

KAJA-TRIIN LAISAAR

People living with HIV in Estonia:
Engagement in medical care and methods
of increasing adherence to antiretroviral
therapy and safe sexual behavior



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of increasing adherence to antiretroviral
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- II. Uusküla A, Laisaar KT, Raag M, Šmidt J, Semjonova S, Kogan J, Amico KR, Sharma A, Dehovitz J. Antiretroviral therapy (ART) adherence and correlates to nonadherence among people on ART in Estonia. *AIDS Care* 2012;24:1470–9. Epub 2012 Apr 25.
- III. Laisaar KT, Raag M, Rosenthal M, Uusküla A. Behavioral Interventions to Reduce Sexual Risk Behavior in Adults with HIV/AIDS Receiving HIV Care: A Systematic Review. *AIDS Patient Care STDS* 2015;29:288–98. Epub 2015 Apr 6.
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PAPER II: Participating in the design and conduction of the study, participating in the data analysis and in writing the manuscript.

PAPER III: Proposing the research question, participating in the design of the study and in the data analysis, drafting the manuscript and preparing final revisions in the manuscript before submission for publication.

PAPER IV: Proposing the research question, participating in the design of the study and in the data analysis, drafting the manuscript and preparing final revisions in the manuscript before submission for publication.

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
AOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
CDC	Centers for Disease Control and Prevention
CI	confidence interval
E-HIV	Estonian HIV-Positive Patients Database
ECDC	European Centre for Disease Prevention and Control
ECDR	Estonian Causes of Death Registry
EEA	European Economic Area
EHB	Estonian Health Board
EHIF	Estonian Health Insurance Fund
EMSA	Estonian Ministry of Social Affairs
EU	European Union
HAART	highly active antiretroviral therapy
HARP	highly active retroviral prevention
HIV	human immunodeficiency virus
IDU	injection drug use
IM	Intervention Mapping
IMB	Information–Motivation–Behavioral Skills (theory/model)
IOM	Institute of Medicine
MSM	men who have sex with men
NA	Neutral Assessment
NSC	Next Step Counseling
OR	odds ratio
PLHIV	people living with HIV
PWID	people who inject drugs
RCT	randomized controlled trial
SD	standard deviation
TasP	treatment as prevention
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

1. INTRODUCTION

In 2014 there were an estimated 37 million people living with HIV (PLHIV) globally, while over 39 million had died from AIDS over the nearly four decades of the epidemic (UNAIDS 2014a, UNAIDS 2015a). In 2011, to guide the expansion of global HIV response beyond the HIV-specific programmes of the past, the World Health Organization (WHO) developed the Global Health Sector Strategy on HIV/AIDS for 2011–2015, aiming at no new HIV infections, no AIDS-related deaths, and no discrimination (WHO 2011).

Although effective response to HIV/AIDS is multidimensional, antiretroviral therapy (ART) is a fundamental element in tackling the disease in people infected with HIV. While first antiretroviral (ARV) drugs were developed already in the mid 1980s, it took another 10 years of intensive research to reach triple-combination therapy (currently known as combined or highly active ART), leading to significant reductions in illness and death among PLHIV (receiving ART). It has been estimated that since 2000, when WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) started setting global targets for ART access (among other measures), the rollout of the therapy has saved about 7.8 million lives worldwide (Fauci & Marston 2015), and in 2015 an estimated 15.8 million people of the approximately 37 million living with HIV in the world had access to ART (UNAIDS 2015a, UNAIDS 2015b).

Combined ART, an effective (biomedical) intervention, is critical for the health and wellbeing of PLHIV, and furthermore significantly reduces the probability of transmitting the virus to others. Focus on preventing new infections has expanded from HIV-negative individuals to PLHIV to mitigate the spread of HIV to their sexual and injection-drug-use partners, and to infants born to HIV-infected mothers. It has been recognized that, from a public health perspective, it could be more efficient to fight the HIV epidemic when attempting to change behavior among the fewer HIV-positives than the many HIV-negatives (Kennedy *et al.* 2010, Mermin 2011, Lasry *et al.* 2012). While initially HIV prevention strategies for PLHIV only encompassed screening for behavioral risk factors and sexually transmitted infections, partner notification, prevention counseling and behavioral risk reduction interventions (CDC *et al.* 2003), the current much broader concept of ‘prevention with positives’ also includes biomedical prevention, the ‘treatment cascade’, the social and structural needs of people living with the virus, and advice for PLHIV wanting to have children (CDC *et al.* 2014).

Globally, substantial progress has been made in impeding HIV, especially in the past 3–4 years and in areas where clear intervention targets have been set. However, in 2014 UNAIDS set new targets: 90% of people living with HIV should know their HIV status, 90% of people diagnosed with HIV should receive ART, and 90% of people on ART should have viral suppression. Modelling suggests that achieving these targets by 2020 would enable the world to end the HIV/AIDS epidemic by 2030 (UNAIDS 2014b, UNAIDS 2014c). In order to

attain the 90–90–90 targets, extensive efforts to expand the coverage and improve the quality of HIV prevention, diagnosis, treatment and care interventions should continue (WHO 2014a). Identification of gaps in connecting PLHIV to sustained and high quality HIV care would enable service providers and policymakers to enhance the system. The HIV/AIDS treatment cascade as a model to map the proportion of PLHIV who actually receive the full benefit of the medical care they need for HIV (including ART) was first described by Gardner and colleagues in 2011 (Gardner *et al.* 2011). Since its development, the cascade approach was immediately recognized worldwide and has since been applied in an escalating number of countries to assess the performance of national response to HIV (Helleberg *et al.* 2013, Pokrovskaya *et al.* 2014, Raymond *et al.* 2014, Levi *et al.* 2015, Medland *et al.* 2015).

However, the number of people newly infected with HIV still exceeds the number of people starting HIV treatment each year – too many people are acquiring HIV, and not enough people eligible for treatment in accordance with the WHO guidelines are receiving it, especially after the recent 2015 recommendation that ART should be initiated in all PLHIV regardless of CD4 cell count (WHO 2014a, WHO 2015a). However, even PLHIV who have been linked to HIV care may drop out of the system – globally the median retention in care rate at 12 months is about 86% and a gradual decrease to 73% after 5 years has been observed (WHO 2014a). Research has also revealed that about one quarter of patients temporarily interrupt treatment (Kranzer & Ford 2011) and another quarter appear to drop out of care within 3 years (Fox & Rosen 2010). While several methods to improve retention in care, including various types of ART adherence support interventions, have been developed, only profound knowledge of local epidemiological situation and healthcare system, including the main barriers to access, will enable the selection of the best and most suitable (counter)measures.

Estonia, with HIV incidence constantly decreasing since 2006, stood out in the European Union/European Economic Area (EU/EEA) with the highest rate of new HIV cases (22.1 per 100 000) in 2014. Based on the 2014 rate of AIDS diagnoses (1.4 per 100 000) Estonia no longer belongs to the top 3 countries in EU/EEA (as in past 3 years), now ranking 6th–7th. Since 2011, deaths among people diagnosed with HIV and/or AIDS in Estonia have been decreasing (ECDC/WHO Regional Office for Europe 2015). Estonia's capacity to manage its response to HIV and AIDS has greatly increased over the past decade, and HIV medical care (including ART) is free of charge for PLHIV, regardless of their medical insurance status (Laisaar *et al.* 2011, PAPER IV). However, to maximize both the individual and public health benefits of ART, the health system must ensure an effective cascade of high quality services provided to PLHIV to enable them obtain ART (Nosyk *et al.* 2014).

This work focuses on people living with HIV, and ART as the cornerstone of their (individual) response to HIV. Adequate long-term adherence to ART, however, is essential not only for individual, but also for the public health benefit

the treatment can provide – impeding the emergence of drug-resistance and virus transmission (Altice *et al.* 2001, WHO 2003, Mannheimer *et al.* 2005, Chesney 2006, Ray *et al.* 2010, Cohen *et al.* 2011, WHO 2015a). Thus, we aimed to study factors influencing ART adherence among PLHIV engaged in HIV care in Estonia, and develop a tailored ART adherence support intervention program with possible applications in further development of HIV treatment services in Estonia, and potentially in neighbouring countries with similar socio-economic and HIV epidemic evolution. As regular assessment and promotion of safe sexual practices to reduce HIV transmission risk are also considered an essential component of the package of support provided to PLHIV in HIV care (WHO 2008, CDC *et al.* 2014, DHHS 2015, EACS 2015), this work also includes a study of sexual risk reduction interventions applicable to the epidemiological and transitional healthcare context in Estonia, and potentially to other countries in Eastern Europe.

This work also contributes to the fast evolving international knowledge base on PLHIV engagement in HIV/AIDS care by describing and quantifying the spectrum of PLHIV engagement in HIV care in Estonia. Identification of the main gaps in the care system performance can assist Estonian policymakers and service providers to develop system improvements and enhance services that best support PLHIV as they move through the continuum of HIV care.

2. REVIEW OF THE LITERATURE

2.1. The HIV epidemic

2.1.1. The HIV epidemic in the world

Worldwide, by end of 2014 about 37 million people were estimated to live with HIV, with 2 million (1.9–2.2 million) of them newly infected in 2014 (UNAIDS 2015a). Although during the past 15 years considered in this work (2000–2014), new infections have come down by more than 1/3 from the 3.1 million (3.0–3.3 million) in 2000, over the total course of the epidemic altogether more than 39 million people have been lost to HIV – died from AIDS. Although since 2006 the global number of AIDS-related deaths has been constantly decreasing, in 2014 AIDS still accounted for 1.2 million (980 000–1.6 million) deaths (UNAIDS 2015a).

The epidemic patterns i.e., the level, main transmission mode(s) of the virus, most vulnerable population groups, and AIDS-indicative diagnoses have varied across the different regions of the world, reflecting the diversity in HIV epidemiology. With Estonia located in Europe, this work further provides an overview of the HIV epidemic in the WHO European Region, one of the 6 world regions by WHO (WHO 2016).

2.1.2. The HIV epidemic in Europe

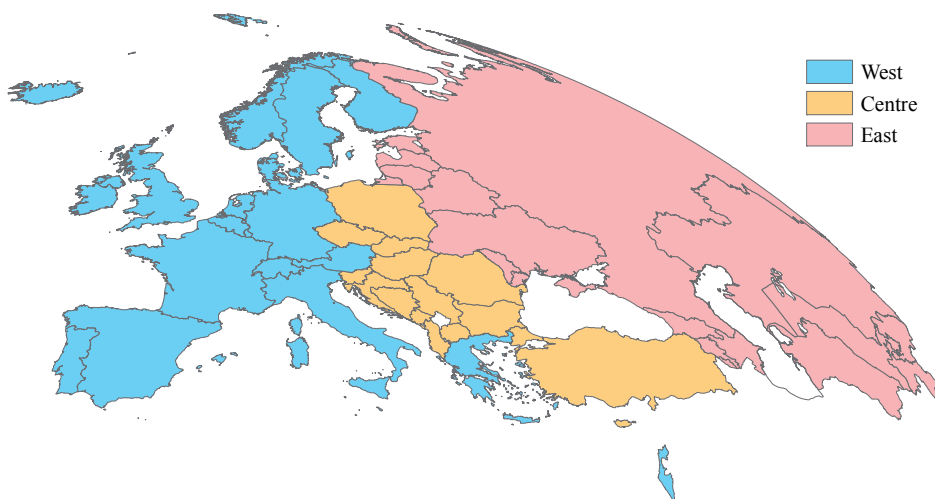
2.1.2.1. HIV cases in Europe

In the *WHO European Region*, by the end of 2014 altogether 1 840 136 people had been diagnosed with HIV over the course of the epidemic. Of those, 995 175 diagnoses were officially reported to the joint ECDC/WHO Regional Office for Europe surveillance system, and an additional 907 607 infections were diagnosed in Russia. In past 15 years, the HIV epidemic in Europe had escalated from 21 337 new cases (4.1 per 100 000) diagnosed in 2000 to 56 945 (7.9 per 100 000) in 2014 (ECDC/WHO Regional Office for Europe 2010, ECDC/WHO Regional Office for Europe 2015). Within *European Union/European Economic Area (EU/EEA)*, the rate of new diagnoses increased from 6.6 per 100 000 in 2000 to 6.9 in 2008, and has thereafter decreased to 5.9 per 100 000 by 2014 (ECDC/WHO Regional Office for Europe 2010, ECDC/WHO Regional Office for Europe 2015).

In 2014, 142 197 people were newly diagnosed with HIV in 50 of the 53 WHO European Member States, being the highest annual number since the reporting started in the 1980s (ECDC/WHO Regional Office for Europe 2015). Of those, 40% (56 945 cases) were officially reported by 49 (of the 50) countries, with almost half (29 992 cases) originating from *EU/EEA*. Among the 49 countries the rate was 7.9 per 100 000 population, compared to the 5.9 per 100 000 in *EU/EEA*. However, when also considering the 85 252 new diagnoses

registered in Russia by the Federal Scientific and Methodological Centre for Prevention and Control of AIDS, the actual rate of new HIV cases in the *WHO European Region* would have equaled 16.4 per 100 000 (ECDC/WHO Regional Office for Europe 2015).

It has been recognized that in Europe, instead of the politico-economic division of countries into *EU/EEA* and *non EU/EEA*, the geographical grouping [into *West*, *Centre* and *East* (see Figure 1)] better reflects the epidemiological pattern(s) of the HIV epidemic(s) in the *Region* (ECDC/WHO Regional Office for Europe 2015). In general, the epidemic in *EU/EEA* mostly mirrors that in the *West*, as majority of countries in *EU/EEA* (18 of the total 31) are located in that area. While Estonia belongs to EU already since 2004, the main HIV epidemic features and trends mostly follow those observed in the *East*, where the country is situated.



West (23 countries): Andorra, Austria*, Belgium*, Denmark*, Finland*, France*, Germany*, Greece*, Iceland, Ireland*, Israel, Italy*, Luxembourg*, Malta*, Monaco, Netherlands*, Norway, Portugal*, San Marino, Spain*, Sweden*, Switzerland, United Kingdom*

Centre (15 countries): Albania, Bosnia and Herzegovina, Bulgaria*, Croatia*, Cyprus*, Czech Republic*, Hungary*, the former Yugoslav Republic of Macedonia, Montenegro, Poland*, Romania*, Serbia, Slovakia*, Slovenia*, Turkey

East (15 countries): Armenia, Azerbaijan, Belarus, Estonia*, Georgia, Kazakhstan, Kyrgyzstan, Latvia*, Lithuania*, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine, Uzbekistan

*EU Member State as of July 1, 2014

Figure 1. Geographical division of the WHO European Region ((ECDC/WHO Regional Office for Europe 2015).

Across the 49 countries that provided their 2014 data to ECDC/WHO, 43% of all people newly diagnosed with HIV (24 669) were reported in the *East* (including Estonia) with a rate of 22.3 per 100 000, 48% in the *West* (6.4 per 100 000 population), and 9% in the *Centre* (2.6 per 100 000 population). However, when

also considering the available 2014 data from Russia, an otherwise nonreporting (to ECDC/WHO) country in the *East* of the *European Region*, the rate of new infections in the *East* would almost double (43.2 per 100 000 population). At country level, the highest rates of newly diagnosed infections in Europe for 2014 were observed in Russia (58.4 per 100 000 population), Ukraine (36.9), and Estonia (22.1), all from the *East* area (ECDC/WHO Regional Office for Europe 2015).

During the HIV epidemic in Europe, cumulatively the biggest proportion of newly diagnosed cases have been reported among people aged 30–39. This also applies to 2 of the 3 geographic areas of the *Region* i.e., the *East* and *West*, both during 2000–2014 and the total course of the epidemic(s). In the *Centre*, people aged 20–29 have prevailed (EuroHIV 2005, ECDC/WHO Regional Office for Europe 2015). In 2014, over a third (36%) of people newly diagnosed with HIV in the *Region* were aged 30 to 39. The rate for new cases for men was 2.4 times higher than for women (11.1 and 4.7 per 100 000 population, respectively), with the male-to-female ratio lowest in the *East* (1.4.), higher in the *West* (3.3), and the highest in the *Centre* (4.4) (ECDC/WHO Regional Office for Europe 2015). While back in 2000 and 2001 people in Europe (the *WHO European Region*) were infected with HIV mainly through injection drug use, since 2002 (cumulatively) HIV has been mainly acquired through heterosexual contact, with already more than 50% of all newly registered cases in 2014 attributable to this mode of transmission (EuroHIV 2005, ECDC/WHO Regional Office for Europe 2015). In the *East*, however, majority of new infections were acquired through injection drug use until 2008, when the proportion of new cases attributable to heterosexual contact started to increase rapidly (EuroHIV 2005, ECDC/WHO Regional Office for Europe 2015). Although in 2014 heterosexual transmission already accounted for 2/3 of all newly diagnosed cases reported from the *East*, still more than ¼ were related to IDU. When also reckon with 2014 data from the fastest evolving epidemic in the area and whole Europe i.e., Russia, where more than half of people with known mode of transmission were infected through IDU, the significance of HIV transmission attributable to IDU would be remarkably higher in the *East*. Whereas in the *West* and the *Centre*, in 2014 sex between men was the leading transmission mode (44% and 28%, respectively) (ECDC/WHO Regional Office for Europe 2015).

In 2014, information on CD4 cell counts of people newly diagnosed with HIV was only provided by 22 of the officially reporting (to ECDC/WHO) countries for less than 2/3 of people newly diagnosed. Although the data were alarming – in all the areas of the *Region* HIV was detected late in the course of the disease (at diagnosis 48% of PLHIV having CD4 cell count < 350 cells/mm³, and another 28% < 200 cells/mm³), further assessment could only be performed on country level (when data available) (ECDC/WHO Regional Office for Europe 2015).

