons learned and ways forward. WHO European Union, 2018. Available from: <https://www.who.int/migrants/publications/EURO-report.pdf>.
19. Puskas CM, Kaida A, Miller CL, Zhang W, Yip B, Pick N, et al. The adherence gap: a longitudinal examination of men's and women's antiretroviral therapy adherence in British Columbia, 2000-2014. *AIDS*. 2017;31(6):827-33.
20. Cescon A, Patterson S, Chan K, Palmer AK, Margolese S, Burchell AN, et al. Gender differences in clinical outcomes among HIV-positive individuals on antiretroviral therapy in Canada: a multisite cohort study. *PLoS One*. 2013;8(12):e83649.
21. Abioye AI, Soipe AI, Salako AA, Odesanya MO, Okuneye TA, Abioye AI, et al. Are there differences in disease progression and mortality among male and female HIV patients on antiretroviral therapy? A meta-analysis of observational cohorts. *AIDS Care*. 2015;27(12):1468-86.
22. Beckham SW, Beyrer C, Luckow P, Doherty M, Negussie EK, Baral SD. Marked sex differences in all-cause mortality on antiretroviral therapy in low- and middle-income countries: a systematic review and meta-analysis. *Journal of the International AIDS Society*. 2016;19(1):21106.
23. Poteat T, Hanna DB, Rebeiro PF, Klein M, Silverberg MJ, Eron JJ, et al. Characterizing the Human Immunodeficiency Virus Care Continuum Among Transgender Women and Cisgender Women and Men in Clinical Care: A Retrospective Time-series Analysis. *Clinical Infectious Diseases*. 2019.
24. Kalichman SC, Hernandez D, Finneran S, Price D, Driver R. Transgender women and HIV-related health disparities: falling off the HIV treatment cascade. *Sexual Health*. 2017;14(5):469-76.
25. Teti M, Bauerband LA, Altman C. Adherence to Antiretroviral Therapy Among Transgender and Gender Nonconforming People Living with HIV: Findings from the 2015 U.S. Trans Survey. *Transgender Health*. 2019;4(1):262-9.
26. Mizuno Y, Frazier EL, Huang P, Skarbinski J. Characteristics of Transgender Women Living with HIV Receiving Medical Care in the United States. *LGBT Health*. 2015;2(3):228-34.
27. Migrant Health Working Group for the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Timing of combined antiretroviral treatment initiation in male and female migrants living with HIV in Western Europe. *AIDS*. 2017;31(6):835-46.
28. Reyes-Uruena J, Campbell C, Hernando C, Vives N, Folch C, Ferrer L, et al. Differences between migrants and Spanish-born population through the HIV care cascade, Catalonia: an analysis using multiple data sources. *Epidemiology & Infection*. 2017;145(8):1670-81.
29. Loos J, Nostlinger C, Vuylsteke B, Deblonde J, Ndungu M, Kint I, et al. First HIV prevalence estimates of a representative sample of adult sub-Saharan African migrants in a European city. Results of a community-based, cross-sectional study in Antwerp, Belgium. *PLoS One*. 2017;12(4):e0174677.
30. Van der Schaaf ML, Prins HAB, Been SK, Van de Vijver DAMC, Pogany K, Verbon A. Risk factors for non-adherence in HIV+ migrants are different between men and women. Netherlands Conference on

- HIV Pathogenesis, Epidemiology, Prevention and Treatment (NCHIV); 21 November 2017; Amsterdam 2017.
31. Baguso GN, Gay CL, Lee KA. Medication adherence among transgender women living with HIV. *AIDS Care*. 2016;28(8):976-81.
 32. Bil JP, Zuure FR, Alvarez-Del Arco D, Prins JM, Brinkman K, Leyten E, et al. Disparities in access to and use of HIV-related health services in the Netherlands by migrant status and sexual orientation: a cross-sectional study among people recently diagnosed with HIV infection. *BMC Infectious Diseases*. 2019;19(1):906.
 33. Genberg BL, Shangani S, Sabatino K, Rachlis B, Wachira J, Braitstein P, et al. Improving engagement in the HIV care cascade: A systematic review of interventions involving people living with HIV/AIDS as peers. *AIDS and Behavior*. 2016;20(10):2452-63.
 34. Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JI, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV*. 2017;4(1):e31-e40.
 35. De Bruin M, Oberje EJM, Viechtbauer W, Nobel HE, Hiligsmann M, Van Nieuwkoop C, et al. Effectiveness and cost-effectiveness of a nurse-delivered intervention to improve adherence to treatment for HIV: a pragmatic, multicentre, open-label, randomised clinical trial. *Lancet Infectious Diseases*. 2017;17(6):595-604.
