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EXPLORING HIV DRUG RESISTANCE IN SUB-SAHARAN AFRICA AS A COMPLEX ADAPTIVE SYSTEM

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There is always a well-known solution to every human problem – neat, plausible and wrong.
- H.L. Mencken

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Abbreviations

ADR	Acquired HIV drug resistance
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CAS	Complex adaptive system
CDC	Centres for disease control
COVID-19	Coronavirus disease 2019
CRF	Circulating recombinant form
DUCS	Dar es Salaam Urban Cohort Study
DTG	Dolutegravir
EFV	Efavirenz
EI	Entry inhibitor
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HIV-2	Human immunodeficiency virus type 2
HIVDR	HIV drug resistance
IF	Institute for the Future
INSTI	Integrase strand transfer inhibitor
KPI	Key performance indicator
MSM	Men who have sex with men
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PDR	Pretreatment HIV drug resistance
PEP	Post-exposure prophylaxis
PI	Protease inhibitor
PLHIV	People living with HIV

PMTCT	Prevention of mother-to-child transmission
POCT	Point of care test
PREP	Pre-exposure prophylaxis
QUAGOL	Qualitative Analysis Guide of Leuven
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
SDGs	Sustainable Development Goals
SIV	Simian immunodeficiency virus
SSA	sub-Saharan Africa
TDR	Transmitted HIV drug resistance
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
WHO	World Health Organisation

Chapter 1

General introduction

Before diving into the introduction, I would like to provide the reader with some context on how this PhD project started and evolved as this thesis is part of a broader initiative of transdisciplinary exploration at KU Leuven. In 2016, three KU Leuven professors, Prof. Anne-Mieke Vandamme, Prof. Griet Ceulemans and Prof. Andreas De Block started the Institute for the Future (IF), an incubator for transdisciplinary research. Their mission was to overcome disciplinary boundaries and bring students and researchers from different disciplines, and non-academic actors together around complex societal problems. As a first activity of the IF an honours programme for master students was set up and a “test run” was held in the spring of 2017. Students from Medicine, Mechanical Engineering, Biomedical Sciences, Philosophy and Arts in Cultural Studies came together to study “a way to understand and instruct on best practices for delivering and accepting HIV drug treatments in Africa”. This topic had been put forward as a complex problem requiring transdisciplinary attention by Prof. Michael Jordan, HIV-expert at Tufts Medical Centre in Boston, US. It was near the end of that first semester that I came into contact with the IF and decided to start my PhD, in which I would research HIV drug resistance (HIVDR) in a transdisciplinary manner. As I was the first PhD student within the IF, starting this research meant finding my way in the world of transdisciplinarity together with the IF. This also implied taking into account the complexity of all aspects of HIVDR in the research, from molecular mechanisms studied in the lab, over adherence issues the people living with HIV (PLHIV) face to policy making at global level. Soon I realized that in order to conduct transdisciplinary research we would first need a way to navigate the complexity of the topic. That is how the thesis as it is today started to gain shape, and the focus of the work became the mapping of the complex system of all known factors influencing HIVDR and the analysis and applications of such systems maps. The novelty of this research is therefore twofold. First, this thesis lays the groundwork for studying HIVDR as a complex adaptive system (CAS), and second, as systems thinking is a developing field within public health, this thesis contributes to operationalizing systems thinking for approaching public health problems as CASs. The general introduction of this thesis thus serves two purposes: 1) to provide sufficient background information on HIVDR in Sub-Saharan Africa, which will also illustrate the complexity of the problem, and 2) to familiarize the reader with systems thinking and systems mapping theory which was used to operationalize a methodology for studying complex public health problems. After introducing the aims of the thesis in chapter 2, the body of the work consists of

four chapters, in the form of research articles. Chapter 3 describes the development of a systems map of factors influencing HIVDR in sub-Saharan Africa, based on the insights of international experts of diverse disciplines. After analysing this broad system at international level and identifying the main feedback loops driving HIVDR, Chapter 4 continues to map the system surrounding HIVDR from the perspectives of people living with HIV (PLHIV) and local actors in a study site in Dar es Salaam, Tanzania. Overlaps and differences in these international and local systems are discussed and potential leverage points are suggested. Chapter 5 entails a reflection on the methodology used in Chapter 4 and 5 and bundles that experience in a practical guideline for developing and analysing systems maps for complex public health problems. In Chapter 6 we illustrate an application of our systems maps, zooming in on the interlinkage between HIVDR and the currently ongoing SARS-CoV-2 pandemic. In Chapter 7 we discuss the transdisciplinary approach supporting this work and the implications for future research.

1.1 Human Immunodeficiency Virus

1.1.1 Virology

Discovery and origin

In 1981, the American Centres for Disease Control (CDC) published a report describing a series of rare opportunistic infections in five young, previously healthy men [1]. This was the first report of what would later become known as the acquired immunodeficiency syndrome (AIDS). In 1983, the causative agent responsible for AIDS, was identified as human immunodeficiency virus type 1 (HIV-1) [2,3]. In 1986, a new virus, the human immunodeficiency virus type 2 (HIV-2) was identified in AIDS patients in Western Africa [4]. As the virus types are phylogenetically distantly related but both originate from simian immunodeficiency viruses (SIV), HIV-1 and -2 most likely originated from different zoonotic transfers of SIV from chimpanzees and sooty mangabey monkeys respectively to humans [5,6]. The generally accepted hypothesis is that these events occurred when hunters came into contact with SIV though blood contact with the animals, after which the virus adapted to its new human host [7].

Disease progression

When left untreated, an HIV infection advances over time and PLHIV can eventually develop AIDS and die. The disease progression is divided in three stages [8]. When the immune response to the virus has not fully kicked in, infected people usually experience an acute retroviral syndrome which is characterized by flu-like symptoms, two to four weeks after infection. This is the first stage. The virus multiplies rapidly and destroys CD4 cells while doing so. During the first stage, PLHIV are very infectious while experiencing limited symptoms. This underlines the need for early detection of HIV infections in order to timely start treatment. When the immune system manages to, at least temporarily to some extent, control HIV replication, HIV infection becomes chronic, the virus replicates at lower levels and PLHIV experience limited to no symptoms. Without therapy, this stage can last for several years before AIDS develops. At the third stage, when the immune system can no longer control the virus, and HIV replicates rapidly, PLHIV are diagnosed with AIDS when they have a CD4 count of less than 200 cells/mm^3 or when they have certain rare opportunistic infections. Without treatment, people with AIDS survive on average for three years.

Transmission

HIV is transmitted through body fluids from infected people [9]. The main route of transmission is through unprotected sexual contact. Other sexually transmitted infections such as syphilis or gonorrhoea increase the risk of HIV transmission. HIV can also be transmitted from mother to child during pregnancy, birth or through breast milk. Other transmission routes include unsafe injections or accidental needle stick injuries, blood transfusions, tissue transplantation or other types of blood-blood contact.

HIV transmission can be prevented by condom use, avoiding needle sharing and other behavioural interventions [10]. Moreover, antiretroviral therapy (ART) combinations can be used to prevent infection before or after a risk contact, respectively called pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), or for the prevention of mother-to-child transmission (PMTCT).

Important to note is that PLHIV who receive ART and have obtained and maintained an undetectable viral load (VL), defined as <200 copies/mL, cannot transmit the virus

to sexual partners [11–13]. In 2016, this concept was launched as the U=U campaign (undetectable equals untransmittable) by the Prevention Access Campaign and has since then been adopted as a communication strategy by several countries and institutions [14].