2.1.2.2. AIDS cases, morbidity and mortality in Europe

By the end of 2014, the number of people diagnosed with AIDS in the *WHO European Region* had approached half a million (487 087), with 451 667 diagnoses officially reported to ECDC/WHO, and another 35 420 diagnosed in Russia (ECDC/WHO Regional Office for Europe 2015). In past 15 years (2000–2014), the rate of new AIDS diagnoses increased by 29% from 1.7 (12 416 cases) to 2.3 (16 037 cases), respectively. However, within the different geographic areas of the *Region* the trends have varied greatly. While the *East* has experienced a 15-fold increase from 0.7 per 100 000 in 2000 (982 cases) to 10.7 in 2014 (11 890 cases), a steady 69% decline has been observed in the *West* from 2.6 per 100 000 (10 464 cases) to 0.8 (3 214 cases) (ECDC/WHO Regional Office for Europe 2010, ECDC/WHO Regional Office for Europe 2015). The yearly rate of AIDS cases diagnosed in the *East* has exceeded the rate in the *West* from 2004 on (ECDC/WHO Regional Office for Europe 2010). In the *Centre*, the rate (0.5 per 100 000) has not changed from 2000 to 2014 (with only 970 and 932 cases registered in 2000 and 2014, respectively), although was lower for a meantime (around 0.4 in 2001–2011) (ECDC/WHO Regional Office for Europe 2010, ECDC/WHO Regional Office for Europe 2015). In 2014, 74% of people newly diagnosed with AIDS (11 890) were reported from the *East*, 20% (3 214) from the *West* and 6% (932) from the *Centre* of the *Region* (ECDC/WHO Regional Office for Europe 2015).

In Europe, the format of collecting HIV/AIDS surveillance data has undergone several changes during the past 15 years. This especially applies to information on diseases indicating AIDS, e.g., data by geographic area are only available since 2002, and on area level differentiation between pulmonary and extrapulmonary tuberculosis has only been made since 2008. Although throughout the years on the *WHO European Region* level most of AIDS cases could be attributed to tuberculosis (ECDC/WHO Regional Office for Europe 2009 – ECDC/WHO Regional Office for Europe 2015, EuroHIV 2004 – EuroHIV 2007, ECEMA 2001 – ECEMA 2003), distinct patterns have been observed within the different areas of the *Region*. In the *East*, pulmonary tuberculosis has been the most common AIDS-indicative disease since 2008, accounting yearly for around 30% of all disease events, with wasting syndrome and oesophageal candidiasis ranking 2nd and 3rd (ECDC/WHO Regional Office for Europe 2009 – ECDC/WHO Regional Office for Europe 2015). However, by 2014 also the frequency of extrapulmonary tuberculosis (not reaching the top 3 in previous years) had increased, and altogether *Mycobacterium tuberculosis* indicated AIDS in almost 40% of the cases (ECDC/WHO Regional Office for Europe 2015). Meanwhile, in the *West* the most common diseases (pneumocystis pneumonia and oesophageal candidiasis; and pulmonary tuberculosis among the 3rd to 5th) have not changed since 2008, when data collection in the current format started. In the *Centre*, ‘wasting syndrome due to HIV’ has been the most common AIDS-indicative disease, with pulmonary tuberculosis switching places with pneumocystis pneumonia in 2009 and becoming (and remaining) the 2nd

most common disease (ECDC/WHO Regional Office for Europe 2009 – ECDC/WHO Regional Office for Europe 2015).

By the end of 2014, in Europe altogether 263 727 people diagnosed with HIV and/or AIDS had died (since the reporting started), with 235 466 officially reported to ECDC/WHO and an additional 28 261 in Russia. In 2014, vast majority (78% of the 5 052) deaths among people diagnosed with HIV and/or AIDS in the officially reporting countries (with 45 providing the data) had occurred in the *East*, and only 15% in the *West* and 7% in the *Centre* (ECDC/WHO Regional Office for Europe 2015). When considering the past 15 years, the number of deaths among AIDS cases in the total *Region* reached the peak in 2005 and has been decreasing since (ECEMA 2001, ECEMA 2003, ECDC/WHO Regional Office for Europe 2015). Although changes in case definitions and data provision issues inhibit detailed analysis of the trend(s) in Europe, disparities by geographic area are evident. In the *East*, over the past decade (with data available in the current format), the number of deaths among AIDS cases has increased by 55% (from 2 553 in 2005 to 3 941 in 2014), whereas mortality in the *West* has been steadily decreasing (altogether more than 4 times), and has remained low in the *Centre* throughout the decade (with 369 cases reported in 2005, and 365 in 2014) (ECDC/WHO Regional Office for Europe 2015).

2.1.3. The HIV epidemic in Estonia

2.1.3.1. HIV cases in Estonia

In Estonia, the number of people diagnosed with HIV reached 8 993 by the end of 2014 (EHB 2015). After HIV was first detected in Estonia in 1988, the rate of new cases remained low for the following 12 years (reaching 0.9 per 100 000 by 1999) (EHB 2015, Statistics Estonia 2015). Half of the cases were identified among homo- or bisexual men, and the rest were presumably acquired heterosexually (Ustina *et al.* 2001). A significant change occurred in the summer of 2000, when the number of new cases, predominantly among people who inject drugs (PWID), was noted to increase rapidly. Officially an epidemic of HIV in Estonia was recognized in 2001. Although by 2014 the rate of new HIV diagnoses had more than halved since the peak in 2001 (from 45.7 to 22.1 per 100 000), the 291 new cases diagnosed in 2014 still placed Estonia first in *EU/EEA*, and second in both the *East* and the total *WHO European Region* (among countries officially reporting to ECDC/WHO i.e., excluding Russia) (Laisaar *et al.* 2011, ECDC/WHO Regional Office for Europe 2015, EHB 2015, Statistics Estonia 2015).

Since the beginning of the epidemic PWID have been disproportionately represented in the HIV-positive population in Estonia (ECDC/WHO Regional Office for Europe 2015). However, in 2010 newly diagnosed infections acquired through heterosexual contact exceeded those related to IDU, a change observed in several other countries in the *East* (e.g., Ukraine, Latvia, Belarus) already in

2008 (Laisaar *et al.* 2011, ECDC 2015). However, in 2014, when nearly half of the new cases in Estonia (46%) had been reportedly acquired heterosexually, and only 23% through IDU, the transmission mode remained unknown in 19% of the cases (ECDC/WHO Regional Office for Europe 2015, EHB 2015).

The HIV epidemic in Estonia has had a distinctive geographic distribution – the two regions most affected i.e., contributing the majority of new HIV cases, have been Ida-Viru county in the easternmost part of the country on the Russian border, where the Estonian epidemic erupted in the chief city Narva in 2001, and Harju county (including Tallinn, the capital of the country). In 2014, these two regions still accounted for 92% of all the new HIV cases registered in the country. Although the absolute numbers of new cases in Harju and Ida-Viru were similar (145 and 122, respectively), the rate was by far the highest in Ida-Viru with 82 per 100 000 inhabitants, compared to 25 in Harju, and 22 in Estonia in general (EHB 2015, Statistics Estonia 2015).

During past 15 years, more than two-thirds (67%) of new HIV cases in Estonia have been diagnosed among men. Although the absolute number of newly infected women has not substantially changed from 2000 to 2014 (78 and 110 cases registered, respectively), the proportion of women has almost doubled – from 20% in 2000 to 38% in 2014 (EHB 2015a). Unlike in the *WHO European Region Europe* (in total) and in the *East* area of it, most new HIV cases in Estonia have been diagnosed in people below the age of 30, both cumulatively and on yearly basis (2000–2014). Yet the mean age at diagnosis has been increasing. While in 2001, the year the epidemic erupted, 92% of new cases were registered among people under 30 years of age, in 2014 the corresponding proportion was only 31% (Laisaar *et al.* 2011, EHB 2016a).

2.1.3.2. AIDS cases, morbidity and mortality in Estonia

The first AIDS case in Estonia was diagnosed in 1992, 4 years after the first case of HIV infection. Although the number of AIDS cases increased rapidly from 3 (0.2 per 100 000 population) in 2000 to 61 (4.6 per 100 000) in 2008, a decrease has been observed thereafter – to 18 cases in 2014 (1.4 per 100 000) (ECDC/WHO Regional Office for Europe 2010, ECDC/WHO Regional Office for Europe 2015).

Altogether in past 15 years (by end of 2014), a total of 434 individuals were diagnosed with AIDS in Estonia (EHB 2015), with ‘tuberculosis and other mycobacterial diseases’ most frequently indicating AIDS, both cumulatively and on yearly basis with data available since 2007 (EHB 2012, EHB 2016). In 2014, tuberculosis was still the most common AIDS-indicative disease in Estonia (in 7 of the 20 newly diagnosed AIDS cases), alike in the total *East* area of the *WHO European Region* (ECDC 2015, EHB 2016b).

The first AIDS death in Estonia was reported in 1996, and according to national mortality statistics the cumulative number of deaths attributable primarily to AIDS had reached 510 by the end of 2014, with a peak (60 deaths registered) in 2011, and a gradual decrease thereafter (to 45 cases in 2014)

(Statistics Estonia 2015). However, these numbers do not include deaths among people diagnosed with AIDS for causes other than AIDS, including overdose-related deaths among HIV-positive PWID, the population group most affected by HIV in Estonia.

2.2. Confronting the HIV epidemic

2.2.1. Antiretroviral therapy for people living with HIV

Without treatment, most HIV-infected individuals eventually develop progressive immunodeficiency, as evident by CD4 T lymphocyte depletion, that leads to AIDS-defining illnesses and premature death. Although effective response to HIV/AIDS is multidimensional, this work focuses on antiretroviral therapy (ART), a fundamental element in confronting the disease and epidemic.

The era of ART began in 1986 with azidothymidine (AZT), also known as zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI) (Fischl *et al.* 1987). The goal of the treatment was to inhibit HIV replication. However, it soon became clear that response to the therapy — zidovudine, and also other nucleosides that soon followed, varied at the different stages of the disease and declined over time (Hammer *et al.* 1996). Thus, the idea of combining antiretroviral drugs emerged (Caliendo & Hirsch 1994, Hammer *et al.* 1996). Although during the following decade dual therapy became well established, the clinical effect on morbidity and mortality remained limited (Hammer *et al.* 1996).

In 1996, cogent evidence on the effect of triple combination antiretroviral regimens (including protease inhibitors) targeting different steps of viral replication to control HIV was presented at the 11th International Conference on AIDS (Cohen & Fauci 1998, Fauci & Marston 2015). In such combination, antiretrovirals were able to inhibit HIV replication so that plasma HIV RNA level (viral load) was kept below detectable (by commercially available assays) level. Durable viral suppression, in turn, improved the immune function i.e., health and overall quality of life of PLHIV. Ever since, the amount of evidence that triple-drug combinations, known as ‘*potent combined or highly active ART (HAART)*’, reduce illness and death among PLHIV has been growing exponentially (Sidibe *et al.* 2014). It has been estimated that since 2000 the rollout of combined ART has saved about 7.8 million lives worldwide (Fauci & Marston 2015).

However, while weighing the benefits and risks of the treatment at the different stages of the disease, evidence on when (at what CD4 cell count) to initiate the treatment had to be gathered (Fauci & Marston 2015). First, the Strategies for Management of Antiretroviral Therapy (SMART) study, published in 2006, confuted the fear (in fact risk) of toxic, especially cardiovascular, effects with long-term ART, compared to all the opportunistic illnesses and death avoided with the help of it (The SMART Study Group 2006). Subsequently, the HIV Prevention Trials Network (HPTN) 052 study, published in 2011, and the

Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) study from 2015, confirmed the evidence from previous cohort and surveillance studies that early ART initiation significantly reduces HIV transmission (Cohen *et al.* 2011). Still, reaching consensus on whether initiating treatment at (near) normal CD4 cell counts (> 500 cells/mm³) would also benefit the person taking the treatment, required time and additional evidence (Piot & Quinn 2013, Fauci & Marston 2015). When finally results from two pivotal randomized controlled trials START and TEMPRANO had demonstrated that clinical benefits of ART are greater when ART is started early in the course of the disease (The INSIGHT START Study Group 2015, The Temprano ANRS 12136 Study Group 2015), by end of 2015 all major ART guidelines had introduced a concordant recommendation that the treatment should be initiated in everyone living with HIV regardless of the CD4 cell count (Günthard *et al.* 2014, DHHS 2015, EACS 2015, IAPAC 2015, WHO 2015a).

In 2000, when the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) started setting global targets to ART access (among other measures) to slow the growth of the global AIDS epidemic, not every PLHIV was considered clinically eligible for the treatment. Soon the global target was detailed and, with data and evidence building, has been steadily raised over the years, reaching 15 million by 2015 (UNAIDS 2015b). In mid 2015 there were an estimated 15.8 million people of the about 37 million living with HIV in the world accessing ART (UNAIDS 2015a, UNAIDS 2015b).

In Europe, data on ART coverage has been gathered by ECDC since 2009 i.e., the 2010 reporting round. However, due to inconsistent reporting, European-level information on HIV treatment over time is limited to 29 countries (ECDC 2013a, ECDC 2013b, ECDC 2015a). Although in these countries the number of PLHIV receiving ART has almost doubled in past 5 years, there is evidence to suggest that disparities in treatment coverage between high-, and low- and middle-income countries still exist (WHO 2013a), and in several countries in the *Region* some key populations still experience difficulties in accessing ART (ECDC 2014).

In Estonia, HIV medical care (including combined ART) is free of charge for PLHIV, regardless of their medical insurance status, and is mainly provided by the government healthcare system through infectious disease clinics/departments in five major hospitals. The European AIDS Clinical Society (EACS) HIV treatment guidelines have been followed i.e., until October 2015 ART was recommended for any HIV-positive person without prior ART exposure with a CD4 cell count < 350 cells/mm³, and carefully considered also for people in special conditions with CD4 cell counts above this level (EACS 2013, EACS 2014). Prophylactic treatment to avoid HIV vertical transmission has also been available to all HIV-infected pregnant women during both pregnancy and delivery, and to their newborns. In Estonia, in past 15 years the number of patients on combined ART has increased from 27 in 2000 to 3 025 in 2014 (Laisaar *et al.* 2011, EMSA 2016).

With regards to ART, this work focuses on HIV treatment in people living with HIV.

2.2.1.1. Adherence to antiretroviral therapy

Adherence in the context of ART is the extent to which a person's behavior – taking antiretroviral (ARV) drugs corresponds to agreed recommendations from a healthcare provider (WHO 2003). This includes not only timing and dosing, but also consistency in taking the drugs (Chaiyachati *et al.* 2014).

Adherence is central to ART success – obtaining control over HIV replication and maintaining CD4 cell count within normal range. Adequate long-term adherence is essential not only for individual, but also for the public health benefit the treatment can provide – impeding the emergence of drug-resistance and virus transmission (Altice *et al.* 2001, WHO 2003, Mannheimer *et al.* 2005, Chesney 2006, Ray *et al.* 2010, Cohen & Fauci 2011, WHO 2015a).

Current once daily ART regimens, including those with low pill burden, without a food requirement, and with few side effects, have been associated with higher levels of adherence (Parianti *et al.* 2009, Raboud *et al.* 2011, Nachega *et al.* 2014). Still, even these more simplified regimens may be challenging to follow over time (Simoni *et al.* 2003, Amico *et al.* 2006, Bae *et al.* 2011).

Adherence is the result of a multilayer process involving acceptance of the diagnosis, perception of the need to follow the recommended treatment, and motivation to do so. Furthermore, appropriate skills to not only reach, but also maintain an optimal level of adherence over time, and ability to overcome any difficulties that may appear, are essential.

Medication adherence, a complex behavior, is influenced by multiple determinants belonging to different domains: the patient, the disease (state), the treatment, the treatment provider, the patient-provider relationship, and the healthcare system (Ammassari *et al.* 2002, DHHS 2015, WHO 2015a). Due to HIV-related stigma and discrimination, supportive social environment also plays a significant role in easing adherence (Rintamaki *et al.* 2006, Rao *et al.* 2007, WHO 2015a). From the patient perspective, failure to adopt practices that facilitate adherence, such as linking medication taking to daily activities or using a medication reminder system, is often associated with treatment failure (Fisher *et al.* 2006, Wolf *et al.* 2007, Holzman *et al.* 2015). Individual patient factors may also include limited understanding of the disease and the benefits of ART, lack of interest or desire to take the medicines, forgetting doses, being away from home or other changes in daily routine, depression or other illness (Pence 2009, Holzman *et al.* 2015), and substance or alcohol abuse (Lucas 2011, Holzman *et al.* 2015, WHO 2015a). Treatment-related factors may include heavy pill burden or complexity of the dosing regimen, dietary prerequisites, and drug adverse events (DHHS 2015, Genberg *et al.* 2015, WHO 2015a). Healthcare system factors include distance to health services (Tuller *et al.* 2010), long waiting times to receive care and obtain refills, and the burden of direct and indirect costs of healthcare (Genberg *et al.* 2015, WHO 2015a). Due to the complex nature of the phenomenon, failure to adhere is often a consequence of a combination of barriers from different domains (Carr & Gramling 2004, Halkitis *et al.* 2005, Stirratt *et al.* 2006, DHHS 2015, Genberg *et al.* 2015, WHO 2015a).