 36. Simoni JM, Aunon FM, Kemp CG, Kutner BA, Ramaiya MK, Vellozo J, et al. Implementation research on HIV adherence interventions: no time to wait. *Lancet Infectious Diseases*. 2017;17(6):564-5.
 37. Cooper V, Clatworthy J, Whetham J, Consortium E. mHealth Interventions To Support Self-Management In HIV: A Systematic Review. *Open AIDS Journal*. 2017;11:119-32.
 38. Van Luenen S, Garnefski N, Spinhoven P, Kraaij V. Guided internet-based intervention for people with HIV and depressive symptoms: a randomised controlled trial in the Netherlands. *Lancet HIV*. 2018;5(9):e488-e97.
 39. Brandt C, Zvolensky MJ, Woods SP, Gonzalez A, Safren SA, O'Cleirigh CM. Anxiety symptoms and disorders among adults living with HIV and AIDS: A critical review and integrative synthesis of the empirical literature. *Clinical Psychology Review*. 2017;51:164-84.
 40. Langebeek N, Gisolf EH, Reiss P, Vervoort SC, Hafsteinsdottir TB, Richter C, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. *BMC Medicine*. 2014;12:142.
 41. Uthman OA, Magidson JF, Safren SA, Nachega JB. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. *Current HIV/AIDS Reports*. 2014;11(3):291-307.
 42. Rhodes SD, Malow RM, Jolly C. Community-based participatory research: a new and not-so-new approach to HIV/AIDS prevention, care, and treatment. *AIDS Education and Prevention*. 2010;22(3):173-83.
 43. Lessard D, Engler K, Toupin I, Team ISC, Routy JP, Lebouche B. Evaluation of a project to engage patients in the development of a patient-reported measure for HIV care (the I-Score Study). *Health Expectations*. 2019;22(2):209-25.
 44. Bartholomew-Eldredge LK, Markham C, Ruiter RA, Fernandez ME, Kok G, Parcel G. *Planning Health Promotion Programs: An Intervention Mapping Approach*. 4th ed. San Francisco. 2016.
 45. Corbie-Smith G, Akers A, Blumenthal C, Council B, Wynn M, Muhammad M, et al. Intervention mapping as a participatory approach to developing an HIV prevention intervention in rural African American communities. *AIDS Education and Prevention*. 2010;22(3):184-202.

46. Fernandez ME, Ten Hoor GA, Van Lieshout S, Rodriguez SA, Beidas RS, Parcel G, et al. Implementation Mapping: Using Intervention Mapping to Develop Implementation Strategies. *Frontiers in Public Health*. 2019;7:158.
47. Gordon LL, Gharibian D, Chong K, Chun H. Comparison of HIV Virologic Failure Rates Between Patients with Variable Adherence to Three Antiretroviral Regimen Types. *AIDS Patient Care and STDS*. 2015;29(7):384-8.
48. Guaraldi G, Arends J, Buhk T, Cascio M, Curran A, Teofilo E, et al. "Moving Fourth": A Vision Toward Achieving Healthy Living with HIV Beyond Viral Suppression. *AIDS Reviews*. 2019;21(3):135-42.
49. Porter ME. What is value in health care? *New England Journal of Medicine*. 2010;363(26):2477-81.
50. Brinkman K, editor Value-based healthcare in HIV management - the patients' perspective, real life. *European Workshop on Healthy Living with HIV; 2017; Barcelona*.
51. Den Daas C, Van den Berk GEL, Kleene MT, De Munnik ES, Lijmer JG, Brinkman K. Health-related quality of life among adult HIV positive patients: assessing comprehensive themes and interrelated associations. *Quality of Life Research*. 2019;28(10):2685-94.
52. Lazarus JV, Safreed-Harmon K, Barton SE, Costagliola D, Dedes N, Del Amo Valero J, et al. Beyond viral suppression of HIV - the new quality of life frontier. *BMC Medicine*. 2016;14(1):94.
53. Joint United Nations Programme on HIV/AIDS (UNAIDS). 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS, 2014. Available from: https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf.
54. De Bruin M, Viechtbauer W, Schaalma HP, Kok G, Abraham C, Hospers HJ. Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials. *Archives of Internal Medicine*. 2010;170(3):240-50.
55. De Bruin M, Viechtbauer W, Hospers HJ, Schaalma HP, Kok G. Standard care quality determines treatment outcomes in control groups of HAART-adherence intervention studies: implications for the interpretation and comparison of intervention effects. *Health Psychology*. 2009;28(6):668-74.