Replication cycle

HIV virus particles consist of a nucleocapsid containing two single stranded RNA molecules, and several viral proteins. HIV infects predominantly CD4+ T-helper lymphocytes, whose depletion results in AIDS, but infection of other cell types is also possible. The replication cycle is depicted in Figure 1 [15].

The virus attaches to the host cells through its glycoprotein gp120 which recognises the host cell CD4 receptor and interacts with co-receptors [16]. After fusion of the viral and cell membranes, the single stranded viral RNA and proteins enter the cell cytoplasm. The enzyme reverse transcriptase transcribes the viral RNA into double stranded DNA, which is integrated in the host DNA by the integrase protein. New viral RNA is formed which is used to transcribe new viral proteins and as genomic RNA. Together they form new infectious virions after cleavage from the host cell.

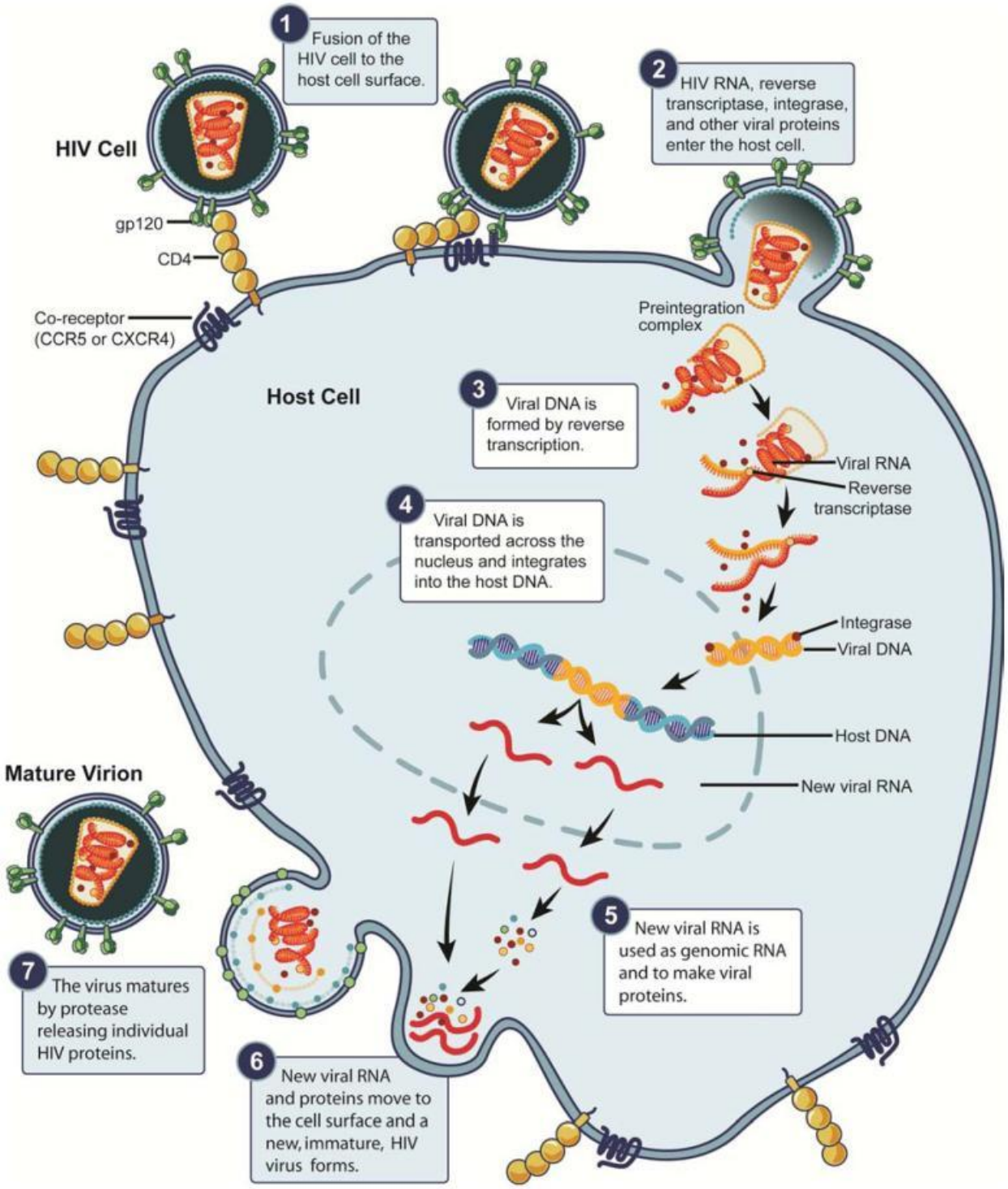

Figure 1: *Illustration of the replication life cycle of HIV. Further explanation about the replication cycle of HIV can be found in the text on page 5. (Image from [15], reused with permission.)*

Testing and treatment

HIV can be detected through serological antibody or antibody/antigen assays or through nucleic acid tests [17]. Laboratory based tests are available, as well as point of care tests (POCT), allowing a return of the result during the same healthcare centre visit. Self-test kits are available as well, which can be used fast and discretely without the help of a healthcare worker.

Since 1987 several drugs have been developed and approved by regulatory agencies [15]. The available medication can be divided in five main drug classes: the nucleoside reverse transcriptase inhibitors (NRTI), the non-nucleoside reverse transcriptase inhibitors (NNRTI), the protease inhibitors (PI), the entry inhibitors (EI) and the integrase strand transfer inhibitors (INSTI). Most treatments consist of a cocktail of three different drugs. The latest WHO guidelines recommend the use of Dolutegravir (DTG), which is an INSTI, or Efavirenz (EFV), an NNRTI, in combination with a backbone of two NRTIs for adults initiating ART [18]. The advised second line therapy, in case of drug resistance against one of the first line regimens, is DTG with an optimized NRTI backbone or a PI with an optimized NRTI backbone. The WHO advises third line regimens to be optimized using genotyping and the inclusion of new drugs which minimize cross-resistance to previously used regimens.

While ART can currently not eradicate HIV, it is capable of suppressing the VL to undetectable levels, restoring the CD4 count and preventing the development of AIDS. Whereas in the past ART consisted of several pills per day, it is now reduced to a minimum of one-pill-a-day, yet lifelong treatment. When taking therapy correctly, PLHIV can have a life expectancy approaching that of the general population [19].

1.1.2 Epidemiology

Today, the World Health Organisation (WHO) estimates that the HIV epidemic has claimed 36,3 million lives globally and that 37,7 million people were living with HIV at the end of 2020. With over two thirds of PLHIV in the WHO African Region, the disease burden is distributed unequally [20].

Key populations

Globally, the population living with HIV accounts for 23% of men who have sex with men (MSM), 11% of sex workers, 9% of people who inject drugs, 2% of transgender women and 20% of partners of those populations [21]. The remaining population, mostly heterosexuals who are not part of the previously mentioned categories, accounts for 35%. However, those numbers differ significantly between sub-Saharan Africa and the rest of the world. In sub-Saharan Africa, 12% of PLHIV are sex workers and 19% are partners of sex workers, people who inject drugs, MSM or transgender women. Here, the remaining population accounts for 61%. In Sub-Saharan Africa, only 6% of PLHIV are MSM whereas in the rest of the world MSM is the largest population (45%).