Measurement of medication adherence is challenging because adherence is an individual patient behavior. Several methods, often classified as subjective, objective, or biological, and validated instruments are available to assess adherence (Chaiyachati *et al.* 2014). The most feasible and thus most frequently used measure of adherence is self-report (Chaiyachati *et al.* 2014). Despite that patients may overestimate adherence, it still allows to assess adherence over time and, unlike other i.e., objective measures, self-report, when completed at each clinic visit, enables to detect any barrier(s) to adherence the earliest and intervene immediately (DHHS 2015). The other measures of adherence include pharmacy records and pill counts (Chaiyachati *et al.* 2014). Pharmacy records can be valuable when medications are obtained exclusively from a single source so that refills can be traced. Pill counts are also common, but can be altered by patients. Therapeutic drug monitoring and electronic measurement devices [e.g., Medication Event Monitoring System (MEMS) bottle caps] are also an option, but are costly and thus used primarily in research settings. The most reliable indicator of adherence is viral load suppression, a biological outcome determined by adherence behavior. When patients initiating ART fail to achieve viral suppression by 24 weeks of treatment, the possibility of suboptimal adherence should always be assessed, along with excluding the possibility of the patient harboring resistance mutations to any of the drugs (DHHS 2015). Optimal viral suppression is generally defined as viral load persistently below the level of detection (HIV RNA < 20 to 75 copies/mL, depending on the assay used (DHHS 2015, EACS 2015). As for monitoring response to ART, combining viral load measurement routinely every 3–6 months (DHHS 2015, EACS 2015) or less frequently (WHO 2013b) with other adherence evaluation methods may yield most beneficial to the patient results.

Regardless of how treatment adherence is measured, the adequate level for adherence has to be defined. In the earliest ART adherence studies the cut-off point for adherence was derived from the level of adherence proved to be effective in tuberculosis prophylaxis (e.g., $\geq 80\%$) (Turner 2002). The optimal level for ART adherence – taking at least 95% of pills as prescribed, was defined by Chesney and colleagues in 2000 (Chesney *et al.* 2000), and has not been overruled. At 95% (or higher) adherence the virus was detectable i.e., treatment failure occurred in only 10% of the patients studied, compared to treatment failing in almost half (47%) of patients with adherence between 80% and 90% (Chesney *et al.* 2000). However, there is some evidence suggesting that the optimum may differ for different classes of ARV drugs (Maggiolo *et al.* 2005, Bangsberg 2006, Apisarnthanarak & Mundy 2010). The cut-off also depends upon the measure used (Turner 2002). For instance, when measuring adherence by self-report, dichotomizing at 100% may be most valid for statistical analyses, given that these continuous values are highly skewed and non-normal, yet as a clinical goal, this level may be unreasonable for patients in the long term. One could also question whether patients can reliably distinguish between less than 80% or less than 85% (or any other selected level) when reporting their adherence (Simoni *et al.* 2006a). Regardless of evidence that long-term viral suppression

requires near-perfect adherence, average rates of adherence to ART around 70% have been observed over the years (Low-Beer *et al.* 2000, Bangsberg 2001, Paterson *et al.* 2000, Golin *et al.* 2002).

Despite international research efforts to examine ART adherence in diverse populations, there is limited information currently available concerning ART adherence among PLHIV and factors influencing it in Eastern Europe, including Estonia.

2.2.2. The continuum and the cascade of HIV care for people living with HIV

Potent combined antiretroviral therapy (ART) has transformed HIV infection from a (sub)acute to a chronic disease, and has significant effects on preventing HIV transmission to HIV-uninfected partners (Cohen & Fauci 2011, UNAIDS 2014b). Yet to maximize the health benefits of ART and to provide it to all in need, health systems must ensure an entire cascade of high quality services to PLHIV (Nosyk *et al.* 2013). Thus also adherence to ART has been recently conceptualized more broadly – including timely engagement and sustained retention in HIV care (DHHS 2015).

In the United States in 2005, looking further from the already proven individual benefit of ART to its population-level effectiveness, Giordano and colleagues pointed out that for the treatment to be effective for the population infected with HIV, certain steps needed to be followed in HIV care: those infected had to be diagnosed, enter care, receive ART, and adhere to it (Giordano *et al.* 2005). Concurrently, the HIV/AIDS Bureau in the Health Resources and Services Administration (U.S. Department of Health and Human Services) developed a continuum of engagement in HIV care model, defining people from ‘not aware of infection’ to ‘fully engaged in care’, potentially moving both directions i.e., entering and dropping out of the system of HIV care (Cheever 2007). The HIV/AIDS treatment cascade as a model to map the proportion of PLHIV actually receiving the medical care they need for HIV at each step in the care continuum, was first applied in the United States by Greenberg and colleagues to the Washington, D.C. area in 2009, then by Gardner and colleagues on national level in 2011, and has been since utilized by the Centers for Disease Control and Prevention (CDC) to monitor PLHIV engagement in HIV care in the country (Greenberg *et al.* 2007, Gardner *et al.* 2009, CDC 2014, Giordano 2015). In 2014, the European Centre for Disease Prevention and Control (ECDC) also added several questions pertinent to HIV continuum of care to data collection when monitoring the HIV epidemic(s) and performance of national HIV care programs in Europe (ECDC 2015b).

Over time, the HIV care cascade model has evolved. Some elements of the cascade appear in most reports/presentations from the constantly increasing number of countries studying their HIV care systems according to this model – the estimates of people living with HIV, those having been diagnosed with HIV,

those on ART, and those known to be virally suppressed. Linkage to and retention in HIV care are also commonly included (ECDC 2015b, Levi *et al.* 2015). However, some cascades also include other categories, such as PLHIV in need of ART (Del Rio 2012, Pokrovskaya *et al.* 2014), or start the cascade from a different (from the PLHIV) population (Levi *et al.* 2015, WHO 2015b).

Although international organizations and institutions monitoring the evolution of the HIV epidemic and response to it have recently intensified efforts to define the steps and definitions to be used when studying and presenting the cascade(s) (WHO 2014b, ECDC 2015b, WHO 2015b), currently data across countries should still be compared or aggregated with great caution due to the methodological diversity. Still, quantifying the steps of the cascade within a country or region enables service providers and policymakers in that area to identify the main ‘local’ gaps in providing PLHIV sustained and high quality HIV care, and implement optimal ‘local’ system improvements and service enhancements that best support ‘local’ people as they move through the continuum of care.

In 2014, UNAIDS announced an ambitious goal to end the HIV/AIDS epidemic in the world by 2030. Special targets, corresponding to 4 of the steps in the HIV care cascade, were set: (i) 90% of people living with HIV should know their HIV status, (ii) 90% of people diagnosed with HIV should receive ART, and (iii) 90% of people on ART should have viral suppression. Modelling suggests that achieving these targets by 2020 would enable the world to end the AIDS epidemic by 2030 (UNAIDS 2014b, UNAIDS 2014c). In order to attain the 90–90–90 targets, efforts are needed to optimize the HIV care continuum. The cascade of HIV care enables to map HIV care systems, uncovering the steps where improvements are needed foremost.

2.2.3. Prevention with people living with HIV

In confronting the HIV epidemic, similarly to HIV treatment, also in HIV prevention the advantages of a combined approach have been recognized. The concept of ‘*highly active retroviral prevention (HARP)*’ i.e., combining potentially synergistic prevention activities into a single, all-inclusive program was proposed by King K. Holmes already in 2007 (Vandenbruaene 2007). ‘*Combination prevention*’ is currently the more widely used term in HIV prevention programming (UNAIDS 2010). Combination prevention relies on simultaneous use of complementary behavioral, biomedical and structural prevention strategies (UNAIDS 2010, Bekker *et al.* 2012). Biomedical interventions comprise clinical and medical approaches to reduce HIV transmission: antiretroviral (ARV) drugs for the prevention of mother-to-child transmission, pre- and post-exposure prophylaxis, and treatment as prevention; and sex and reproductive health services (UNAIDS 2010). However, biomedical interventions are rarely implemented independently, as even those with proven efficacy are affected by human behavioral factors (adherence and risk compensation) and thus rely on behavioral

interventions to strengthen their effectiveness (Padian *et al.* 2008, UNAIDS 2010). HIV combination prevention programs can be implemented on different levels (e.g., individual, relationship, community, societal) (UNAIDS 2007). Choosing the optimal package always relies on clear and evidence-informed understanding of the local HIV epidemic and setting (e.g., the infrastructure, culture and traditions) – the approach often referred to as “Know Your Epidemic/ Know Your Response” (UNAIDS 2007, UNAIDS 2010).

In preventing HIV transmission, the more traditional focus from protecting HIV-negative individuals from becoming infected has gradually expanded to HIV-positive people, and helping them to avoid spreading the infection to their sex and injection drug use partners, and infants born to HIV-infected mothers (Bekker *et al.* 2012). It has been recognized that, from a public health perspective ‘*prevention with positives*’ i.e., targeting the fewer HIV-positives than the many HIV-negatives could be more efficient to fight the HIV epidemic (Kennedy *et al.* 2010, Mermin 2011, Lasry *et al.* 2012). This is also encompassed in the UNAIDS ‘test and treat’ strategy of rolling out universal HIV testing in order to diagnose all people living with HIV, and initiate ART regardless of CD4 cell count or viral load to reduce the rate of new HIV infections (UNAIDS 2014b), the latter currently encompassed in all major HIV treatment guidelines (Günthard 2014, DHHS 2015, EACS 2015, IAPAC 2015, WHO 2015a).

Already in early 1990s, prior to the era of potent triple-combination ART, evidence started to build on HIV treatment also preventing the transmission of the virus, both from mother to child (Connor *et al.* 1994) and in serodiscordant partnerships (Musicco *et al.* 1994). As ART can reduce HIV viral load to very low (undetectable) levels not only in blood, but also other body fluids (semen, vaginal and rectal fluids) of HIV-infected individuals, and thus significantly reduce their risk of transmitting the virus to others (Granich *et al.* 2010, WHO 2012), the concept of ‘*treatment as prevention*’ (TasP) emerged (WHO 2012). However, the success of TasP highly depends not only on the HIV-positive individual adhering to ART, but in serodiscordant partnerships also the risk behavior of both the partners accessing TasP – overstating the preventative benefits of ART might lead people to take higher behavioral risks, either sexual or IDU-related (Hasse *et al.* 2010). Although TasP includes preventive measures for both – people already infected with HIV (e.g., combined ART) and people at high risk of getting infected with HIV (e.g., prevention of mother-to-child transmission, pre- and post-exposure prophylaxis, and microbicides), this work only focuses on people already living with HIV.

2.2.3.1. Supporting antiretroviral therapy adherence

In HIV care the ultimate goal is to achieve control over the virus – for people already infected with HIV translating into not only achieving, but also maintaining viral suppression. While ART reduces HIV viral load to an undetectable level in the serum, replication still takes place in lymphatic reservoirs (Lorenzo-

Redondo *et al.* 2016), implying that for prolonged viral suppression optimal ART adherence, challenging to maintain, is essential.

Optimising ART adherence is attracting considerable research attention. While several systematic reviews and meta-analyses suggest that interventions can improve adherence (Amico *et al.* 2006, Simoni *et al.* 2006b, Charania *et al.* 2014, de Bruin *et al.* 2010, Mbuagbaw *et al.* 2015), evidence on the effect on viral load is less consistent (Simoni *et al.* 2006b, Mbuagbaw *et al.* 2015), and some still question the ability of interventions to enhance ART adherence (Rueda *et al.* 2006, Mathes *et al.* 2013). In addition to researcher initiated reviews on supporting ART adherence, in 2008 the HIV/AIDS Prevention Research Synthesis Project at the Centers for Disease Prevention and Control (CDC) started keeping track of evidence-based interventions to help HIV care providers in the United States select interventions best befitting their practice. Currently (last updated on April 1, 2015) only 12 ART adherence interventions have been identified as having good evidence of effect (CDC 2016a).

While adherence may be determined by a variety of factors from individual (patient) to system (healthcare) level, this work considers the patient dimension of adherence. Adherence as a behavior is a dynamic phenomenon (Remien *et al.* 2003) and accrues from local circumstances and culture. Thus, an adherence intervention should be chosen based on or adapted to the socio-cultural context, feasibility, acceptability (to the patient), and healthcare system organization in the particular setting. Methodologies that allow greater tailoring of the intervention activities to address the specific barriers and facilitators of adherence, likely differing from person to person receiving the intervention and at any given moment in time, show promise and are needed foremost (Robbins *et al.* 2014).

Research has demonstrated that health promotion, including treatment adherence interventions are likely to benefit recipients most, when guided by social and behavioral science theories of health behavior and health behavior change (WHO 2003, Kok *et al.* 2004). Several systematic reviews and meta-analyses of behavioral interventions (Amico *et al.* 2006, Simoni *et al.* 2006b, Chaiyachati *et al.* 2014) have concluded that “the most effective interventions used cognitive-behavioral models and shared a core set of psycho-educational components: (i) education about HIV and adherence; (ii) teaching self-monitoring skills; (iii) identifying adherence barriers; (iv) improving problem-solving skills; and (v) reframing treatment beliefs and attitudes” (Robbins *et al.* 2014). Other key features noticed in studies with interventions improving adherence indicate that most successful interventions were delivered (i) to individuals (*vs* groups), (ii) over at least 12 weeks, and were (iii) targeting practical medication management skills (*vs* cognitive behavioral or motivational approaches) (Rueda *et al.* 2006). A recent systematic review by Chaiyachati and colleagues also found that the effects of interventions combining several strategies to promote adherence were similar to those including only one strategy, and long-term effects on adherence were either difficult to achieve or had not been studied (Chaiyachati *et al.* 2014).

In Eastern Europe, the number of HIV-infected patients who are being prescribed ART is increasing. While support for enhancing ART adherence is a growing area of interest amongst treatment providers, there are currently limited data available to guide such efforts, in Estonia specifically, but also more broadly among patients in Eastern Europe. Application and adaptation to the local context of intervention(s) to support ART adherence among PLHIV in the region require targeted attention.

2.2.3.2. Supporting safe sexual behavior

PLHIV linked to and retained in HIV care attend HIV care settings for a variety of medical services. Those regular interactions with patients provide caregivers great opportunity for patient education and interventions to reduce ongoing risk behaviors and maintain safer practices. According to the Centers for Disease Control and Prevention (CDC), “behavioral interventions are strategies designed to change persons’ knowledge, attitudes, behaviors, or practices in order to reduce their personal health risks or their risk of transmitting HIV to others” (CDC *et al.* 2003). Reducing sexual risk behaviors among PLHIV has been the focus of many behavioral interventions (Crepaz *et al.* 2006, Fisher *et al.* 2010, Carvalho *et al.* 2011, Crepaz *et al.* 2014). As behavior change occurs in incremental steps, messages delivered to patients receiving HIV care by clinicians or other qualified staff at HIV clinics during several or each visit could result in patients, over time, adopting and maintaining the suggested safer practices (CDC *et al.* 2003).

Although majority of people make changes in their sexual behavior after being diagnosed with HIV to avoid transmitting the infection, some continue to engage in unprotected sexual practices (CDC *et al.* 2003, The Healthy Living Project Team 2007, Fisher *et al.* 2010). As high sexual risk behavior among HIV-infected people (CDC *et al.* 2003, Fisher *et al.* 2010) can have serious personal and public health consequences (Kennedy *et al.* 2010, Mermin 2011, Lasry *et al.* 2012), safe sexual practices should be actively promoted among PLHIV.

Researchers in the field have identified, and the CDC HIV/AIDS Prevention Research Synthesis Project has defined efficacy criteria for HIV behavioral interventions to help HIV prevention planners and providers select rigorously evaluated and effective interventions for HIV prevention within their communities (CDC 2016b). Reviews of evidence on sexual risk reduction among PLHIV have looked at interventions at different levels, including individual, group and community level interventions of very different types (Crepaz *et al.* 2006, Fisher *et al.* 2010, Carvalho *et al.* 2011, Crepaz *et al.* 2014). Analyses have shown sexual risk reduction interventions to be effective at promoting protected sexual intercourse among adults living with HIV/AIDS especially when guided by behavioral theories, and more intensive and longer in duration (Crepaz *et al.* 2006, Johnson *et al.* 2006, Crepaz *et al.* 2014.). Interventions, delivered by healthcare providers during routine interactions with patients in medical care settings on an individual level, have demonstrated reduction in sexual risk

behavior (Crepaz *et al.* 2006, Crepaz *et al.* 2014). Although one metaanalysis of behavioral interventions to promote condom use among HIV-positive women showed behavioral interventions to have little effect, the authors did not discourage such interventions altogether, rather recommended combining them with other strategies (Carvalho *et al.* 2011).

Currently, based on the body of available evidence, regular assessment and discussion of HIV transmission risk and related safe sexual practices is considered an essential part of the package of services provided to PLHIV in HIV care, and has thus been incorporated into major HIV treatment and related guidelines (WHO 2008, DHHS 2015, EACS 2015). In the United States, HIV care providers are advised to take *any opportunity* for brief HIV-related risk behavior reduction interventions whenever a patient with HIV visits (CDC *et al.* 2003). However, the efficacy of such feasible clinician-delivered individual level behavioral interventions has still not been studied extensively, especially in Eastern Europe (including Estonia). Also, according to our knowledge the most applicable interventions to the local epidemiological and transitional healthcare system context in Eastern Europe have not been defined.

3. AIMS OF THE RESEARCH

The general aim of this research was to describe the engagement of people living with HIV (PLHIV) in HIV care in Estonia and their adherence to anti-retroviral treatment (ART), and to develop methods to support ART adherence and safe sexual practices among HIV-positive adults in HIV care in Estonia.

The specific aims were:

1. To describe and quantify PLHIV engagement in HIV care in Estonia, and identify the main gaps in coverage with applicable health services with implications for health system improvement (PAPER IV);
2. To characterize ART adherence and understand factors associated with it among adult PLHIV receiving HIV medical care in Estonia (PAPER I, PAPER II);
3. To develop a feasible evidence-based ART adherence support program targeting the needs of HIV-positive adults receiving HIV medical care in Estonia, and potentially in other countries with similar socio-economic history and HIV epidemic evolution (PAPER I).
4. To systematically identify and synthesize research on interventions supporting safe sexual behavior among HIV-positive adults in HIV care, provided on an individual level by caregivers in HIV care settings, applicable in Estonia, and potentially in other countries with similar socio-economic history and HIV epidemic evolution (PAPER III).

4. MATERIALS AND METHODS

The current work is based on a research project combining quantitative and qualitative methods of data collection and synthesis. The research was lead by the HIV/AIDS research group at the Institute of Family Medicine and Public Health, University of Tartu.

Research for this dissertation began in 2010 with mapping the HIV epidemic and response to the epidemic (from testing to treating HIV) in Estonia in the context of other Eastern European countries, and the trends of HIV/AIDS and related conditions in Estonia during the preceding decade from 2000 to 2009 (Laisaar *et al.* 2011). These results are incorporated into the ‘Review of the literature’ of this work.

For developing a feasible evidence-based ART adherence support program, tailored to the needs of HIV-positive adults in HIV medical care in Estonia, a study using mixed methods was conducted in 2010–2011 (PAPER I). The data collection was complemented by a cross-sectional study in 2010 to understand factors associated with ART adherence among PLHIV in HIV medical care in Estonia (PAPER II).

To inform the development of an intervention supporting safe sexual practices among PLHIV in Estonia, a systematic review was conducted in 2014 (PAPER III).

To characterize the full spectrum of PLHIV engagement in HIV care (not limited to ART) in Estonia, a cross-sectional review was conducted in 2014–2015, applying the HIV cascade of care model (PAPER IV).

4.1. Research project on antiretroviral therapy adherence among HIV-positive adults receiving HIV medical care (PAPER I, PAPER II)

4.1.1. Project setting, study design and procedures

An ART adherence research project (PAPER I and PAPER II) was conducted in Ida-Viru Central Hospital in Ida-Viru County, the Eastern part of Estonia. In 2010, the Infectious Diseases Department of this hospital was staffed by 3 infectious diseases trained physicians, 8 nurses, and a part-time social worker/case manager. The hospital served about 1/5 of PLHIV in medical care in Estonia (EHIF 2011), and ART adherence support was generally limited to treatment regimen information provision.

PAPER I

To identify in-clinic strategies that could leverage patient-centered practices to best support the specific needs of adult PLHIV in care in Eastern Estonia, we conducted a mixed methods study, applying a theory- and evidence-based health promotion intervention development and evaluation framework – Intervention

Mapping (IM) (Kok *et al.* 2004, Bartholomew *et al.* 2006). The IM protocol consisted of 6 steps: (1) target group needs assessment, (2) proximal program objectives identification, (3) intervention theory and strategy selection, and program (4) development, (5) implementation and (6) evaluation.

Methodologically each step in IM drew from and built upon the following data sources and procedures (summarized in Table 1 in PAPER I):

- (i) *Literature review through electronic information space (MEDLINE, Cochrane CENTRAL, ISI-Web of Science) search* on key domains: HAART, medication adherence/patient compliance, behavior theory/methods, intervention and program development; from 2000 to 2009.
- (ii) *Individual data evaluation and team discussions (at meetings and teleconferences) amongst the multidisciplinary international research team*, consisting of 2 public health researchers, experienced in HIV/IDU, medical doctors (University of Tartu, Estonia); a researcher/instructor in health behavior change, experienced in ART adherence, a psychologist (University of Connecticut, USA); 2 nurse counselors (Ida-Viru Central Hospital, Estonia), supporting the researchers in adapting the intervention to local conditions.
- (iii) *Formative research* to obtain data on local ART adherence determinants in Ida-Viru County: interviews with 4 medical service providers, held by research team member (medical doctor, University of Tartu, Estonia); two focus-group discussions with ART-experienced HIV-positive adults, held by a sociologist (University of Tartu, Estonia).

Previously published methods for intervention development were followed or adapted (Kok *et al.* 2004, Perez-Rodrigo *et al.* 2005, Bartholomew *et al.* 2006, Kok *et al.* 2006, Wolfers *et al.* 2007, Côté *et al.* 2008).

PAPER II

For implementation and evaluation of the efficacy of the developed intervention (the final steps in the IM framework), a small-scale feasibility randomized controlled trial (RCT) was conducted at Ida-Viru Central Hospital in 2010–2011 (with 1:1 randomization, comparing the developed ART adherence intervention to usual care with 12 months follow-up). Analysis of baseline data from this study sample of 161 (11 pilot and 150 randomized) consecutive consenting patients presenting for routine HIV clinical care visits at the hospital between July and December 2010 is presented in this dissertation.

At the time of the study, Ida-Viru Central Hospital provided HIV care to 651 patients, with 372 of them receiving ART (EHIF 2011). Convenience sampling was used to recruit the study subjects. Patients were included when at least 18 years of age, able to read/write in Estonian or Russian, and on ART. A structured interviewer-delivered questionnaire was administered by a trained nurse, taking approximately 45–60 minutes to complete. These interviews were conducted in a private location in the clinic following the participant's medical

visit. Medical data were abstracted from clinical records by the study physicians using a standardized data abstraction form.

In patient interviews, adherence was assessed via a 3-day recall of doses missed (Chesney *et al.* 2000). Rates of adherence were calculated as the proportion of total doses taken in full as prescribed over total doses prescribed (in past 3 days). Data collected from the interview also included participants' socio-demographic and health status characteristics, self-reported health insurance status as a proxy for access to healthcare, HIV testing and healthcare (including ART) utilization history, knowledge and beliefs about ART, and history of risk behaviors (sexual and substance abuse). Data abstracted from clinical record included the ART regimen prescribed, duration of ART, co-infections such as hepatitis C, CD4 cell counts, and HIV RNA level (viral load) with sensitivity of 50 copies/ml.

From all participants in the adherence support intervention arm of the study also data on facilitators and barriers to adherence were collected during adherence counseling session(s) (PAPER I).

Participants (PLHIV) in the adherence research project received a supermarket voucher with a value of 6.40 EUR as an incentive for study participation.

4.1.2. Data analysis

PAPER I

Coding data were descriptive and thematic (Miles & Huberman 1994). Interviews in focus groups were coded initially for emerging core descriptive content, and further refined in an iterative process of data coding, charting and interpretation. Data were processed by hand. Transcripts of both interviews were summarized in a separate file on the computer with participants only identified by age and sex.

PAPER II

For the analysis presented in PAPER II, baseline (cross-sectional) data of the pilot RCT were used. In statistical analysis nonadherence was selected as the primary outcome (dichotomized, with the cut-off of < 100% as nonadherent). Socio-demographic, substance abuse, and other factors were compared between the adherent and the nonadherent group. Correlates of adherence were explored using the Fisher's exact test and Wilcoxon rank sum test; crude odds ratios of nonadherence were calculated. Logistic regression was used to estimate adjusted odds ratios. Factors associated with adherence in bivariate analyses at significance level of 0.1 or lower (and not considered an outcome of adherence) were adjusted for. Generalized variance inflation factor was calculated for all independent variables (Dobson & Barnett 2008).

4.2. Systematic review of interventions supporting safe sexual behavior among HIV-positive adults receiving HIV medical care (PAPER III)

4.2.1. Study search and selection

Studies were selected for the systematic review (PAPER III) based on study design and implementation criteria of effective behavioral interventions reducing HIV sexual risk taking among PLHIV, identified in previous research (Crepaz *et al.* 2006), and defined by the CDC HIV/AIDS Prevention Research Synthesis Project (CDC 2016b).

We included randomized and quasi-randomized controlled trials implementing individual-level behavioral interventions specifically designed for sexual risk behavior reduction (in comparison to ‘no such intervention’) to be delivered in healthcare settings by HIV care providers to adult PLHIV in care.

The outcome of interest was sexual risk behavior reduction, based on at least one behavioral measure (number of sexual partners, number of condomless sexual acts or condom use consistency) or one biological measure (sexually transmitted infection, hepatitis B acquisition). The studies had to assess the outcome(s) after at least 3 months (90 days) from intervention initiation.

Specific search terms were developed for the following concepts: HIV/AIDS, sexual (risk) behavior, behavioral intervention, and (quasi)randomized study design. Between February 21 and 23, 2014 relevant studies from 1981 (the year AIDS was first reported in the world) (CDC 1981) to 2013 (year end) with no language or publication status restrictions were searched from:

- (i) electronic biomedical literature databases: MEDLINE (PubMed), MEDLINE (Ovid), Embase (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library), PsycINFO (EBSCOhost), and CINAHL (EBSCOhost);
- (ii) abstracts of HIV/AIDS conferences recommended by the Cochrane Review Group on HIV/AIDS (Cochrane Review Group on HIV/AIDS 2014): International AIDS Conference (AIDS), International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS), and Conference on Retroviruses and Opportunistic Infections (CROI).

Also references of the retrieved publications were screened for additional reports of same studies and other relevant studies.

All the search, selection, data abstraction, and evaluation methods were standardized, and applied independently by two reviewers at each stage. Citations retrieved from electronic databases were merged and duplicates deleted, then screened by title and abstract. Full texts of all potentially eligible publications were read to assess the study design, types of participants, interventions, and outcome measures. Agreement between reviewers was measured with Cohen’s kappa (Higgins & Green 2011), and studies were promoted to the next phase after inclusion consensus was reached. Characteristics of each study that met the review inclusion criteria were extracted.

4.2.2. Study quality and results analysis

Methodological quality of studies included in the review was assessed according to the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions (Higgins & Green 2011). Potential selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and study personnel), detection bias (blinding of outcome assessment), attrition bias (intention to treat analysis, outcome data completeness and how incomplete data were dealt with), reporting bias (selective outcome reporting) and other biases, if applicable, were evaluated. Risk of bias was categorized as either 'low', 'high' or 'unclear'. At any stage of the evaluation all disagreements and uncertainties were discussed, and consensus was reached between the two reviewers. The results of the assessment were organized and presented in a 'risk of bias' table.

Results of the original studies included in the review were synthesized qualitatively. In studies with interventions targeting several transmission risk behaviors only the sexual risk behavior component was assessed, and in studies with multiple follow-ups only data from the last were considered. Authors of all the studies (included in the review) were contacted to clarify the results and request data not provided in the publication(s). For count data (e.g., number of sexual partners or unprotected sexual acts) means with standard deviations (SDs) were considered. For dichotomous outcomes (e.g., condom use consistency: always/not always using a condom) the effect sizes [odds ratios (ORs) with 95% confidence intervals (CIs)] in comparing the intervention and control groups were considered. The results of the original studies were organized and presented in a summary of findings table.

Systematic review conclusions were drawn, considering the intervention effect magnitude and methodological quality in the original studies.

4.3. Cross-sectional review of people living with HIV engagement in HIV care in Estonia (PAPER IV)

4.3.1. Study data sources and operational definitions

In the cross-sectional review (PAPER IV) national level HIV data, applying the HIV care cascade model, and the metrics developed by CDC (CDC 2011) and the Institute of Medicine (IOM) (Ford & Spicer 2012), were synthesized. The number of people (1) living with HIV, (2) diagnosed with HIV, (3) linked to HIV care, (4) retained in HIV care, (5) on ART, and (6) with suppressed viral load (HIV RNA < 200 copies/mL) in Estonia in 2013 was assessed. In addition to the 6 cascade steps, we also evaluated the timing of initiation of HIV care and PLHIV health state (based on CD4 cell count) at reaching specialized HIV care, and at ART initiation.

The number of people estimated to live with HIV in Estonia in 2013 was based on the UNAIDS Spectrum estimate (AIDSinfo 2014). For the number of

PLHIV at the next steps of the cascade, data were obtained from local country-level sources – the Estonian Health Board (EHB), the Estonian Health Insurance Fund (EHIF), the Estonian HIV-Positive Patients Database (E-HIV), and the Estonian Causes of Death Registry (ECDR), characterized in Tabel 1.

Table 1. Overview of study data sources, Estonia, 2013

Data source	Characteristics
Estonian Health Board (EHB)	Agency of the Estonian Ministry of Social Affairs (EMSA) Responsible for passive surveillance of communicable diseases (including HIV), hence recording all newly diagnosed (confirmed) HIV cases in Estonia; nationwide coverage
Estonian Health Insurance Fund (EHIF)	Institution, operating within the administration area of EMSA as an independent legal body Core purchaser of healthcare services for the compulsory health insurance system in Estonia, hence possessing healthcare utilization data, covering all medical services and service costs (except ART medication costs) provided to PLHIV; nationwide coverage An identification code is assigned to each individual, enabling longitudinal tracking of care provided to individuals without personal identification (pseudo-identification)
Estonian HIV-Positive Patients Database (E-HIV)	Database, operated by the Estonian Society for Infectious Diseases Contains detailed, longitudinal demographic and clinical data of PLHIV in Estonia, including date of HIV confirmation, mode of HIV acquisition and course of HIV care (with dates of clinical appointments, ART provision, dates and results of CD4 cell counts, viral load values), and concomitant diseases (Soodla <i>et al.</i> 2015) Data from consenting PLHIV in HIV medical care, recorded since April 2009 (when the database was established); also includes some retrospective data
Estonian Causes of Death Registry (ECDR)	Registry, operated by the Estonian National Institute for Health Development (NIHD). Collects data on all cases of death (including the cause); nationwide coverage

To calculate an indicator for each step in the HIV care cascade, the most relevant of the data sources was/were selected, and a timeframe (period) for data to be included in the calculations was specified, as summarized in Table 2.

Table 2. Operational definitions and data (with time and source) for the six steps of the cascade of HIV care in Estonia, 2013

	Operational definition, data with respective time period	Data source(s)
Living with HIV	The Spectrum estimate for 2013	Joint United Nations Programme on HIV/AIDS (UNAIDS)
Diagnosed with HIV (alive in 2013)	Aggregated number of confirmed HIV-positive tests (individuals) minus the aggregated number of deaths (AIDS deaths, specified proportion of illicit drug overdose related deaths) <i>Time period: 1.01.1988^a– 31.08.2013^b</i>	Estonian Health Board (EHB); Estonian Causes of Death Registry (ECDR)
Linked to HIV care (alive in 2013)	The number of individuals with at least one HIV-related healthcare visit, based on individual anonymized reimbursement claims of HIV-related healthcare services: visit dates, medical services provided to PLHIV (with dates), healthcare providers issuing the claims <i>Time period: 3.02.2000^c–31.08.2013^b</i>	Estonian Health Insurance Fund (EHIF)
Retained in HIV care	The number of individuals with 2 or more HIV-related healthcare visits (at least 3 months apart) within the past 12 months <i>Time period: 1.09.2012–31.08.2013^d</i>	Estonian Health Insurance Fund (EHIF)
On ART	<i>Step 1:</i> The proportion of individuals on ART among those retained in care, based on individual anonymized data from E-HIV: HIV verification time, ART initiation time, dates and results of CD4 cell and HIV RNA tests, dates of other medical services provided to and visits of PLHIV <i>Step 2:</i> The number of individuals on ART among those retained in care according to EHIF, when applying the proportion obtained in <i>Step 1</i> to individuals retained in care according to EHIF <i>Time period: 1.09.2012–31.08.2013^d</i>	Estonian HIV-Positive Patients Database (E-HIV); Estonian Health Insurance Fund (EHIF)
Virally suppressed	<i>Step 1:</i> The proportion of individuals on ART with the most recent (within the past 12 months) HIV RNA < 200 copies/mL, based on individual anonymized data from E-HIV <i>Step 2:</i> The number of individuals virally suppressed according to EHIF, when applying the proportion obtained in <i>Step 1</i> to individuals on ART according to EHIF <i>Time period: 1.09.2012–31.08.2013^d</i>	Estonian HIV-Positive Patients Database (E-HIV); Estonian Health Insurance Fund (EHIF)

^a First HIV case in Estonia was diagnosed in 1988

^b End of our study period

^c Earliest date appearing on a HIV-related medical service reimbursement claim (the date of “opening” the medical service account) in the EHIF electronic database since its inception

^d To evaluate the situation in 2013, data from this 12 months period were used

For the timeliness of PLHIV accessing HIV care, we looked at individuals newly diagnosed with HIV in past 12 months and calculated the time from HIV diagnosis to linkage to HIV medical care for each patient. For this analysis, linkage to care was defined as the first visit to an infectious disease doctor (qualified to follow and treat people infected with HIV in Estonia) when a CD4 cell count and/or HIV RNA level was measured. Linkage to HIV medical care was considered timely when this first visit took place within 90 days of HIV verification (Ford & Spicer 2012). We also looked at E-HIV data on patients' CD4 cell counts obtained during the first HIV medical visit (as defined above) and at ART initiation.

4.3.2. Data management

The number of PLHIV estimated to live in Estonia in the year of study (according to UNAIDS) was used as a denominator for calculating indicators for all the subsequent steps in the HIV care cascade. Carefully constructed case-finding algorithms were applied to identify individuals from local health administrative databases. When the most applicable data source did not have nationwide coverage, the result was extrapolated to another source with national coverage to obtain a population-based estimate.