Subtypes

HIV-1 and HIV-2 are lentiviruses from the retroviridae family. Worldwide, HIV-1 is responsible for the vast majority of the infections. Although HIV-2 is less infectious and the disease progression is slower, treatment is usually needed to prevent AIDS [22]. HIV-1 can be categorised into four groups [23,24]. Group M is responsible for about 90% of the global HIV epidemic. Group O has caused limited infections, mainly in clusters in West and Central Africa, and group N and P have been identified in a limited number of cases in Cameroon. Group M consists of nine subtypes (named with the letters A to K). Moreover, around hundred circulating recombinant forms (CRF's) have been identified so far, being recombinants between those subtypes that are significantly contributing the epidemic [24]. Many unclassified recombinants exist, and the epidemic is increasingly being driven by recombinant viruses. While in Western and Central Europe and in North America subtype B is most dominant, globally subtype C is responsible for the most infections. Subtype C causes the vast majority of the HIV infections in Southern Africa, India and Ethiopia. In Eastern Africa, subtype A, B, C and D are most dominant. The highest diversity of subtypes can be found in Central Africa (Figure 2).

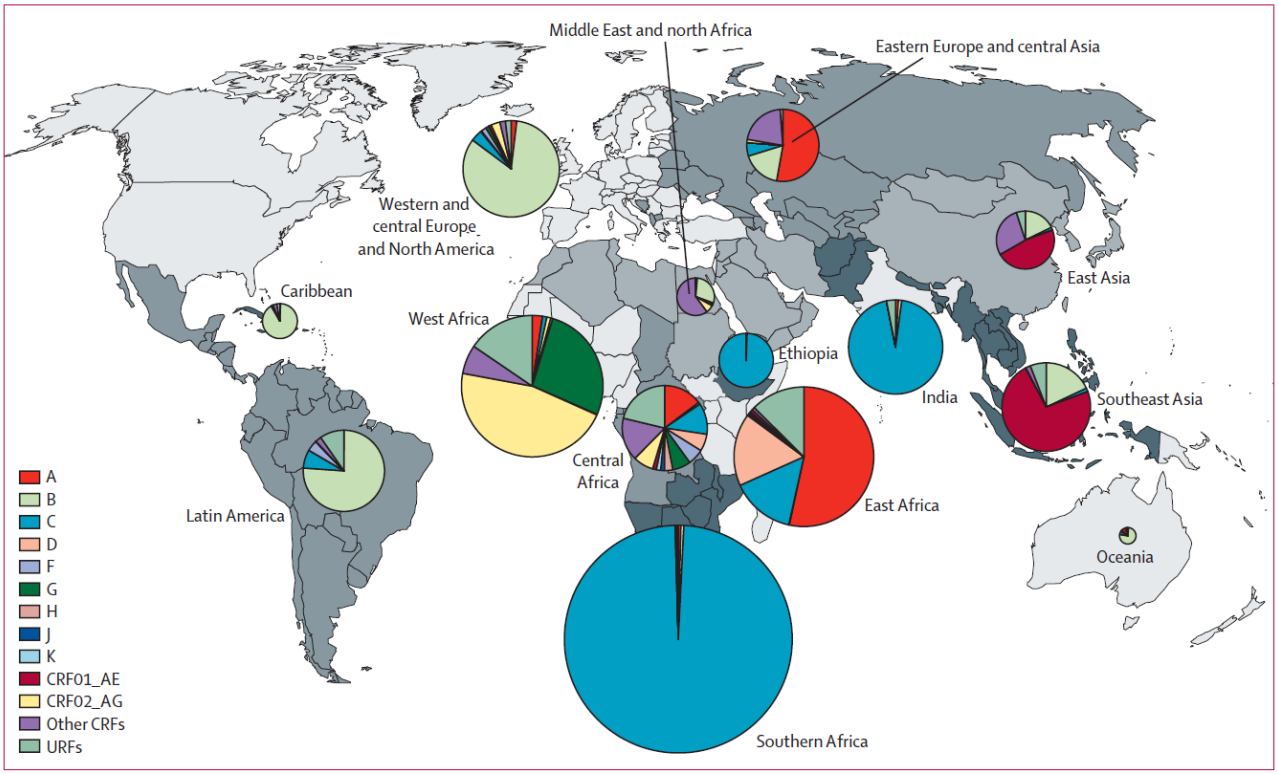

***Figure 2**: Regional distribution of HIV-1 subtypes and CRFs. (Reused from* [24]*, with permission.)*

1.1.3 Global action

Although HIV tests and ART facilitate the diagnosis and life-long suppression of the virus, the HIV epidemic remains difficult to control. This is due to a number of causes such as access to medicines, the availability of testing facilities, sub-optimal adherence to therapy and the selection and spread of HIV drug resistance (HIVDR). In the past years, several of the United Nations Sustainable Development Goals (SDG's) have been addressed in the fight against HIV.

In particular, SDG 3, good health and well-being includes a target to end AIDS as a public health threat by 2030. In an ambitious attempt to fight the epidemic, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced their 90-90-90 strategy in 2014 [25]. The goal was for 90% of all PLHIV to be diagnosed, 90% of those to be on ART, and 90% of those to have a suppressed VL by 2020. In 2020 those numbers were 84%, 73% and 66% respectively and new targets of 95-95-95 were set for 2030 [21].

In 2016 the WHO launched the universal test and treat strategy, supporting the 90-90-90 goals, recommending to widely screen for HIV infection and to start treatment for those found positive, regardless of their VL or CD4 count [26]. These guidelines have been gradually adopted by several countries, which has expanded the ART coverage significantly.

There are also large-scale HIV-programmes with a main focus on other SDGs. For example, one of the programme areas of UNAIDS is on social protection, including advocacy for social protection programmes, social health insurance and economic support [27]. This helps to reduce the risk of HIV infection for vulnerable people, through SDG 1 on ending poverty. In relation to SDG 2 on ending hunger, the world food programme supports countries in providing food and adequate nutrition for PLHIV [28]. Also SDG 5 on achieving gender equality is being addressed in order to prevent HIV, among others through the UN Joint Programme on AIDS on preventing and responding to violence against women and girls [29]. Preventing and treating HIV is important as well for reaching several other SDGs such as SDG 4 on quality education, SDG 10 on reducing inequality and SDG 16 on promoting peaceful and inclusive societies [21,30].

1.2 HIV drug resistance

While the widespread roll-out of ART has saved many lives of PLHIV, it has also contributed to the increase of HIVDR, which remains one of the main challenges in the fight against the HIV epidemic. Patients carrying a drug resistant virus have a higher risk of virologic failure and therefore developing AIDS, transmitting the drug resistant virus and further acquiring other drug resistance mutations [31]. This could lead to a global increase of AIDS deaths, HIV infections and ART-related costs. For sub-Saharan Africa alone, an additional 890 000 deaths, 450 000 HIV infections and 6.5 billion USD ART costs due to HIVDR were predicted for the period between 2017 and 2030 [32]. Indeed, a cohort study in a hospital in Malawi by Gupta-Wright et al. found an increased mortality in patients with HIVDR compared to those without, after adjustment for age, sex, time on ART and tuberculosis treatment. At day 56 of follow-up, mortality in patients without drug resistance, with resistance to one drug and with multidrug resistance was 6%, 13% and 28% respectively [33].

HIVDR can be divided into three categories: acquired HIVDR (ADR), transmitted drug resistance (TDR) and pretreatment drug resistance (PDR). ADR is when a patient develops a drug resistant virus due to selective pressure created by the replication of the HIV virus in the presence of ART in a concentration insufficient to suppress the virus. TDR refers to the transmission of a drug resistant virus to a previously uninfected person. The term PDR is used when a person who has not been previously enrolled in ART, is diagnosed with a drug resistant virus. In this case, the patient may have been infected with a drug resistant virus or may have acquired drug resistance during previous exposure to ART such as PREP or PMTCT or because the patient chooses not to disclose earlier treatment or was not sufficiently aware of taking an earlier treatment at a different site.