Information bias in data sources was mitigated by detailed data review at face-to-face meetings of the research team, and consultations with HIV medical care providers and community partners. We compiled cross-comparisons of the data and discussed any discrepancies and, if necessary, obtained additional data and consultations until consensus was reached.

4.4. Ethical considerations

Until HIV cure will be developed, complex measures have to be taken to control the virus. Selecting the most effective evidence based measures includes research among people living with HIV (PLHIV). As HIV infection still carries more stigma than most other diseases and health conditions, special precautions have to be taken in research projects involving PLHIV (Rennie & Sugarman 2010, UNAIDS/WHO 2012, Lo *et al.* 2013).

For research on ART adherence among PLHIV presented in this dissertation ethical review took place at the Ethics Review Committee on Human Research of the University of Tartu, Estonia. The research presented in Papers I and II was conducted at infectious diseases clinics in Kohtla-Järve and Tallinn, and recruited HIV-positive patients as study subjects (ERC approvals no 190T-17, 2010 February 22; 195/M-25, 2010 August 30).

In terms of special populations we were guided by the following ethical considerations:

- (i) *Exclusion of intoxicated persons:* Intoxicated persons were not eligible for the study by virtue of inability to provide true informed consent. The interviewers queried potential subjects on their use of drugs prior to informed consent procedures, and used their observation and judgment to determine whether the potential subject was not eligible due to intoxication and whether the interview underway needed to be ended.
- (ii) *Inclusion of women:* Our recruitment procedures did not in any way discriminate against women.
- (iii) *Inclusion of minors:* Recruitment was limited to people aged 18 and older.

Information was obtained from interviews and abstracted from clinical records. Data collection in qualitative interviews was undertaken by experienced and specially trained researchers. Data collection from the clinic population (standardized questionnaire based interviews, clinical record abstracts) was undertaken by study participants' routine HIV care providers and added to routine clinic visits. Each participant was assigned a unique study identification (ID) number, and all study participants' data were identified only by the study ID numbers (with identification information known only to the care provider). The research team at the University of Tartu did not collect (qualitative research: focus groups) or receive (clinical study) any data that would have enabled to identify the study participants.

The primary risks to clinical study participants foreseen were stress from loss of privacy and the psychological risks of disclosing personal alcohol/drug use and sexual behavior information. The approaches in place to protect against these risks were the following:

Recruitment and informed consent: Potential participants were informed that their participation in the study was strictly voluntary and that they were free to withdraw from the study at any time. Following a careful explanation of the study, eligible patients were given the consent form to read or, if necessary, the consent form was read to the patient by project staff (in Estonian or Russian). For participation in the study a written consent was secured.

The psychological risk: The content of the interviews contained sensitive information such as the possibility of developing a potentially fatal illness and engaging in highly stigmatized behaviors. Such content could prove upsetting to some subjects. In order to guard against the possibility of extreme distress subjects were informed before the interview that they were free to decline to answer any questions or to stop the interview at any time should they feel anxious or uncomfortable in answering. We must emphasize, however, that based on all of our previous research, we considered the likelihood of extreme personal distress in reaction to the content of the questions to be very low.

Protection of individual privacy: A private room was used for study procedures and conducting the interview.

Protection of confidential information: All study data including behavioral and clinical information were kept in a confidential manner and concerted efforts were made to ensure confidentiality. Specifically: (1) all files were in locked areas, (2) patient identification information was not available to the research team at the University of Tartu, (3) study staff was trained on confidentiality issues (no discussions on individual respondents with anyone else, even in general terms; holding interview in private with only the respondent and the interviewer present; careful following of standard study procedures).

While not dismissing the abovementioned risks, we suggested the potential benefits, including ART adherence counseling and development of HIV prevention programs, substantially outweighed the risks to the participants. There was an opportunity to address important research questions that could not have been easily or readily addressed elsewhere. Effective interventions supporting ART adherence presume systematic development, and should be built on mapping the situation (e.g., ART adherence level, main barriers and facilitators) and the target population (i.e., PLHIV initiating or receiving ART) values and needs. We saw the lessons learnt from the project being potentially important and results applicable for a wider community in Europe, especially in neighbouring countries with similar socio-economic history that have witnessed similar HIV epidemics.

The research undertaken and presented in PAPERS III and IV did not warrant research ethics board review, as was based on published research or aggregated surveillance and administrative data. The research in PAPER IV was in agreement with data protection regulations in Estonia.

5. RESULTS

5.1. Antiretroviral therapy adherence and factors associated with it among HIV-positive adults receiving HIV medical care in Estonia (PAPER I, PAPER II)

PAPER I

In the ART adherence support intervention development study adult ART-experienced HIV-positive focus groups participants (n = 14, five female, aged 18–50) identified lack of time, drug/alcohol abuse, side-effects of ARV drugs, and considering ART unnecessary as the main individual barriers to ART adherence. Whereas, support from a family member or friend, desire to remain healthy to raise a child, tools or methods for organizing pill-taking or linking it to other routine daily activities were noted to facilitate adherence.

The focus groups interviews also revealed another facet of treatment adherence – gaps in patients’ ART adherence knowledge. While PLHIV were aware that not taking their pills as prescribed would lead to resistance, they did not fully understand how would it develop and how missing one pill or a few every once in a while could contribute to this. Misconceptions related to ART included defining nonadherence as not taking medication for a long period – a month or two, as well as uncertainty about the actual function and effects of ARV drugs were detected. The importance of taking every pill was especially hard to recognize by patients who did not feel ill, but experienced medication side effects. In some patients adherence had eroded over time (before the intervention) when HIV-related symptoms diminished, yet medication side-effects increased.

Adherence determinants were also studied among patients, randomized to the intervention arm of the ART adherence support intervention (developed for Estonia) feasibility testing trial. In this sample (n = 75, 2/3 male; median age 32; predominantly unemployed; 65% reporting IDU related HIV acquisition, median of 6 years living with HIV, and 2 years on ART; and 7% acknowledging missing at least 1 pill in past 3 days), the main barriers to ART adherence identified were in good agreement with the information obtained in the focus-group interviews (described above). More than half of patients in the RCT intervention arm identified ‘social support (including having a child)’ and ‘future perspectives (desire to stay alive/healthy)’ (59% and 55%, respectively), and 29% ‘routinization of pill-taking (a well-established method)’ as facilitators to staying adherent to the treatment prescribed. ‘Medication side effects’, ‘irregular, intensive personal or working-life’ and ‘alcohol/illicit drug abuse’ were the barriers most frequently reported (44%, 27% and 13%, respectively). Overall, only 3% of respondents claimed having no problems with pill-taking.

PAPER II

Among the 161 study participants at Ida-Viru Central Hospital at study baseline in 2010 a small subset ($n = 17$) lacked experience with ART as were just starting the therapy, and were thus excluded from further analysis. Participants retained for the analysis ($n = 144$) were aged 19 to 77 years (mean 33.8, SD 8.23), and 55% (79) male. Over half of them lived in a relationship (26.6% married, and 28.7% living with a sexual partner). Two-thirds (70%) of participants had completed more than 9 years of education. Most (73%) were unemployed and lived on social benefits (53%) or income from relatives/partner (20%). However, vast majority (91%) were covered by Estonian state health insurance. Based on self-reported time of testing positive for HIV, on average these 144 patients had been aware of their HIV seropositive status for 5.6 years (SD 3.49). Two-thirds (63%) had acquired HIV through IDU (82.9% of men, 39.1% of women). One-third also reported illicit drug use within the preceding year, and almost $\frac{1}{4}$ scored as having increased likelihood of hazardous and harmful alcohol use. One-third also reported signs of clinically significant depression. The study participants had been on ART for an average 1.5 years (SD 1.5). While 88% (95% CI 81–92%) of participants reported 100% adherence over the past 3 days, viral load was undetectable for only 56% ($n = 80$). Although the mean CD4 cell count was 355 cells/mm³ (SD 225 cells/mm³), a quarter of the sample (26%) had a CD4 cell count below 200 cells/mm³.

Bivariate analysis showed that ART nonadherence was not associated with assessed concurrent morbidities (depression, alcohol, and drug use) or ART regimen factors (number of pills and dosing frequency). No differences were found in adherence between those reporting having ever injected drugs and those not, and between PWID currently in opioid substitution therapy or not. Although less than perfect adherence was reported more commonly among drug users compared to nonusers, the difference was not statistically significant.

Multivariate analysis, when adjusting for insurance status and self-rated health, showed that study participants who exhibited greater concerns about perceived negative consequences of taking ART had five times the odds of being nonadherent than those with lower concerns [adjusted odds ratio (AOR) 4.8, 95% CI 1.2–34.0]. Nonadherence was also associated with average (versus good/very good) self-reported health status (AOR 4.6, 95% CI 1.2–31.4). While already in bivariate analysis study participants with detectable viral load were more likely to be nonadherent (OR 5.3, 95% CI 1.5–23.2), it also remained significantly associated with nonadherence in multivariate analysis (AOR 3.9 95% CI 1.3–14.7). However, viral load should rather be interpreted as an outcome of than a predictor for (non)adherence.

5.2. A feasible evidence-based antiretroviral therapy adherence support program tailored to HIV-positive adults receiving HIV medical care in Estonia (PAPER I)

In addition to our findings from the ART adherence support intervention development study focus group interviews among ART-experienced adult PLHIV (described above in paragraph 5.1.), interviews with HIV medical care providers revealed inconsistencies in how ART adherence was discussed with patients as well as how frequently nonadherence was identified – no standard protocol was followed and most discussions occurred early in the course of prescribing ART. It also appeared that later in the treatment nonadherence was reported by patients infrequently, and doctors tended to “discover” problems with adherence only from poorly controlled viremia, drops in CD4 cell count, or failure to pick up medication refills.

Findings from the *first step* in developing the adherence support program i.e., the gaps in patient information, motivation, social support, and skills, combined with an understanding that the current standard of support for adherence did not involve a strong patient-education component or open discussions concerning challenges (or successes) with adherence, guided the following identification of program objectives and development.

Secondly a guide, informed by all data sources (focus groups, research team, literature) was developed to map objectives for the intervention program (Figure 1 in PAPER I). Two core sets of behaviors – ‘integrating the treatment plan into one’s daily routine’ and ‘handling situations in which ART is difficult to take’, were selected for promotion. These were the topics that patients could discuss during the intervention without having to disclose whether drug doses were actually missed.

At the *third step* in developing the intervention, the Information–Motivation–Behavioral Skills (IMB) theory of ART adherence (Fisher *et al.* 2006, Munro *et al.* 2007, Fisher *et al.* 2008) was chosen to build on. Further, based on the IMB model and our initial work, patient knowledge, motivation, and skills were identified as the critical change objectives. For the intervention approach, the Next Step Counseling (NSC) to ART adherence was selected and adapted. NSC, previously used in HIV pre-exposure chemoprophylaxis trials (Amico *et al.* 2010, Grant *et al.* 2010), involved brief and flexible guided discussions targeting identification of adherence-related needs and strategizing on them, using motivational interviewing techniques.

At the *fourth step*, an intervention program entitled “Situational Optimal Adherence Intervention (sOAI) Estonia”, comprising of 3 one-on-one sessions with a trained study nurse, was developed (Figure 2).

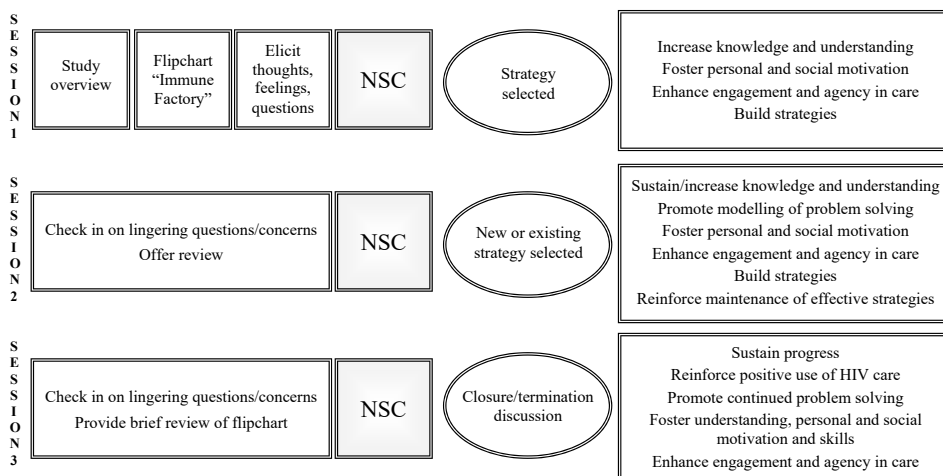


Figure 2. Antiretroviral Therapy Adherence Promotion Session Flow in Situated Optimal Adherence Intervention Estonia (sOAI Estonia).

The frequency of sessions (approximately 3 months apart) was chosen to distribute the intervention over an optimal time period, yet minimizing extra visits by linking the counseling sessions to patients' regular medication refill and other clinic visits. The first intervention session included an explanation of the study and the role of nurse as a collaborator with the participant; going through an educational flipchart on HIV and ARV drugs and eliciting patient reactions to this. A standardized flipchart, using figurative metaphors to promote understanding and personalized knowledge of HIV in the body and how ARV drugs can protect the immune system, was created specifically for the sOAI Estonia program (Figure 3 in PAPER I). After eliciting participant reactions to the flip chart, the nurse initiated a NSC discussion (Figure 4 in PAPER I). For assessment of information obtained from the patient during counseling, Neutral Assessment (NA) strategies (Amico *et al.* 2010) were adopted to promote participants' sense of candor and comfort in having open discussions about ART adherence. Intervention Sessions 2 and 3 involved a brief check on any questions from the previous session(s), and implementation of the NSC discussion (Figure 2). Each NSC discussion concluded with identifying something the participant would try to help him/her with adherence between the clinic visits. At the following session, the nurse asked the participant how this had gone and then discussed the current experiences with ART and what the participant now felt would be most helpful to integrate daily ART into his/her life.

The *fifth step* in developing the intervention program resulted in implementing the sOAI Estonia program in Ida-Viru Central Hospital. At this stage the intervention nurse and interviewer were trained in study procedures and methods, and a study manual on NSC and NA, a one page NSC counseling record form, and a standard questionnaire for patient interviews including adherence

assessment were employed to standardize and monitor the implementation. Further methodological and practical intervention implementation support was provided to the hospital-based study team at least once a month during whole study period in regular on-site meetings with project manager (a researcher from the University of Tartu).

Lastly, as the *sixth step* in developing the intervention program in 2010–2011, a RCT to compare sOAI Estonia to regular counseling in a convenience sample of 150 consecutive adult patients attending the infectious diseases department at Ida-Viru Central Hospital, and receiving or initiating ART, was undertaken. Treatment adherence level, measured by patient 3-day recall self-report and hospital medication dispensing records at baseline, and at 6 and 12 months, was chosen as the primary outcome. In addition, data on HIV RNA level and CD4 cell count were evaluated at same time points. As part of the intervention program evaluation alongside with the RCT, also the feasibility, acceptability, and fidelity of sOAI Estonia were reviewed. Whereas for patients the brief counseling sessions (in the intervention arm) were added to their routine clinic visits, also the hospital personnel did not complain about excessive workload during the study, but reported better understanding of their patients through enhanced communication. The nurse counselors also reported feeling rewarded by the “Aha!” effect their explanations about HIV and ARV drugs generated in many counseled patients.

5.3. Systematically identified and synthesized evidence for supporting safe sexual behavior among HIV-positive adults receiving HIV medical care in Estonia (PAPER III)

As a result of rigorous publication search with terms addressing all the main concepts of the review question, 950 citations from electronic biomedical literature databases and 34 abstracts from conference proceedings from 1981 to 2013 were retrieved. After systematic assessment and evaluation, the originally retrieved body of evidence on behavioral interventions for adult PLHIV, provided on individual level by caregivers in HIV care settings, to determine their efficacy in reducing sexual risk behavior was limited to 5 randomized studies (The Healthy Living Project Team 2007, Cornman *et al.* 2008, Gilbert *et al.* 2008, Safren *et al.* 2013, Kurth *et al.* 2014^{*}) (Figure 1 in PAPER III).

Interventions in the studies included in the review had been conducted in real life conditions, yet differed greatly in duration and intensity – from brief (15-minute) sessions a few months apart (Cornman *et al.* 2008) to fifteen 90-minute sessions in a year (The Healthy Living Project Team 2007). Participants in all

** Remark: The Kurth et al. study here in text and list of references was published in 2014. However, at the time of publication search for the systematic review an earlier (electronic) version was retrieved, and thus the study still fitted into the pre-defined for the review time frame for publication search, ending with December 31, 2013.*

the studies had been both men and women, except in one study among men who have sex with men (MSM), and included different ethnic groups. All studies had included main HIV risk groups (PWID, MSM), based on HIV acquisition mode or reported risk-behavior. The risky sexual behavior of participants varied greatly, because two studies (The Healthy Living Project Team 2007, Safren *et al.* 2013) had only recruited people reporting prior sexual acts not protected with condom (in past 3 months), while others had no precondition of recent sexual activity. Overall, the quality of evidence in the studies included was relatively low, even when ignoring blinding of participants and providers which is not possible in behavioral intervention studies. Only two of the five studies had low risk of bias (Safren *et al.* 2013, Kurth *et al.* 2014).