A systematic review of literature published between 2001 and 2016 revealed that PDR NNRTI resistance was increasing in all low- and middle-income regions studied, with the highest increase in Eastern Africa [34]. In its HIVDR report of 2021, the WHO reported that of the 30 countries participating in a HIVDR survey between 2014 and 2020, 21 reported NNRTI PDR above the 10% threshold which triggers immediate national action [35]. For the WHO Africa region, PDR among adults initiating ART was 15.4%, 6.1%, 0.3% and 0.1% against NNRTI's, NRTI's, PI's and INSTI's respectively. Of the 14 surveys done worldwide, 6 reported ≥90% VL suppression in patients 12 months after starting treatment. In patients with unsuppressed VL 12 months after starting NNRTI-based first-line treatment, NNRT resistance ranged from 50% in Lesotho to 97% in Uganda.

1.2.1 Selection of HIVDR

HIVDR arises when the drug concentration in the body is high enough to exert selection pressure, but not high enough to suppress the virus, thereby allowing it to replicate and mutate. At such intermediate drug concentrations, a virus strain with pre-existing mutations will have an evolutionary advantage and become dominant while the original susceptible viral strain will be suppressed. The virus (either wild-type or with pre-existing mutations) can accumulate further mutations and become increasingly more resistant [36] (Figure 3).

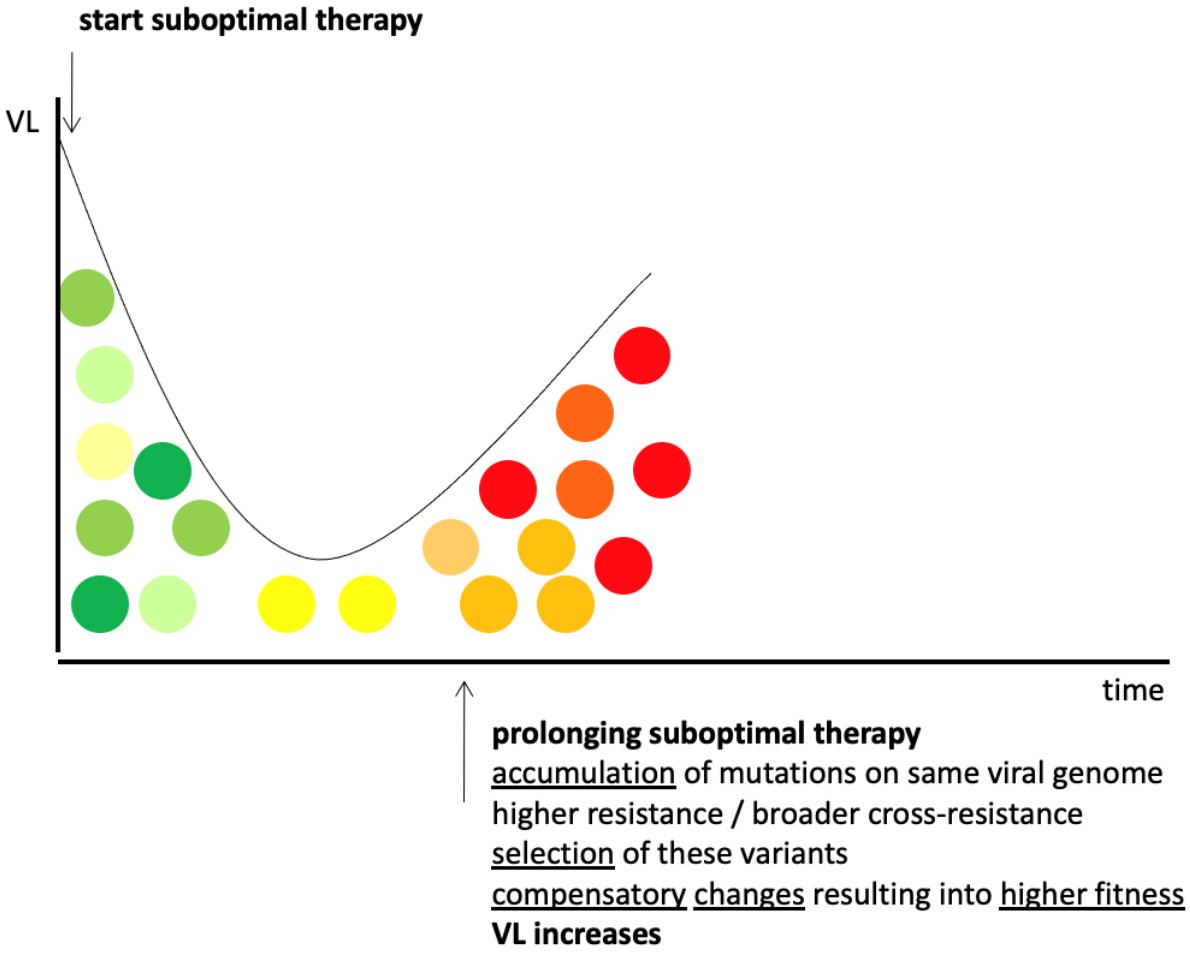

Figure 3: *Emergence and selection of HIVDR. Colour code: the greener the more susceptible the virus is to ART, the more red the more resistant. After start of therapy the viral load decreases. When therapy is suboptimal mutations can accumulate, and variants with a selective advantage become dominant over the wild-type therapy sensitive strains. (Figure of Prof. Kristel Van Laethem, used with permission.)*

ART regimens available today consist of a combination of three different drugs so that resistance mutations developing in the HIV virus are always suppressed by at least one of the drugs. However, even after the implementation of the triple-drug therapies in 1995, drug resistant mutations kept arising. Although the details of the conditions needed to develop drug resistance to triple-therapy are still not fully understood, several routs to drug resistance have been described in the literature.

One of the main factors linked to the selection of HIVDR is incomplete adherence patterns. When one of the three ART drugs has a longer half-life than the others, treatment interruptions will result in periods of monotherapy. This is due to the two

drugs with a short half-life being eliminated while the third one persists [37]. This was the case with the previous recommended first-line treatment consisting of an NNRTI with a long half-life and two NRTIs with shorter half-lives. During such periods drug resistance against the remaining drug can be selected. This underlines the importance of adherence to therapy in order to keep the drug levels sufficiently high at all times. While the association between adherence and drug resistance has been proven, it remains unclear how different adherence patterns (such as regularly skipping the medication, or a declining adherence over time) influence the risk for drug resistance selection even after several years on treatment [37–40].

Next to adherence-levels also differences in individual drug metabolism and differences in penetration rates of the drugs within different areas of the body, can cause periods and places of monotherapy, allowing for the selection of drug resistance [40]. However, the exact impact of those effects on the development of drug resistance remains to be fully understood. Another cause of decreased drug concentration allowing the selection of HIVDR, is drug-drug interactions between the ART and other medication. The most prominent example is the interaction between different ART drugs and anti-tuberculosis medication. For example, the concentration of efavirenz, a potent NNRTI, decreases in the presence of rifampicin, which is used for the treatment of tuberculosis [41]. Therefore, treatment should be adapted in patients with HIV and tuberculosis co-infection.

The most recent drug class, the INSTI's, have a higher genetic barrier, and thus a higher number of mutations are needed to overcome drug-selective pressure. However, also those drugs are at risk of losing their efficiency due to drug resistance. Since 2019 the second-generation integrase inhibitor DTG is included in the WHO-advised first- and second-line treatments. While the introduction of DTG is expected to reduce the impact of NNRTI PDR, some cases of DTG resistance in both treatment naïve and treatment experienced patients have already been described [42,43]. This underlines the need to keep the quality of healthcare services and adherence support at a high level, also when new and successful drugs become available [44].

1.2.2 The complexity of therapy adherence

As described above, one of the main drivers of HIVDR is incomplete adherence. Adherence is influenced by a multitude of factors which have been extensively

described in the literature. Adherence is generally described as the extent to which a person's behaviour corresponds with the recommendations of a healthcare provider, implying an active choice of the patient to comply with the prescribed therapy. However, for the purpose of this study we also consider the impact of structural factors influencing the ability to take the therapy as prescribed, such as ART availability. Therefore, we here define adherence in the broader sense of taking ART as prescribed by the healthcare provider, as influenced by factors within and out of control of PLHIV themselves. A meta-analysis including 125 studies reporting barriers to ART adherence, found that PLHIV most frequently reported not taking their ART because they forgot (41.4%), were travelling (30.4%), were busy with other things (29.4%), experienced a change to routine (28%) or were asleep (24.8%) [45]. This shows that the effort needed to adapt to a lifelong daily treatment is not to be underestimated. The other reported barriers to adherence for the adult participants are shown in Figure 4 and are discussed below.

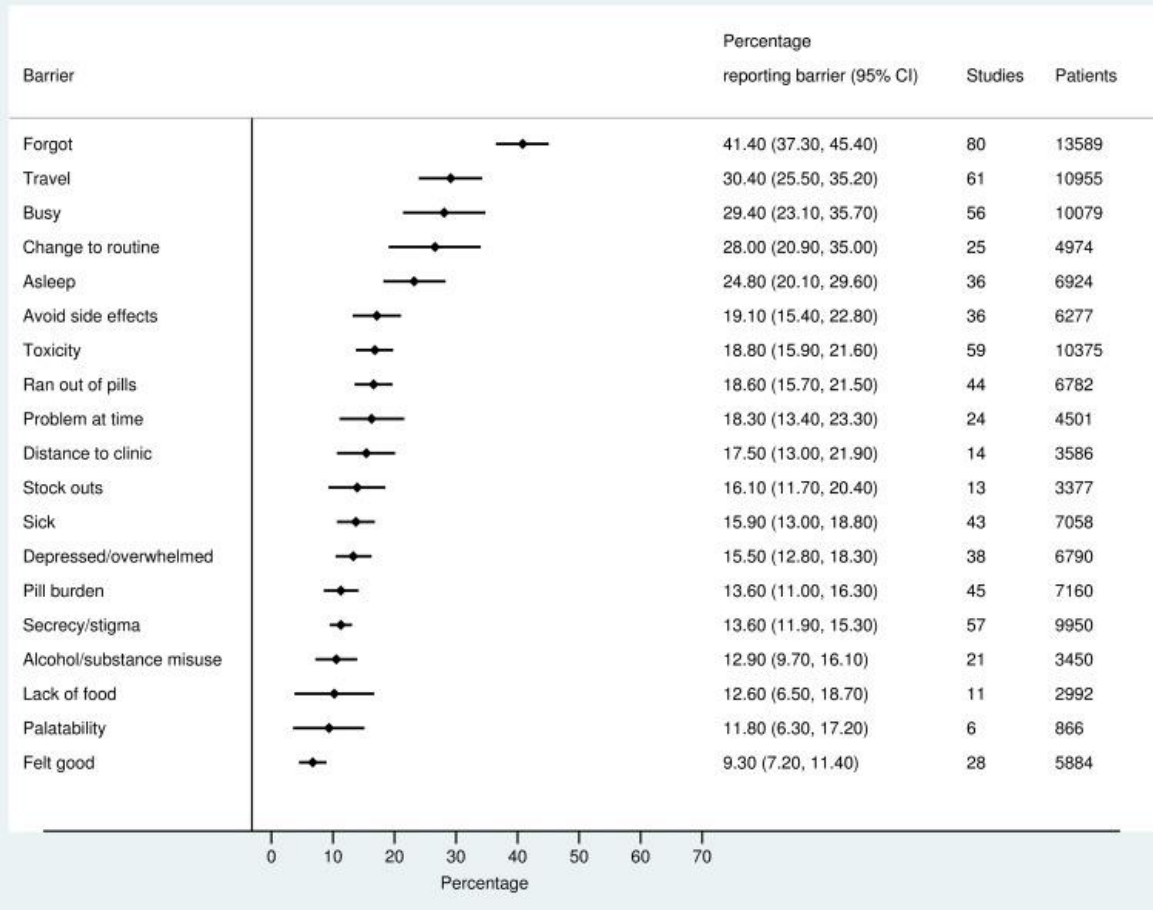

Figure 4*: Meta-analysis of barriers to adherence among adults on ART. (Reused from* [45]*, under a CC BY 4.0 Licence)*

The help of SMS reminders, especially combined with an appointed supporting person, can help to better incorporate the ART into the daily life and improve adherence [46]. The above indicated reasons for missing doses of ART may also be related to the still very stigmatized nature of HIV. Patients may choose not to take their medication when they are away from home or when other people are nearby, in order not to disclose their HIV status. A qualitative study on the different forms of experienced stigmatisation in Dar es Salaam, found that stigma is present on different levels, such as spousal discrimination, mistreatment by healthcare workers and other relational discrimination [47]. The study also found that PLHIV kept their HIV status undisclosed and preferred to attend to a more distant clinic in order to avoid being seen by people who know them.

Another barrier is food insecurity, which can impede adherence through various mechanisms [48]. For example, PLHIV can refrain from taking their medication out of fear of having an increased appetite or out of fear of side effects when taking ART on an empty stomach [49]. Also the need to make financial choices between getting the ART or other resources such as food has been described in the literature [50]. Poor adherence has also been associated with substance abuse, depression and gender imbalance [51,52]. A structural barrier to adherence, is treatment stock-outs, which has been one of the major limiting factors in the efforts to widely roll out ART. A study in six sub-Saharan African countries reported that 11% of the 145 facilities experienced a stock-out in the previous year in 2015/2016 [53]. Other structural barriers to adherence can be for example limited education of healthcare workers or overburdened healthcare facilities [54].

1.3 Case study: Ukonga and Gongolamboto areas of Dar es Salaam, Tanzania

1.3.1 Study area for empirical data collection

In Chapter 4 we study the complex adaptive system of HIVDR in the Gongolamboto and Ukonga administrative wards of the Illala district in Dar es Salaam, Tanzania. This study site was chosen because of an existing collaboration and the rich data availability due to a well-established cohort study which has been in place for several years. This provides an excellent opportunity to investigate HIVDR and later develop interventions and test their system-wide effects. The fact that the cohort study has been going on for

several years and citizens are familiar with the organization and field workers, meant that this study did not cause significant disruptions in the daily functioning of the study site which may have impacted our findings. As the prevalence of NNRTI pretreatment resistance is increasing the fastest in Eastern Africa, choosing a study site in Tanzania is also particularly relevant for other sub-Saharan African countries [34].

In these administrative wards, all of the more than 100,000 residents are followed by the Dar es Salaam Urban Cohort Study (DUCS) [55]. Households are visited every six months by field workers who collect sociodemographic data such as in-and out-migration, births, deaths and marital status. In 2015, the population consisted of 52.5% women and 38% of the population was younger than 15 years old, while only 1.5% of the population was 64 years or older. The population knows a modest to high mobility with an in-migration rate of 57.1 per 1000 between 2011 and 2015 and an out-migration rate of 98.6 during that period. In the region, 54.5% of the households had access to electricity, while in 94.5% of the households at least one member had a phone. 57.8% of the households reported some level of food insecurity in the preceding four weeks. There are three hospitals and 13 dispensaries in the area, of which respectively two and five offer care and treatment for PLHIV.