No evidence was available about the effect of sexual risk reduction intervention(s) on the more objective *biological measures of sexual risk behavior*, as none of the studies included in the review measured sexually transmitted infection (STI) and/or hepatitis B acquisition. Although all the predefined (for the review) *behavioral effect measures* were likely recorded in all of the 5 selected studies, judging from the list of characteristics reported for study participants at baseline or described in other parts of the publications, filling in the data gaps (by contacting the corresponding authors of the publications) failed. Thus, the intervention effect analysis for each of the outcome measures was based on less than 5 studies, reducing the ability to draw extensive conclusions on the effect of the intervention(s). Three different quality and size studies evaluated the intervention effect on the *number of condomless sexual acts*, yet failed to support the interventions (The Healthy Living Project Team 2007, Cornman *et al.* 2008, Safren *et al.* 2013).

The following results supporting sexual risk reduction interventions (Table 3), based on the selected for the review effect measures, were obtained from studies by:

- (i) Gilbert and colleagues, where a statistically significant difference between the study arms in reduction in the mean *number of casual sex partners* (among those who completed the study) was observed [-2.7 (SD 8.4) in the intervention group versus -0.6 (SD 5.6) in the comparison group; $p = 0.042$] (Gilbert *et al.* 2008);
- (ii) Kurth and colleagues, where sexual risk behavior change was assessed through *condom use consistency*, and the odds of not always using a condom (a dichotomized outcome) in HIV transmission risk acts was lower in the intervention group than in the control group (OR = 0.46, 95% CI 0.25–0.84, $p = 0.012$) (Kurth *et al.* 2014);
- (iii) The Healthy Living Project team, where the difference between the mean *number of sexual transmission risk acts* was not significant in the study groups at study end (month 25), yet had been statistically significant when measured at months 15 and 20 (The Healthy Living Project Team 2007).

Table 3. Characteristics of systematic review studies with interventions reducing sexual risk behavior (to be continued)

Study	Setting(s) and study period	Sample characteristics	Intervention design	Intervention description	Sexual outcomes
Gilbert <i>et al.</i> 2008	5 outpatient HIV clinics; San Francisco Bay Area, US <i>Study period:</i> 12.2003–09.2006	HIV-infected (≥ 3 mo); receiving HIV care <i>no precondition of sexual activity, and only had to report at least 1 of 3 risk behaviors (alcohol, drugs, sex) for sexual risk behavior past 3 months</i> (n = 476) ≥ 18 years old, mean age 44.1 years (SD 9.09) ^a ; 51% male; 29% white / 50% black/African-American / 13% Hispanic/Latino / 8% other; 51% reported MSM/W ^b / 16% IDU-related HIV acquisition; data on ART not provided	RCT (2 arms, 2:1) <i>Intervention:</i> Behavioral intervention; multitopic <i>Level:</i> Individual <i>Provision:</i> Interactive computer program, using Motivational Interviewing approach <i>Intensity-duration:</i> Average 24 min session prior to regularly scheduled medical appointment with booster at 3 months; post-session doctor-patient discussion (based on computer-suggested risk counseling statements) during medical appointment; behavioral assignment (take-away) <i>Follow-up (post intervention):</i> 3 months <i>Data collection:</i> baseline, months 3, 6	<i>Aim:</i> Reduce illicit drug-use, risky alcohol consumption and condomless vaginal/anal sexual acts <i>Theoretical basis:</i> N/A <i>Intervention group</i> (n = 243): Positive Choice intervention with computer-based risk assessment preceding tailored "Video Doctor" risk reduction counseling session; printout of behavioral assignment and referrals to substance use and harm-reduction services <i>Comparison group</i> (n = 233): Computer-based risk assessment, followed by standard care, risk counseling at providers' discretion	Sexual risk, measured by: (1) 100% (consistently) / < 100% (inconsistently) using condom during last 3 months with main and/or casual partner(s); (2) % of condomless vaginal/anal sexual acts (stat.sign) ↑ condom use, all partners: trend in both arms, no difference between arms (2) no. of sexual partners: ↓ no. of casual partners (SIGN ^c)
Kurth <i>et al.</i> 2014	HIV clinic and community setting; Seattle, WA, US <i>Study period:</i> 03.2006–07.2007	HIV-infected, on ART <i>no precondition of sexual activity, past ? months</i> (n = 240) ≥ 18 years old; mean age 45 (SD 10.37) ^a years; 91% male; 46% white / 25% black or African American / 7% Hispanic/Latino, 22% other; 62% MSM; 11% PWID Participation rate 80%, overall retention 87%	RCT (2 arms) <i>Intervention:</i> Behavioral intervention; multitopic <i>Level:</i> Individual <i>Provision:</i> Computerized, personal, using motivational interviewing and social cognitive techniques <i>Intensity-duration:</i> 4 sessions with 3-month intervals; during 9 months <i>Follow-up:</i> 9 months <i>Data collection:</i> at baseline and months 3, 6, 9	<i>Aim:</i> Reduce HIV transmission risk and support ART adherence <i>Theoretical basis:</i> Information-Motivation-Behavioral Skills Model, Transtheoretical Model of Change <i>Intervention group</i> (n = 120): computerized CARE+ ^c (audio-narrated assessment, tailored feedback, skill-building videos, health plan, and print-out) plus standard care <i>Comparison group</i> (n = 120): computerized risk assessment plus standard care	Transmission risk composite outcome, incl. no condom use or condom use with problems/errors (past 3 months) and ART adherence (30 days): ↓ odds of transmiss.risk 0.55 lower at mo 9 compared to baseline in intervention group (stat.sign), while ↑ in control group; ↓ odds of transmiss.risk based on condom use consistency (SIGN ^c)

Table 3. Characteristics of systematic review studies with interventions reducing sexual risk behavior (continued)

Study	Setting(s) and study period	Sample characteristics	Intervention design	Intervention description	Sexual outcomes
The Healthy Living Project Team 2007	HIV clinics and other community settings; 4 US cities (Los Angeles, CA; Milwaukee, WI; New York, NY; San Francisco, CA); <i>Study period:</i> 04.2000–02.2004 recruitment 04.2000–01.2002	HIV-infected (women, MSM, PWID; at later stage also heterosexual men) considered at risk of sexually transmitting HIV; <i>eligible only: if reported at least 1 condomless sex act in past 3 months: with any HIV-? partner OR HIV+ partner other than main</i> (n = 936) ≥ 18 years old, mean age 39.8 years (range 19–67 years); 79% male (of whom 72% MSM); 32% white / 45% African-American / 15% Hispanic / 8% other; 12% PWID / 70% not PWID; 69% on ART Participation rate 87%, overall retention 83%	RCT (2 arms) <i>Intervention:</i> Behavioral intervention; multitopic <i>Level:</i> Individual <i>Provision:</i> Facilitators (social workers, therapists, community-based service providers) face-to-face, using cognitive-behavioral techniques <i>Intensity-duration:</i> 15 sessions (90 min each); during 12 months <i>Follow-up (post intervention):</i> appr 13 months <i>Data collection:</i> baseline and months 5, 10, 15, 20, 25	<i>Aim:</i> Reduce number of sexual risk acts; execute effective coping responses; enhance access and adherence to medical services and Theory <i>Theoretical basis:</i> Social Action <i>Intervention group</i> (n = 467): 3 modules (safer behaviors; stress, coping and adjustment; health behaviors) <i>Comparison group</i> (n = 469): No active psychosocial intervention (on waitlist)	Transmission risk, measured by no. of condomless sexual risk acts during last 3 months with HIV-/? partner(s); ↓ mean no. of sex risk acts with HIV-/? partners (SIGN ^c at mo 15 and 20); ↓ no. of sex risk acts with HIV-/? partners from baseline; observed in both arms, no difference between arms

^a Total sample mean age (SD) calculated by review authors based on means (SDs) of different study arms

^b MSM/W: men having sex with men and women

^c SIGN: changes in outcomes between the intervention and the comparison group statistically significant ($p \leq 0.05$)

^d CARE+: Computer Assessment & Rx Education for PLHIV

Still, the evidence should be interpreted with some caution due to the relatively low quality of the Gilbert study (Gilbert *et al.* 2008), and one other study (in addition to the one conducted by Kurth and colleagues) reporting on *condom use consistency* (Safren *et al.* 2013) that failed to demonstrate ‘positive’ intervention effect.

5.4. People living with HIV engagement in HIV care in Estonia (PAPER IV)

According to UNAIDS most recent (when conducting the study) estimation there were 8 628 (6 941–10 783) PLHIV in Estonia in 2013 (AIDSinfo 2014). A total of 8 605 new HIV cases had been registered in Estonia from 1988 to 31.08.2013 (the end of our study period) according to the Estonian Health Board (EHB 2013). However, taking into account the potential multiple registration of new cases until 2009, and the AIDS and IDU related deaths among PLHIV over the years, we calculated that 5 077 to 7 424, mean 6 251 individuals diagnosed with HIV had been living in Estonia at our study end. Hence, altogether 72% (47–100%) of the 8 628 PLHIV estimated to live in Estonia in 2013 had been diagnosed with HIV.

Since the inception of the Estonian Health Insurance Fund (EHIF) electronic database of medical claims in 2000, altogether 4 375 HIV-positive patients (alive by the end of our study) had received at least one HIV-related medical service by designated HIV medical care provider(s). According to these data, 51% (41–63%) of the 8 628 HIV-positive people estimated to live in Estonia in 2013 were considered to have ever accessed i.e., been linked to HIV medical care (by our study end).

In the past year (01.09.2012–31.08.2013) according to EHIF 1 855 PLHIV had received HIV-related healthcare at least twice, and at least 3 months apart. This translates into 21% (17–27%) of the total 8 628 HIV-positive people estimated to live in Estonia in 2013 being retained in HIV care in 2013.

Based on data obtained from the Estonian HIV-Positive Patients Database (E-HIV), 82% of PLHIV considered retained in care (1 022 of 1 250) were also receiving ART. Applying this proportion to EHIF data, an estimated 1 521 of PLHIV retained in care according to EHIF in 2013 could also have received ART. Altogether, this translates into 18% (14–22%) of the 8 628 HIV-positive people estimated to live in Estonia in 2013 receiving ART in 2013.

E-HIV included at least one viral load test result for the study period for 1 021 of the 1 022 PLHIV continuously in care and on ART. Of these, 70% (712) had achieved viral suppression (HIV RNA < 200 copies/mL) in their most recent test. Applying this proportion to EHIF data, we estimated that 1 065 of PLHIV continuously in care and on ART according to EHIF had achieved viral suppression. This would translate into 12% (10–15%) of all 8 628 HIV-positive people estimated to live in Estonia in 2013 having achieved viral suppression.

When looking at the timing of PLHIV linkage to HIV care, according to E-HIV 111 individuals had been newly diagnosed with HIV during the study period (1.09.2012–31.08.2013). Excluding patients with missing data, and allowing all patients the optimal 90 days to reach HIV care, we found that 86% of those newly diagnosed (74 patients of 86) had accessed HIV care within 90 days of testing positive for HIV. At the same time, regardless of how long it had taken people diagnosed with HIV to access HIV medical care, more than half (62%) of those registered during the past year (n = 90), had had a CD4 cell count ≤ 350 cells/mm³ at registration.

6. DISCUSSION

6.1. People living with HIV engagement in HIV care in Estonia

The HIV care cascade model allows to map PLHIV at certain steps in the continuum of care and define the proportion that has achieved the ultimate goal of HIV care – viral suppression. This should translate into understanding where interventions to improve coverage with care are needed foremost (Medland *et al.* 2015). In Estonia, as in other countries where engagement in HIV care has been evaluated, PLHIV were “lost” at each step of care, and in 2013 only 12% (10–15%) of all the 8 628 (6 941–10 783) HIV-positive people estimated to live in Estonia had achieved viral suppression. Engagement in care at the different steps of the HIV care cascade in Estonia in 2013 most resembled that recently described in Georgia (Raymond *et al.* 2014), a country with similar politico-economic history and HIV epidemic, driven by injection drug use until 2011 (UNAIDS 2014d). Regarding the ultimate goal for PLHIV in HIV care (i.e., viral suppression), large disparities in the world, apparent also within Europe, have been recently described: while in Western European countries over 50% of PLHIV were virally suppressed, in Eastern European countries this proportion remained below 20% (Levi *et al.* 2015).

According to our study, in Estonia the main gaps in HIV care in 2013 were:

- (i) about $\frac{1}{4}$ of the 8 628 persons estimated to live with HIV had not been diagnosed with HIV;
- (ii) another $\frac{1}{4}$, although aware of their HIV-positive serostatus, had not accessed HIV medical care;
- (iii) over $\frac{1}{2}$ of PLHIV, having accessed HIV medical care from an infectious disease specialist after diagnosis, were not retained in care.

With a quarter of PLHIV unaware of their HIV status, HIV testing appeared to be the primary bottleneck in reaching the UNAIDS HIV care coverage targets in Estonia. Also the issue of PLHIV not accessing applicable care after diagnosis was likely related to testing i.e., the current counseling and referral to care procedures and practices (WHO Regional Office for Europe 2014). Our research also revealed that even for PHIV linked to specialized care within 3 months of the diagnosis, this timely linkage often occurred too late in the course of the disease, given the low CD4 cell counts of PLHIV at initiation of specialist care (62% with ≤ 350 cells/mm³). Late linkage to care seemed to be related to delayed testing for HIV, supporting the need to evaluate the current HIV testing policies in Estonia to better reach all key settings and populations with effective services (WHO Regional Office for Europe 2014, UNAIDS 2015b). Whereas according to national recommendations, in 2013 HIV testing was mandatory for blood and organ donors (and in some cases for people in the armed forces) and recommended for several risk groups (including pregnant women, prisoners,

people with hepatitis, tuberculosis, sexually transmitted diseases, and a history of injection drug use or engagement in risky sexual behaviors) (Rüütel *et al.* 2011), screening only these target groups would not suffice. Recent local guidelines also recommended routine HIV screening for all outpatients aged 16–49 in healthcare facilities in regions most affected by HIV in Estonia (EMSA 2012), yet a 2014 HIV treatment and care evaluation by WHO uncovered that healthcare providers in Estonia were experiencing challenges in following these guidelines due to lack of training and support (WHO Regional Office for Europe 2014). In Estonia, in addition to enhancing routine HIV testing, more emphasis on groups most at risk of acquiring HIV could also facilitate earlier diagnosis (WHO 2014a), as a recent study among PWID, the key HIV risk population in Estonia, revealed that only a third of supposedly HIV-negative respondents had taken a HIV-test in the past year (Vorobjov *et al.* 2015). Thus, focusing on the recently introduced option of HIV testing in settings frequently attended by PWID (i.e., needle and syringe exchange sites), could augment HIV testing among PWID in Estonia. Also new testing options (e.g., HIV self-testing) could be considered in addition to the existing practices in Estonia (UNAIDS 2015b).

Our research also revealed that in Estonia 58% of PLHIV who had accessed HIV medical care at least once after being diagnosed with HIV, were not retained in care in 2013. In absolute terms i.e., based on the number of PLHIV “lost” between any two steps in the care cascade, retention was the biggest issue in HIV care in Estonia in 2013. However, unlike the relatively “strict” definition for ‘retained in care’, applied in our study (Ford & Spicer 2012), Europe (ECDC) seems to be heading towards a more “permissive” approach in monitoring PLHIV retention in HIV care – considering at least one medical care visit per year (in consecutive years) sufficient for PLHIV to be defined as ‘retained in care’ (WHO 2014b, ECDC 2015c). Altogether, we believe that getting tested/diagnosed was the main issue in HIV care in Estonia in 2013. Also, the 2015 recommendation to prescribe ART to all PLHIV upon diagnosis, introduced by all major international HIV treatment guidelines by the end of the year (DHHS 2015, EACS 2015, IAPAC 2015, WHO 2015a) should rapidly scale up ART distribution, and thus retention as an independent step in the HIV care cascade will likely lose value. In our study, had we considered all PLHIV on ART (according to our Ministry of Social Affairs, the coordinator of ART in Estonia) “automatically” also ‘retained in care’, the public health significance of the retention issue in Estonia would have also decreased remarkably.

We acknowledge several limitations of the HIV care cascade analysis. First, as the true number of people infected with HIV in Estonia is not known, the UNAIDS Spectrum estimate was applied (AIDSinfo 2014). However, the estimates for the following steps in the HIV care cascade are very sensitive to the HIV prevalence estimate. Secondly, the different sources of data about PLHIV and services provided to them were established at different times, for different purposes, by different institutions. Data availability was the main obstacle to mapping HIV care, as also recognized by other researchers (Haber *et al.* 2016).

Although we applied carefully constructed case-finding algorithms to identify HIV-positive individuals from all the health administrative databases, some cases may have been misclassified. However, we believe that the nationwide coverage of the Estonian Health Insurance Fund (EHIF), and the Estonian Health Board (EHB) strengthen our analysis. In particular, we considered EHIF data (used to derive population based estimates on medical care linkage, retention and ART coverage) relatively complete, as EHIF reimburses healthcare providers on a fee-for-service basis. However, none of the databases included all the information needed to characterize PLHIV at all the steps of HIV care in Estonia, and therefore several assumptions, and data extrapolation from one database to another (to obtain a population-based estimate) had to be made. While these limitations were important, we feel it is extremely unlikely that they created the patterns that we observed in the data.

6.2. Antiretroviral therapy adherence and factors associated with it among HIV-positive adults receiving HIV medical care in Estonia

The proportion of people virally suppressed among all people living with HIV is often viewed as the main indicator for the success of HIV care. While combined ART enables to achieve viral suppression, only adhering to the therapy enables to maintain it.