1.3.2 Epidemiology of HIV in Tanzania

In 2020, 1.7 million people were living with HIV in Tanzania, corresponding to a prevalence of 4.8% [56]. These numbers differ strongly per region, with the highest prevalence being 11.4% in the Njombe region and the lowest being 0.4% in Zanzibar. The HIV prevalence in Dar es Salaam, former capital of Tanzania and largest city, is 4.7%. Moreover, the prevalence is higher in women (6%) than in men (3,6%). In Tanzania, the HIV pandemic is affecting all population groups, although some key affected populations with a higher HIV prevalence can be distinguished. The key populations include 1) people who inject drugs, of whom 35% was estimated to be living with HIV in 2014, 2) sex workers, among whom the HIV prevalence was estimated to be 15.4% in 2018, 3) MSM, with an estimated prevalence of 8.4% in 2018 and 4) mobile populations with an average prevalence of 14% [57–59]. However, as these groups are difficult to reach and, with exception of the mobile populations, also criminalized, the prevalence estimations can vary strongly between studies.

1.3.3 Treatment and care in Tanzania

ART treatment is freely available since 2004 and the test and treat strategy, allowing all PLHIV to start treatment immediately after testing is being implemented since 2017 [60]. This in combination with the scale up of the testing strategy has considerably contributed to the progress towards the 95-95-95 goals. In 2019, 82% of PLHIV in Tanzania were aware of their status, of which 91% were on treatment. Of those on treatment, 92% were virally suppressed [59]. This corresponds to 74% and 68% of all PLHIV being on treatment and being virally suppressed respectively.

Tanzania differentiates care for stable and unstable clients [61]. Clients who just initiated treatment or are unstable are required to return to the healthcare centre on a monthly basis to renew their prescription and are closely followed up. Stable clients have received treatment for more than six months without considerable adverse effects or complications, have an undetectable VL, keep appointments and adhere well. Those clients receive a health check-up twice per year and pick-up their medication every three months, with the possibility to switch to 6-montly dispensing later on. When a client has a high VL test result (defined as >1000 copies/ml), they will receive enhanced adherence counselling. When after three months, the VL is still unsuppressed, the client will be switched to second line therapy. In case a switch to third line therapy is needed, a multidisciplinary team will be consulted to discuss the specific case before switching to the last line of therapy.

As is the case for other countries, several barriers to adherence in Tanzania have been described in the literature. For instance, the national Tanzania stigma index report of 2013 reported that more than half (52.9%) of the participants from Dar es Salaam had one or more days without food during the previous month [62]. In Tanzania, traditional and religious practices can have both a positive and negative effect on adherence as certain traditional and religious leaders encourage adherence whereas others may discourage ART use and replace it by traditional medicine or a miracle cure [63–65]. In terms of ART supply, a study reported that in 2015/2016 33% of Tanzanian health facilities experienced a stock-out during the previous year [53]. In another study in the Kinondoni District in Tanzania, 16 out of 20 clinics reported drug stock-outs during the previous 12 months [66].

1.3.4 HIVDR in Tanzania

Very little HIVDR data is available for Tanzania. The Tanzania HIV impact study conducted in 2016-2017 found four cases of resistance in 31 samples of recently infected PLHIV [67]. One study conducted in Tanzania, Kenya, Uganda and Nigeria between 2013-2015 and 2016-2019 included 801 ART-naïve patients, of which 154 were Tanzanian [68]. The prevalence of NNRTI resistance mutations in the cohort increased from 6.5% to 12.4% and the NRTI resistance mutations from 3.4% to 7.3%, although this was mainly due to an increase in prevalence in the Ugandan population. For the Tanzanian population, the NNRTI resistance mutation prevalence remained limited to 6% and NRTI mutations to 3%. In contrast, a small-scale study in Dar es Salaam, conducted in 2017 reported a prevalence of HIVDR mutations of 29.8% (14/47) in patients who had not started treatment [69]. Of those 47 tested patients, 7 (14.9%) had already developed high-level resistance to at least one of the standard first-line regimens in Tanzania. In patients who were on therapy but were virally unsuppressed, the drug resistance rates were much higher, with 95% (95/100) carrying mutations against NNRTI's, 92% (92/100) against NRTI's and 13% (13/100) against PI's. Another small scale study in Dar es Salaam found resistance mutations in 19 out of 23 samples taken from patients under therapy (83%) [70]. Because all of the above studies have a limited sample size, the results should be interpreted with caution. Moreover, the Tanzanian HIVDR rates are possibly in line with those in neighbouring countries of which WHO reports national HIVDR survey data, being 15.4% resistance to EFV or NVP (two NNRTI's) in treatment initiators in Uganda, and 16.2% in Zambia.

Survey data published in the 2021 WHO HIVDR report, reveal that in 2019 the viral load testing coverage in Tanzania was <70%, and in 2020 the proportion of people receiving second line ART <5%, scoring unsatisfactory for both indicators [35]. While the lack of data underscores the need for larger national HIVDR monitoring, from the information above taken together, we should work under the assumption that in Tanzania the prevention of HIVDR remains an important aspect in the fight against HIV.

1.4 HIVDR as a wicked problem

As can already be deducted from the previous sections, HIVDR is a very complex problem with different interconnected causes that relate to many disciplines of science,

various population and organizational levels, and conflicting value systems. Such problems are also called *wicked problems*, first described by Rittel and Webber in 1973 [71]. Wicked problems differ from complicated problems in that they don't have one clearly identifiable cause and there is no single solution that can resolve the whole problem. Rather, solutions are aimed at reducing the problem. An example of a complicated problem is building a rocket [72,73]. To do so, much knowledge, time and resources are required, but eventually the problem can be solved. Wicked problems on the other hand, are rather societal problems which have slightly different characteristics in different locations. The elements that drive HIVDR are largely similar, yet still different between high income countries and low-and middle-income countries, or between rural and urban areas. Where motivation to adhere to therapy may be the main issue in one place, the lack of consistent ART availability may be the most prominent cause in another place. Both issues would require different interventions at different institutional levels. Moreover, different wicked problems are interconnected with each other. For example, HIVDR is intrinsically interconnected with poverty (e.g. poor adherence due to food insecurity or low retention in care due to financial constraints) and gender inequality (e.g. the difference in stigma associated with men and women who are HIV positive or the possibility to opt for safe sex), which are both wicked problems on their own [45,74]. When addressing wicked problems, there is no model solution that can be implemented everywhere. Rather than trying to design one solution that fits all, one should aim to improve the situation by understanding its complexity and local context.

1.4.1 Inter- and transdisciplinarity

Wicked problems should be studied and addressed in a transdisciplinary manner, incorporating viewpoints and expertise from different disciplines and societal actors. Transdisciplinary research differs from interdisciplinary research in that it aims to create a common intellectual framework between researchers from different disciplines, as well as non-academic societal participants. Such research often starts from a societal problem, rather than a discipline and aims to shape real processes of change while integrating the knowledge of several disciplines and involving societal actors [75]. Transdisciplinarity has the potential to reach a system-wide impact as it takes into account the local conditions, implementation possibilities and various levels of effects in order to avoid unintentional outcomes [76].