In our study vast majority of PLHIV (88%, 95% CI 81–92%) self-reported 100% ART adherence in past 3 days. This high rate was in line with findings from studies in other countries, with self-reported adherence among vulnerable populations (including people using drugs) ranging from 84–97% (Walsh & Sherr 2002, Giordano *et al.* 2004, Oyugi *et al.* 2004, Amico *et al.* 2005). It has been suggested that by self-report patients tend to overestimate adherence (Chesney *et al.* 2000), also likely in our study mostly due to social desirability bias. Despite the efforts to minimize the bias, we still suspect some adherence over-reporting in our study, as 40% of “perfect adherers” by self-report were not virally suppressed.

Although the cross-sectional data did not allow causal analysis, we were able to study ART adherence association with several potential adherence determinants. We found that general health status, measured as self-rated health, was a correlate to ART nonadherence. Participants rating their health less than good were more likely to be nonadherent. However, the few previous studies that have assessed this association, have derived conflicting results on whether lower self-rated health is a risk factor for (Cardarelli *et al.* 2008) or protective against (Christofides *et al.* 2006) nonadherence. In our study nonadherence was also associated with higher ART concerns, in line with previous studies where nonadherence has been linked to concerns about medication side effects (Johnson *et al.* 2011, Langebeek *et al.* 2014) and long-term toxicities, scheduling demands

and personal capacity to adhere, concerns about the impact of ART on self-identity, and the possibility that taking treatment might lead to disclosure of the one's HIV status (Gonzales *et al.* 2007, Langebeek *et al.* 2014).

In our study we found no relation between ART adherence and drug use, consistent with growing international evidence (Carrieri *et al.* 2003, Malta *et al.* 2010, Walsh *et al.* 2014). In the context of the Estonian mainly IDU-driven HIV epidemic this finding hopefully helps to refute the myth that drug-users are less likely to adhere to ART (Beyrer *et al.* 2010), and affects positively the treatment decisions made by HIV medical care providers in Estonia.

In the same cohort of patients at Ida-Viru Central hospital, among the 75 individuals who had been randomized to the intervention arm in the RCT evaluating the ART adherence support intervention developed for Estonia, medication side-effects as a barrier to adherence were also brought up most frequently by the patients (44%) in the first intervention counseling session.

Our study participants, PLHIV treated at Ida-Viru Central Hospital, serving about 1/5 of PLHIV in care in Estonia at the time of the study, did not differ significantly from HIV-positive patients in care in Estonia in general, except to some extent with regards to age, and the profile of HIV disease diagnoses (EHIF 2011). However, using the nonprobability sample may have limited the representativeness and generalizability of our findings. Due to the small study sample size, with the relatively small proportion of participants reporting non-perfect adherence, some of our measures of association may have lacked statistical significance simply due to insufficient power or data cell sparsity. While appropriate statistical methods were adopted to account for the low cell counts, generalizability to larger populations of nonadherent individuals, who may only infrequently attend the clinic, was clearly limited.

6.3. A feasible evidence-based antiretroviral therapy adherence support program tailored to HIV-positive adults receiving HIV medical care in Estonia

The importance of building an intervention on both theory and empirical evidence has been well recognized (Bartholomew *et al.* 2006, Craig *et al.* 2008). We followed Intervention Mapping (IM) as a framework to keep the program objectives and activities grounded on both theory and evidence, and not to lose focus of both the target population and the program development process (Kok *et al.* 2004). From start, we also recognized the importance of having a multi-disciplinary team (WHO 2003, Bartholomew *et al.* 2006, Rueda *et al.* 2006), as no single specialist would have possessed expertise to cover all the methodological and practical issues of the complex topic of ART adherence within the local environment and medical care system.

One prerequisite for developing any intervention is assessing the need(s) of the target population – in our case, PLHIV in HIV care and on ART in Estonia.

Although the issue of low treatment adherence was first recognized by service providers, focus group interviews were essential to understand the patient perspective of adhering to HIV treatment.

Our research program began with what we identified as a minimum intensity intervention with high generalizability due to low use of resources, as we were most interested in identifying promising interventions with immediate application to our clinical care environments. The theoretical basis for our program i.e., the Intervention-Motivation-Behavioral Skills model of adherence, and all the strategies applied had either been tested in other ART adherence interventions (Sabin *et al.* 2010) or recommended by professional organizations or other researchers (APA 1997, Simoni *et al.* 2003, Jani 2004, Rueda *et al.* 2006, Chesney 2015). Although several intervention approaches were reviewed and other(s) could have been adapted to our setting, Next Step Counseling was selected due to flexibility and focus on facilitators to and experiences with adherence (versus focusing on barriers). The feasibility, acceptability, and fidelity of the intervention were evaluated alongside with the intervention effect (compared to standard adherence support in the RCT) outside the scope of this work. However, in initial spontaneous feedback from the study site the clinic personnel did not complain about excessive intervention-related work load, but reported better understanding of their patients through enhanced communication. The nurse counselors also reported feeling rewarded by the “Aha!” effect their explanations about HIV and ART generated in many counseled patients.

6.4. Systematically identified and synthesized evidence for supporting safe sexual behavior among HIV-positive adults receiving HIV medical care in Estonia

We conducted a meticulous search for research published since the era of HIV began in 1981, with terms addressing all the main concepts of our review question, and feel confident that located all the available studies. However, only 5 studies of behavioral interventions for adult PLHIV that were provided on individual level by caregivers in HIV care settings and promoted safe sexual behavior, met our review criteria (The Healthy Living Project Team 2007, Cornman *et al.* 2008, Gilbert *et al.* 2008, Safren *et al.* 2013, Kurth *et al.* 2014). The small number of intervention trials focusing on PLHIV was unexpected, though in line with findings from a previous review (Johnson *et al.* 2006). Although RCTs provide the strongest evidence regarding the efficacy of HIV risk-reduction interventions, we admit that including studies with other minimally biased methods of assigning participants to study arms may have added valuable evidence. We also excluded many studies from our review because of group-level interventions or using peer(s) as intervention provider(s), as requiring patients to attend extra sessions at the clinic (for pre-scheduled group meetings)

or additional human resources (peers present during clinic opening hours). Choosing individual level interventions was justified by the need to fit the intervention into busy HIV clinic situations during routine interactions with patients, potentially combining the sexual behavior intervention with the ART adherence intervention developed for Estonia. However, in HIV clinics with more and different specialty care providers (including peer counselors) available, more diverse interventions could better meet the needs of PLHIV.

Our ability to draw conclusions was further limited by the quality of evidence. Although currently 3 of the 5 studies included in our review (The Healthy Living Project Team 2007, Gilbert *et al.* 2008, Kurth *et al.* 2014) have been considered ‘best evidence’ by the CDC’s HIV/AIDS Prevention Research Synthesis Project (CDC 2016b), we had several concerns about the risk of bias in 2 of these studies (The Healthy Living Project Team 2007, Gilbert *et al.* 2008). This discrepancy likely derives from a more rigorous risk of bias evaluation in our study, following the Cochrane systematic review methodology (Higgins & Green 2011).

Although we looked at one outcome – sexual risk behavior reduction, we allowed multiple measures from one study, thus maybe “diluting” the intervention effect to some extent. Also definitions for the outcome measures varied across the studies, e.g., a HIV transmission risk act was defined either as a sexual act with a serodiscordant partner when a condom was not used, or an act when a condom was either not used or used with a problem/error, despite the latter perhaps suggesting low condom use skills rather than willingness to use a condom.

To support safe sexual behavior among PLHIV, we found evidence on the intervention reducing the *number of (casual) sexual partners* in one study with relatively low quality (Gilbert *et al.* 2008). Regarding *condom use consistency*, results from two studies (Safren *et al.* 2013, Kurth *et al.* 2014) were contradictory, yet good quality evidence from one of the studies (Kurth *et al.* 2014) suggested that an individual behavioral intervention aimed at sexual risk reduction is likely to increase safe practices. The complex nature of the dichotomous ‘always/not always using a condom’ measure (i.e., *condom use consistency*) might have affected the “negative” result of the other study (Safren *et al.* 2013), as PLHIV in the intervention group having never or seldom used a condom prior to the study might have started to use condoms sometimes, but not in 100% of sexual acts and were thus still considered not consistently using condoms at follow-up, despite the potentially “positive” effect of the intervention and sexual risk behavior reduction among study participants in the intervention group. Although in one of the studies (The Healthy Living Project Team 2007) the intervention effect did not last till study end, interim analysis at study months 15 and 20 deducted reduction in the *number of sexual transmission risk acts* (i.e., acts with a partner with HIV-negative or unknown sero-status). It is important to note that the other 4 studies had only run for 6–12 months. Still, the intensity of the Healthy Living Project intervention (15

sessions a year, 90 minutes each) is likely to limit the applicability of this intervention in busy HIV clinic situations.

Two of the three interventions found to reduce sexual risk behavior among PLHIV in our review (Gilbert *et al.* 2008, Kurth *et al.* 2014) could be considered for adaptation in Estonia. Although both the interventions were multi-topic, the issues addressed in addition to sexual risk behavior would also be relevant in Estonia – ART adherence (Kurth *et al.* 2014), and illicit drug-use and alcohol consumption (Gilbert *et al.* 2008). Despite that both the interventions were computerized, this should not limit their application in HIV medical care settings in Estonia.

Although we were not overwhelmed with good quality evidence, we still strongly believe that regular interactions between care providers and PLHIV in HIV care setting provide valuable opportunities for evidence-based sexual risk reduction interventions (Flickinger *et al.* 2013), as also recognized in the United States, where HIV care providers are advised to take any opportunity for brief HIV-related risk behavior reduction interventions whenever a patient with HIV visits (CDC *et al.* 2003).

7. CONCLUSIONS

1. In Estonia, in 2013 people living with HIV (PLHIV) were “lost” to care at each step of the HIV care cascade, and only 12% (10–15%) of all the 8 628 (6 941–10 783) HIV-positive people estimated to live in Estonia had achieved viral suppression. The main gaps in HIV care in 2013 were that about a quarter of PLHIV had not been diagnosed with HIV, and over half of PLHIV who had accessed HIV medical care from an infectious disease specialist after diagnosis, were not retained in care. With HIV testing (including late testing) as the primary bottleneck in HIV care in Estonia, in addition to enhancing routine HIV testing (including the current counseling and referral to care procedures and practices), more emphasis on groups most at risk of acquiring HIV and key settings could facilitate (earlier) testing for HIV.
2. In Estonia, adult PLHIV receiving HIV care including antiretroviral therapy (ART) in an area with high prevalence of injection drug use, self-reported ART adherence rates were high despite low viral suppression. Adherence was most strongly associated with perceived health status and beliefs about the consequences of ART. Nonadherence was not differentially higher among people who inject drugs. Adherence support programs or approaches may be most effective if they target beliefs about ART necessity and efficacy, concerns about side effects and long-term toxicities.
3. A feasible evidence-based ART adherence support intervention was developed, tailored to the needs of HIV-positive adults in HIV medical care in Estonia, transferable to all medical institutions providing HIV/AIDS care in Estonia and potentially abroad to other countries with similar socio-economic history and HIV epidemic evolution. The intervention would fit into the daily routine of a clinic as could be performed in a relatively short amount of time and thus added to other routine interactions with patients in the clinic, would reach the patients when they attend the clinic and not require additional visits, and would not (in most part) require extra staff.
4. Research on behavioral interventions supporting safe sexual behavior among adult PLHIV in HIV care was systematically searched and synthesized. Two interventions, provided on individual level by caregivers in HIV care settings and applicable to the local epidemiological and healthcare context in Estonia, and potentially in other countries with similar socio-economic and HIV epidemiologic history, were identified. One of the interventions resulted in significant increase in condom use consistency in HIV transmission risk acts, and the other reduced the number of casual sexual partners of PLHIV.

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SUMMARY IN ESTONIAN

HIV-positiivsed inimesed Eestis: hõlmatus raviteenustega ning antiretroviirusravi soostumust ja turvalist seksuaalkäitumist toetavad sekkumised

2014. aastal elas maailmas hinnanguliselt ligi 37 miljonit HIVi nakatunud inimest, samas oli HIVi-epideemia tõttu ligi nelja kümnendi jooksul surnud üle 39 miljoni inimese (UNAIDS 2014a, UNAIDS 2015a). Tänapäeval on olemas tõhus HIV-infektsiooni vastane ravi – kombineeritud antiretroviirusravi (ARV-ravi) – ning tänu sellele on HIV-infektsioon muutunud ägedast haigusest krooniliseks. 2015. aastal sai maailmas kõigest HIVi nakatunud inimestest ARV-ravi hinnanguliselt ligi 15,8 miljonit (UNAIDS 2015a, UNAIDS 2015b) ning kokku oli ARV-ravi käesoleval aastatuhandel päästnud ligi 7,8 miljoni inimese elu (Fauci & Marston 2015). ARV-ravi ei ole elulise tähtsusega mitte üksnes juba HIVi nakatunud inimesele, vaid see vähendab olulisel määral ka viiruse ülekande tõenäosust teistele (Altice jt 2001, WHO 2003, Mannheimer jt 2005, Chesney 2006, Ray jt 2010, Cohen jt 2011, WHO 2015a). Et ARV-ravi viirust lõplikult ei hävita (Lorenzo-Redondo jt 2016), ei ole HIVi leviku tõkestamisel vähenenud ka HIV-positiivsete inimeste turvalise seksuaalkäitumise olulisus (Kennedy jt 2010, Mermin 2011, Lasry jt 2012). Viimasel ajal on HIVi-vastases võitluses nihkunud fookus HIV-negatiivsetelt inimestelt HIV-positiivsetele, sest rahvatervishoiu vaatevinklist on epideemia tõkestamiseks tõhusam keskenduda pigem suhteliselt väiksemale HIVi nakatunud kui suuremale mitte veel nakatunud osale rahvastikust (Kennedy jt 2010, Mermin 2011, Lasry jt 2012). Ühinenud Rahvaste Organisatsiooni HIVi-AIDSi ühendprogrammis (UNAIDS) seati 2014. aastal HIVi-vastasele võitlusele uued ambitsioonikad eesmärgid: 90% HIVi nakatunud inimestest peaks olema oma (sero)staatusest teadlikud ehk saanud HIVi diagnoosi, 90% HIVi diagnoosiga inimestest peaks saama ARV-ravi ning 90% ravisaajaist peaks olema saavutanud HI-viiruse üle kontrolli ehk viirus-supressiooni. UNAIDSi prognoos näitab, et kui need eesmärgid suudetakse 2020. aastaks täita, on võimalik maailmas 2030. aastaks HIVi-epideemiale piir panna (UNAIDS 2014b, UNAIDS 2014c).

Tänapäeval peaks inimene HIVi nakatumise järel sujuvalt asjakohaste raviteenusteni jõudma ning mõne aja möödudes HIVi üle kontrolli saavutama. Rahvusvahelised uuringud on aga näidanud, et märgatav osa HIV-positiivseid inimesi langeb sellest (ravi)protsessist (ingl *continuum*) eri ajal ning erinevatel põhjustel välja. Viimastel aastatel on HIVi-vastase võitluse tulemuslikkuse hindamisel järjest enam kasutatud Ameerika Ühendriikides 2011. aastal E. Gardneri ja kolleegide väljatöötatud HIVi raviastmestiku mudelit (Gardner jt 2011), et mõõta HIV-positiivsete inimeste hõlmatus HIVi raviteenustega selle mudeli eri astmetel (Helleberg jt 2013, Pokrovskaya jt 2014, Raymond jt 2014, Levi jt 2015, Medland jt 2015). Nii on lisaks ravile ning laiemalt kõigi HIVi korral näidustatud tervishoiuteenuste olemasolule vaja tagada neile ka juurdepääs ning igati toetada nende teenuste kasutamist (Nosyk jt 2014). Näiteks tuleb ARV-ravimeid

võtta elu lõpuni iga päev mitu korda. Aja jooksul võib see HIV-positiivsele inimesele parimagi teadlikkuse ja tahtmise korral osutada väljakutseks, mistõttu on välja töötatud ravisoostumust toetavad meetodid ja sekkumised. Neist optimaalse valimine eeldab aga head ülevaadet nii kohalikest oludest kui ka HIV-positiivsete inimeste vajadustest.

Kuigi Eestis on esmashaigestumus HIVi alates 2006. aastast pidevalt vähenenud, oli Eesti 2014. aastal Euroopa Liidus ning Euroopa Majanduspiirkonnas 22,1 esmaselt registreeritud HIVi-juhuga 100 000 inimese kohta jätkuvalt esikohal (ECDC/WHO Regional Office for Europe 2015). HIVi ravi (sh ARV-ravi) on Eestis kõigile seda vajavatele HIV-positiivsetele inimestele tervisekindlustuse olemasolust sõltumata kättesaadav ja tasuta (Laisaar jt 2011, IV publikatsioon).

Doktoritöö üldeesmärk oli kirjeldada HIV-positiivsete inimeste kaasatust HIVi ravisse (sh soostumust ARV-raviga) Eestis ning töötada välja täiskasvanud HIV-positiivsetele ARV-ravil olevatele inimestele ravisoostumust ja turvalist seksuaalkäitumist toetavad sekkumised.

Uurimistöö alaeesmärgid:

- 1) kirjeldada ja hinnata Eestis elavate HIV-positiivsete inimeste hõlmatust asjakohaste tervishoiuteenustega (sh ARV-raviga) ning teha kindlaks peamised lüngad tervishoiuteenuste osutamisel, et aidata kaasa süsteemi parendamisele (IV publikatsioon);
- 2) kirjeldada ja hinnata Eestis ARV-ravi saavate HIV-positiivsete täiskasvanute ravisoostumust ja sellega seotud tegureid (I ja II publikatsioon);
- 3) töötada välja Eestis elavate HIV-positiivsete ARV-ravi saavate ja alustavate täiskasvanute vajadustele vastav ning ravisüsteemi võimalusi arvestav tõendus põhine ravisoostumust toetav sekkumine, mis oleks rakendatav ka teistes sarnase HIVi-epideemia ning sotsiaalmajandusliku taustaga riikides (I publikatsioon);
- 4) töötada süstemaatiliselt läbi uuringud, mis on keskendunud ravi saavate HIV-positiivsete täiskasvanute turvalist seksuaalkäitumist toetavatele raviteenuste osutajate poolt individuaalselt rakendatud sekkumistele; võtta need tulemused kokku, et valida välja tõhusad sekkumised, mis sobiksid kasutamiseks Eesti raviasutustes ning tõenäoliselt ka teistes sarnase HIVi-epideemia ning sotsiaalmajandusliku taustaga riikides (III publikatsioon).

Uurimistöö metoodika

Uurimistööd juhtis Tartu Ülikooli peremeditsiini ja rahvatervishoiu instituudi HIVi-AIDSi teadusrühm. Uurimistöö algas 2010. aastal Eesti HIVi-epideemia ning riiklike ja muude eelneva kümnendi (2000–2009) jooksul rakendatud vastumeetmete (HIVi-testimisest ARV-ravini) väljaselgitamisega ning Eesti ja teiste Ida-Euroopa riikide olukorra võrdlemisega. Selle töö tulemusi (Laisaar jt 2011) on kasutatud käesoleva uurimistöö kirjanduse ülevaates.

Tõenduspõhise ja Eestis HIVi ravi saavate täiskasvanute vajadustele ning tervishoiusüsteemi võimalustele kohandatud ARV-ravi soostumust toetav sekkumine töötati välja aastail 2010–2011 korraldatud uuringu käigus, tuginedes sekkumisraamistikule (ingl *Intervention Mapping*, IM) (Bartholomew jt 2006, Kok jt 2004), kombineerides kvalitatiivseid ja kvantitatiivseid andmete kogumise ja sünteesi meetodeid. IM-protokoll koosnes kuuest astmest: 1) sihtrühma (täiskasvanud HIV-positiivsed ARV-ravi saajad Eestis) vajaduste väljaselgitamine, 2) sekkumisprogrammile (lõpp)eesmärkide seadmine, 3) sobivate meetodite (teooriate) ja rakenduste valimine, 4) sekkumise (kitsamas mõttes) väljatöötamine, 5) sekkumisprogrammi rakendusplaani koostamine ja programmi elluviimine, 6) sekkumisprogrammi hindamine. Kõigil IM-raamistiku etappidel kasutasime järgmisi andmekäitluse meetodeid: elektroonilises informatsioonis kättesaadava kirjanduse ülevaate koostamine; ARV-ravi soostumusest arusaamade ja ARV-ravi soostumuse mõjurite väljaselgitamine (intervjuud ravi saanud HIV-positiivsete inimestega ja raviteenuse pakkujatega Ida-Viru maakonnas); kogutud andmete analüüs multidistsiplinaarse uuringumeeskonna arutelude (kohtumiste ja telekonverentside) käigus ning individuaalselt. (I publikatsioon)

ARV-ravi soostumuse määra ning sellega seotud tegurite kohta Eestis saadi andmed läbilõikelisest uuringust, mis korraldati 2010. aastal Ida-Viru Keskhaiglas ARV-ravi saajate seas. Uuritavate ravisoostumust mõõdeti nende endi hinnangul viimase kolme päeva jooksul võtmata jäänud ravimiannuste alusel (Chesney jt 2000). Statistilises analüüsis oli peamiseks tulemiks raviga mittesoostumine: uuritav arvati mittesoostujaks, kui ta ei olnud võtnud kõiki ravimiannuseid õigel ajal. Standardiseeritud küsimustiku alusel korraldatud küsitluse käigus koguti uuritavate sotsiaaldemograafilised, HIV-infektsiooni ja ravikogemuse, narkootikumide tarvitamise jm andmed, mida võrreldi raviga soostujate ja mittesoostujate rühmas. Uuriti erinevate tunnuste seost ravisoostumusega, arvatati kohandamata mittesoostumise šansisuhted. Seejärel kohandati šansisuhted tunnustele, mis olid kohandamata analüüsis osutunud mittesoostumisega statistiliselt olulisel määral seotuks ning mida ei saanud pidada ravisoostumuse tulemiks. (II publikatsioon)

Ravisoostumust soodustavate ja takistavate tegurite kohta saadi andmed sekkumiserühma uuritavate nõustamissessioonide ajal toimunud osaliselt struktureeritud (nõustaja poolt uuritavate sõnade kohaselt kirja pandud) vestlustest, mis peeti juhuslikustatud kontrollitud uuringu käigus, mis korraldati Eestis väljatöötatud ravisoostumust toetava sekkumise (kirjeldatud eespool) hindamiseks. (I publikatsioon)

Potentsiaalselt Eesti oludesse sobiva HIV-positiivsete inimeste turvalist seksuaalkäitumist toetava efektiivse sekkumise väljaselgitamiseks koostati 2014. aastal teaduskirjanduse süstemaatiline ülevaade. Publikatsioonide otsimiseks elektroonsetest andmebaasidest koostati uuringuküsimuse alusel otsinguterminite nn puu, mis sisaldas järgmisi üldmõisteid: HIV/AIDS, seksuaalne (riski)käitumine, käitumuslik sekkumine, (kvaasi)randomiseeritud uuringukavand. Ajaliselt vaadati publikatsioone aastatest 1981 kuni 2013 (k.a). Lisaks vaadati läbi Cochrane Collaboration'i HIVi-AIDSi töörühma soovitatud HIVi-AIDSi vald-

konna samal ajavahemikul toimunud teaduskonverentside teesid. Süstemaatilise ülevaate koostamisel järgiti Cochrane Collaboration'i metoodikat (Higgins & Green 2011). Ülevaatesse kaasati (kvaasi)randomiseeritud kontrollitud uuringud, milles oli uuritud HIV-positiivsete HIVi ravi saavate inimeste seas individuaalselt raviteenuse osutaja(te) läbiviidud seksuaalset riskikäitumist mõjutavate sekkumiste mõju võrreldes mitteseksumisega. Tulemiks oli seksuaalse riskikäitumise vähenemine, mida mõõdeti partnerite arvu, kondoomita vahekordade arvu ja/või kondoomi kasutamise järjekindluse muutuse ja/või seksuaalsel teel levivasse infektsiooni, B-hepatiiti haigestumise alusel. Et huvi pakkusid pikemaegse mõjuga sekkumised, kaasati ülevaatesse vaid need uuringud, kus sekkumise mõju oli hinnatud mitte varem kui 90 päeva pärast sekkumistegevuse algust. Ülevaatesse kaasatud uuringute tulemusi analüüsiti kvalitatiivselt. (III publikatsioon)

Eestis elavate HIV-positiivsete inimeste raviteenustega hõlmatus hindamiseks tehti aastail 2014–2015 läbilõikeline analüüs, mis tugines HIV-positiivsete inimeste andmeid sisaldavatele riiklikele ja muudele olemasolevatele rahvastiku-põhiste andmebaasidele. Analüüsi aluseks võeti UNAIDSi hinnanguline Eestis elavate HIV-positiivsete inimeste arv ning tugineti Ameerika Ühendriikides riiklikult kasutatavale metoodikale (CDC 2011, Ford & Spicer 2012). 2013. aasta seisuga hinnati järgmisi HIVi raviastmestiku näitajaid ehk inimeste arvu (ning alates teisest astmest ka osakaalu kõigist HIVi nakatunuist), kes olid 1) HIVi nakatunud, 2) saanud HIVi diagnoosi, 3) jõudnud HIVi ravile ja/või jälgimisele nakkushaiguste arsti juurde, 4) said püsivalt HIVi ravi või olid jälgimisel, 5) said ARV-ravi ning kellel oli 6) HIV supresseeritud (HIV-RNA < 200 koopia/ml). (IV publikatsioon)

Peamised tulemused ja arutelu

Uurimistöö käigus töötati välja Eestis HIVi ravi saavate täiskasvanute vajadustele ning tervishoiusüsteemi võimalustele kohandatud ARV-ravi soostumust toetav tõenduspõhine sekkumine nimetusega *Situated Optimal Adherence Intervention (sOIA) Estonia*. Tuginedes intervjuudest selgunud vajadusele parandada patsientide arusaamu ARV-ravimite toimest ning ravisoostumusest, töötati välja 3-seansiline nõustamine, mis tugineb ravisoostumusega seotud teavitamise-motiveerimise-käitumisoskuste (ingl *Information–Motivation–Behavioral Skills*, IMB) teooriale (Fisher jt 2006 Munro jt 2007, Fisher jt 2008) ja rajaneb nõustamis-metoodikal *Next Step Counseling* (Amico jt 2010, Grant jt 2010) ning mille rakendamine lisati patsientide tavapärastele, muu hulgas ravimivaru täiendamise visiitidele haigla nakkushaiguste osakonda. Ehkki selle sekkumise mõju hindamiseks korraldatud juhuslikustatud kontrollitud uuring jääb käesoleva uurimistöö piiridest välja, selgus juba esimeste nõustamiseansside järel, et nõustamine sobitus haigla tihedasse tööruumi, selleks ei olnud vaja lisapersonali, ning nõustajad (õed) tunnistasid, et nad hakkasid oma patsiente parema suhtluse tulemusena enam mõistma ning et nad rõõmustasid ahhaa-efekti üle, mida patsiendid nõustamise käigus jagatud teabe tulemusena kogesid.

ARV-ravi saavate HIV-positiivsete täiskasvanute ravisoostumuse uurimisel selgus, et suurem osa (144st uuritust 88%) hindas oma ravisoostumust heaks, samas objektiivselt ehk HIV RNA analüüsi tulemuste põhjal oli haigus tegelikult kontrolli all ehk HIV supresseeritud neist vähem kui pooltel (40%-l). See tulemus viitab patsientide võimalikule enese ravisoostumuse ülehindamisele, tõenäoliselt eelkõige tänu soovile end tervishoiutöötajatele meelepärases valguses näidata. Kõige enam osutus ravisoostumus seotuks uuritute ARV-ravi ja ravi võimalikke mõjusid puudutavate uskumustega, samuti enesehinnangulise tervise seisundiga. Ka ravisoostumust toetava sekkumise mõju hindamiseks korraldatud juhuslikustatud kontrollitud uuringu esmavisiidil nimetati sekkumisrühmas ravisoostumuse tõkkena kõige sagedamini ARV-ravimite võimalikke kõrvaltoimeid (75st uuritust 44%). Mõlema uuringu tulemused viitavad sellele, et ARV-ravi soostumust toetavate sekkumiste puhul peaks keskenduma ARV-ravimite toime (sh kõrvaltoimete) selgitamisele.

Ravisoostumuse määra ja mõjurite uuring näitas veel, et süstivate narkomaanide (SNide) seas ei olnud ARV-raviga mittesoostujaid oluliselt rohkem kui mitte-SNide seas. See tulemus on kooskõlas mitmete mujal maailmas tehtud uuringute tulemustega (Carrieri jt 2003, Malta jt 2010, Walsh jt 2014) ning aitab loodetavasti Eesti süstitavate narkootikumide sõltuvusega seotud HIVi-epideemia kontekstis kummutada müüte SNide halvemast ravisoostumusest ning kõrvalda tervishoiutöötajate kõhklusi SNide ravimise otsuste tegemisel.

Süsteemaatilises ülevaates, milles keskenduti HIV-positiivsete ravi saavate inimeste turvalist seksuaalkäitumist toetavatele sekkumistele, vastas uuringusse kaasamise kriteeriumitele vaid viis teaduslikku uuringut (The Healthy Living Project Team 2007, Cornman jt 2008, Gilbert jt 2008, Safren jt 2013, Kurth jt 2014). Neist vaid kahes olid uuritud sekkumised positiivse mõjuga: ühes uuringus vähenes sekkumise tulemusel uuringus osalenute juhuslike seksuaalpartnerite arv (Gilbert jt 2008) ning teises paranes HIV-positiivsete inimeste kondoomikasutuse järjekindlus seksuaalvahekordades, kus teine osapool oli kas HIV-negatiivne või teadmata HIVi-staatusega (Kurth jt 2014). Sobiva tõendusmaterjali hulka vähendasid nii küllaltki ranged uuringute ülevaatesse valimise tingimused kui ka sõelale jäänud uuringute metoodilised puudused. Sellele vaatamata tekkis uuringu tulemusel veendumus, et HIV-positiivsete patsientide ja tervishoiuteenuste pakkujate regulaarsed kokkupuuted raviasutuses on heaks võimaluseks selgitada patsientidele turvalise seksuaalkäitumise olulisust ning seda toetada.

Eesti HIV-positiivsete inimeste raviteenustega hõlmatus hindamisel selgus, et 2013. aastal oli 8628-st (6941–10 783) hinnanguliselt Eestis elanud HIVi nakatunust (AIDSinfo 2014) HIV-infektsioon diagnoositud 72%-l (47–100%-l). Vähemalt ühe visiidi nakkushaiguste arsti juurde oli teinud 51% (41–63%) ning püsivalt oli ravil ja/või jälgimisel 21% (17–27%) HIV-positiivsetest inimestest. Kuigi ARV-ravi sai 18% (14–22%), oli viirus supresseeritud vaid 12%-l (10–15%-l) kõigist 2013. aastal Eestis elanud HIV-positiivsetest inimestest. Olulisi-

maks kitsaskohaks HIV-positiivsete inimeste HI-viiruse kontrolli alla saamisel ehk hea ravitulemuseni jõudmisel osutus HIVi diagnoosimine, mis on võimalik vaid HIVi-testimise abil.

Järeldused

1. 2013. aastal jäi Eestis HIVi raviteenuste igal astmel mingi osa HIV-positiivseid inimesi asjakohastest teenustest kõrvale ning üksnes 12% (10–15%) kõigist 8628-st (6941–10 783) hinnanguliselt Eestis elanud HIV-positiivsest inimesest oli saavutanud HIVi üle kontrolli ehk viirusupressiooni. Kokkuvõttes ei olnud ligi veerandil arvatavalt HIVi nakatunuist HIVi diagnoositud – neid ei olnud HIVi suhtes testitud ning nad ei olnud oma sero(staatus)est teadlikud. Lisaks ei olnud üle poole diagnoosi saanuist ning ka nakkushaiguste arsti vaatevälja jõudnuist püsivalt ravil ja/või jälgimisel. Olukorras, kus heade ravitulemusteni jõudmisel on esmaseks kitsaskohaks HIV-testimine (sh võimalikult varane testimine), oleks HIV-testimise ning sellele järgneva nõustamise ja ravile suunamise kehtiva korra järgimise tõhustamisele lisaks vaja senisest enam tähelepanu pöörata testimisele HIVist enim ohustatud rahvastikurühmades ning piirkondades.
2. Eesti piirkonnas, kus süstitavate narkootikumide sõltuvuse levimus on suur, hindas suur osa HIV-positiivsetest ARV-ravi saajatest oma ravisoostumust heaks, samas kui suurel osal neist ei olnud viirus supresseeritud. Kõige enam oli ravisoostumus seotud enesehinnangulise tervise seisundiga ning ARV-ravi ja selle võimalike (kõrval)mõjudega seotud uskumustega. Süstivate narkomaanide seas ei olnud mittesoostujaid oluliselt rohkem kui mittesüstivate uimastisõltlaste seas. Eelnevale tuginedes võib arvata, et ravisoostumust toetavad sekkumised annaksid paremaid tulemusi, kui nende rakendamisel käsitletak ARV-ravi vajalikkuse ja toime (sh kõrvaltoimete) küsimusi.
3. Töötati välja Eesti patsientide vajadusi ning ravisüsteemi võimalusi arvestav ravisoostumust toetav sekkumine, mis on rakendatav ka teistes ravi-asutustes peale haigla, kus uuring korraldati, nii Eestis kui tõenäoliselt ka teistes sarnase HIVi-epideemia ning sotsiaalmajandusliku taustaga riikides. Raviasutuste töökorraldust arvestav sekkumine ei ole ressursimahukas ning tänu sellele saab seda rakendada patsientide tavapärase (ravi)visiitide käigus.
4. Täiskasvanud HIV-positiivsete ravi saavate inimeste turvalist seksuaalkäitumist toetavatele sekkumistele keskendunud uuringute süstemaatilise ülevaate tulemusena tehti kindlaks kaks tõenduspõhist sekkumist, mida raviteenuse osutaja saab individuaalselt rakendada ja mis sobiksid kasutamiseks Eesti raviasutustes, kuid tõenäoliselt ka teistes sarnase HIVi-epideemia ning sotsiaalmajandusliku taustaga riikides. Üks neist sekkumistest vähendas olulisel määral HIV-positiivsete inimeste juhuslike seksuaalpartnerite arvu ning teine suurendas kondoomikasutuse järjekindlust seksuaalvahekordades HIV-negatiivse või teadmata serostaatusega partneriga.

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- kõrge HIV-riskiga rahvastikurühmad Eestis: ennetus- ja ravivajadused
- ravijuhendite koostamise meetodika

8 rahvusvahelises eelretsenseeritud ajakirjas avaldatud teaduspublikatsiooni (sh 6 artikli ja 2 konverentsi-ettekande), 5 rahvusvahelise konverentsi (suulise) ettekande ning 3 muu teaduskirjutise autor.

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