Figure 5 shows the different types of disciplinarity and their core values. While disciplinary research stays within its disciplinary boundaries, multidisciplinarity describes a collaboration between researchers in which a common topic is studied but each research group contributes to the study drawing on their own disciplinary knowledge. In interdisciplinary research, methods and insights of different disciplines are integrated and the boundaries between disciplines start to become vague.

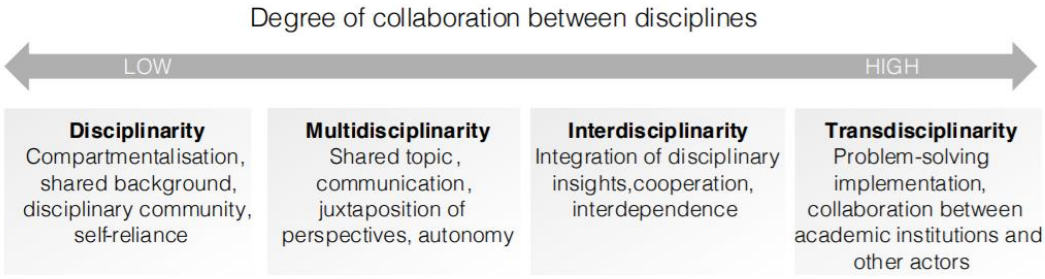

Figure 5. *Different types of collaboration between disciplines. (Reused from* [75] *Under a CC BY-SA 4.0. licence)*

As mentioned in the beginning of the general introduction, this thesis stems from need to approach HIVDR in sub-Saharan Africa in a transdisciplinary way. The work presented here is meant to provide a baseline for future transdisciplinary endeavours and aims to reflect the viewpoints of different scientific and societal actors as well as PLHIV themselves. This is done by studying the complexity of HIVDR, which came from the need to have deeper insight in the interconnected network of all elements involved before starting up a transdisciplinary process. To this end, I have continuously aimed to include different scientific and societal perspectives throughout this work in order to integrate knowledge from different sources in the systems maps and guard the societal relevance of the work.

1.4.2 Complex adaptive systems

When addressing a wicked problem, there is a need to understand the diverse underlying factors influencing it as one interconnected system. Interventions should be designed keeping this whole dynamic system in mind, rather than aiming to reduce the problem to a linear cause-effect model (Figure 6). Such dynamic systems are also called complex adaptive systems (CASs) and have been defined by Plsek et al. as *"a collection of individual agents with the freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent's actions changes*

the context for other agents" [77]. This means that when an intervention is successful in one part of the system, it does not necessarily guarantee that the core issue is resolved as well.

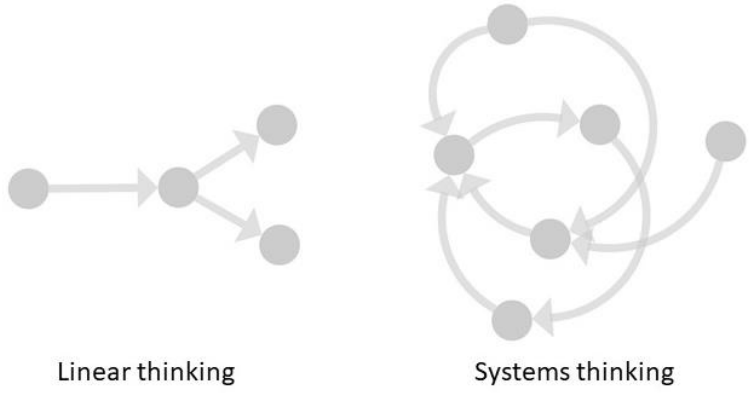

Figure 6*: Difference between linear thinking, which aims to reduce the problem to a limited set of cause-effect interactions, and systems thinking, taking into account the whole dynamic, interconnected system and feedback loops.*

Additionally, successfully resolving an issue in one place of the system, may result in an unwanted or counterproductive effect elsewhere in the system. An example of this is the case of the additional duty hours allowance in Ghana, described by Agyepong et al. (2012) [78]. The case study describes how one military hospital in Ghana decided to increase the salary for doctors in order to make the job more attractive and to recruit young doctors. While this is a linear solution for the problem, the pay raise in this one hospital led to a whole cascade of country-wide strikes. First the doctors in the public sector who had also been dissatisfied about their low wages went on a strike, eventually leading the government to increase their salary by means of additional duty hours allowances. A whole series of strikes followed, in which different healthcare worker groups and later also other sectors demanded a salary reform. Agyepong et al. analyse the case in depth and suggest that a systems thinking approach and the use of tools such as causal loop diagrams could have helped decision makers in Ghana to mitigate this crisis.

While originally systems thinking was mainly used to study climate change and sustainability challenges, in recent years it is also increasingly being used to address

complex public health problems [79–82]. A literature review about systems thinking in health research found that while some terminology is common in systems thinking related manuscripts, in general the vocabulary used is still dispersed and a core jargon has not yet been established [82]. In Table 1 we summarize and define the most important terminology used in this thesis.

Table 1: *Systems thinking/complexity science related terminology used in this thesis.*

Term	Definition
Adaptation	The capacity of the system to modify its behaviour in order to adapt to an internal or external change.
Complex adaptive system	*"A collection of individual agents with the freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent's actions changes the context for other agents"* [77].
Connection	The causal relationship between two elements.
Culture	The shared values and believes which are intrinsically part of the system and which, as such, contribute to the system dynamics and information flows [83].
Element	A single component of the system which interacts with other components. These can be individuals in for example social network models, but in this thesis the elements represent factors such as viral load or stigmatization.
Emergence	Spontaneous behaviour which arises when individual actors or elements reorganize themselves into a bigger whole [83].
Feedback loop	A series of elements that influence each other in a circular way [83].
Path dependence	Events that started at the same point, can lead to different outcomes, depending on the choices that are made during the process [83].
Tipping point	A point at which the system will rapidly change and eventually settle into a new balanced state [83].

1.4.3 Systems mapping

A common way to visualize a CAS is through systems mapping. Systems maps visualize the interactions between the elements of a system. The nature of these elements and connections are different for different types of systems maps. Table 2 gives an overview of three commonly used mapping methods. While in this thesis we will focus on the use of causal loop diagrams, it is important to note that other types of mapping also exist. Causal loop diagrams are sometimes transformed in stock and flow diagrams to make a more quantitative representation of the system or make computer simulations [84]. Social network maps can be of value to study the complexity of the interactions between different actors and institutions [85].

Table 2: *Overview of common systems mapping methods.*

Mapping type	Elements	Connections
Causal loop diagrams	Factors with a certain polarity, which can for example increase vs decrease, or improve vs worsen	Positive or negative causal relations
Social network maps	Individuals or institutions	Represents information flows between actors
Stock and flow diagrams	Stocks of entities that increase or decrease	Flows between entities (exchange rate over time)

The causal relations between elements can be positive, negative or both (Figure 7). A positive causal relation indicates that both elements will evolve in the same direction. For example, when more HIV tests are done, more HIV-positive cases will be detected. The detected cases are therefore a direct effect of the number of HIV tests done. Vice versa, we can also say that when less HIV tests are done, less HIV-positive cases will be detected. In case of a negative causal relation, both elements evolve in the opposite direction. For example, when there are more hospitalizations, the number of free hospital beds will decrease and vice versa, less hospitalizations will result in a higher number of free beds. It is also possible that a relationship can be both positive or

negative depending on the circumstances. For example, a better health can lead to an increase in adherence because the client has felt the benefits of adhering to therapy and wants to stay healthy, but it could also lead to a decrease in adherence when the client for example believes he or she is cured and does not need any more therapy.

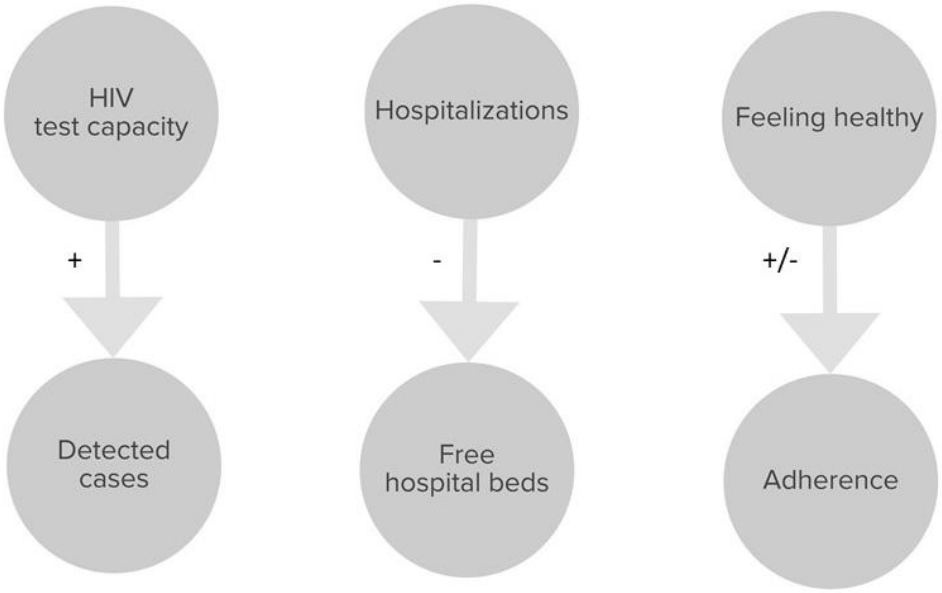

Figure 7: *Illustration of positive, negative and mixed connections as described in section 1.4.2 of this manuscript.*

1.4.4 Leverage points

Because CASs are non-linear, constantly changing and unpredictable, intervention points can be difficult to identify and can sometimes even be counter-intuitive. In CASs, interventions should be aimed at leverage points, which are points in the system where a relatively small intervention can have a system-wide impact, positively affecting the core problem. In 1999, Meadows published a list of 12 leverage points in a system, which was later summarized by Abson et al. into four main groups (Table 3) [86,87]. The leverage points are divided between deep and shallow leverage points. An intervention in a shallow leverage point is relatively easy to implement but will also have a rather short-term impact which is limited to only part of the system. Interventions at deep leverage points on the other hand, are more difficult to implement but will also have a system-wide and long-term impact.

Table 3: *Places to intervene in a system as categorized by by Abson et al. with an explanation and examples in the field of HIV for each category.*

	Leverage points (Abson et al., 2016)	Explanation	Examples
Shallow leverage points	Parameters	Modifiable numbers or set targets	Patient/provider rate, funds spent on HIVDR research, HIVDR testing rate
	Feedbacks	Reinforcing or balancing feedback loops giving more information on the interactions between elements	In absence of treatment or prevention the larger the infected population, the more people would be at risk which again increases the infected population. This is a reinforcing feedback loop.
Deep leverage points	Design	The structure, rules and organization of a system and information flows	The pill pick-up frequency as foreseen by local guidelines. Centralized versus decentralized care.
	Intent	This depend on the goal towards which the system is oriented and is related to its underlying values and paradigms	95-95-95 goals by 2030: eliminating HIV by testing, treatment and suppressing viral load

The lower in the table the deeper the leverage point. Several studies have engaged in the identification of leverage points for wicked problems, mainly in the field of sustainability science [88–90]. A literature review on interventions targeted at different leverage points for sustainability transition found that the vast majority of sustainability research articles focus on shallow leverage points [91]. While no such literature review has been done yet for public health research, we assume that also in this field the main intervention focus lies on shallow leverage points as these are simply more tangible and straight-forward to implement. Yet, interventions should preferably be targeted at deep leverage points in order to have a system-wide effect. While there is a growing body of theoretical literature on systems thinking and the identification of leverage

points, there is a lack of practical tools and guidelines on how to go about such research [82].

Complex interventions aimed at leverage points can be evaluated through the realist synthesis approach, first described by Pawson et al. [92,93]. This review method aims to understand which interventions work, how they work, for whom and in which context, by understanding the underlying causal relations. This method has predominantly been used for understanding the complexity of healthcare interventions. The realist synthesis approach starts from another perspective than Meadow's leverage points as it is a review method to understand the complex workings of already implemented interventions, whereas Meadow's theory aims to help researchers and policy makers to identify good points in the system to implement new interventions. Moreover, the realist synthesis approach does not include a visualization of the system as such. Nevertheless, both approaches may complement each other in identifying complexity-informed interventions at leverage points, potentially based on empirical data from a realist review of already existing interventions.

1.4.5 Qualitative research design

The integration of systems mapping methodology into a qualitative research design described in this manuscript is rooted in a grounded theory perspective. This is a widely used theory in social science in which a phenomenon is studied based on the analysis of real-world data, which leads to the development of new theories [94]. In this dissertation, the adoption of a grounded theory perspective is mainly reflected in the fact that the developed methodology was inspired by the Qualitative Analysis Guide of Leuven (QUAGOL) which on its turn is rooted in grounded theory [95]. Grounded theory has certain methodological characteristics, some of which were used in this research to build up a methodology for qualitative systems mapping [96]. For instance, theoretical sampling is used to select research participants based on progressive insights formed during the analysis of previously collected data. Data is collected until theoretical data saturation is reached, implying that a point is reached in which further data collection does not bring further insights into the phenomenon. Another important aspect of grounded theory is the constant comparison in which the researcher constantly links back codes or emerged theories to the original data.

Chapter 2

Objectives

Although much is understood about the causes of HIVDR, rising resistance levels are threatening the efficiency of ART, especially in low-and middle-income countries. As the factors influencing HIVDR are diverse and related to different scientific disciplines, societal actors and social structures, we studied HIVDR as a CAS in order to identify local drivers, feedback mechanisms and leverage points, laying a basis for sustainable systems change. Additionally, while there is a significant body of literature available on systems thinking and CASs, this concept is not yet well known and operationalized in the field of medicine.

The general objective of this dissertation is therefore twofold:

1) Exploring the potential of systems mapping for studying the complexity of HIVDR as a CAS, in order to identify drivers, feedback loops and leverage points of HIVDR in sub-Saharan Africa.
2) To operationalize a systems mapping approach for the analysis of complex public health problems as CASs.

The specific objectives addressed in Chapter 3-5 are the following:

1. Systems mapping as a **foundation** for a transdisciplinary approach towards HIVDR: integrating diverse disciplinary viewpoints on HIVDR to generate complexity-informed insights in the CAS of HIVDR.
2. **Case study:** systems mapping to identify the local drivers and feedback loops of the CAS of HIVDR in the Ukonga and Gongolamboto area of Dar es Salaam, Tanzania, identifying potential leverage points, and comparison with the international systems map.
3. **Methods**: operationalizing systems mapping methodology to visualise and analyse complex public health problems as CASs, facilitating the transfer of methodology to other study sites and other topics.

The novelty of this study relates to both the subject and the methodology. First, while several wicked problems have been studied by means of systems thinking methodology, by our knowledge this is the first time HIVDR is approached as a CAS. Gaining insight in the complexity of the system by incorporating insights from different scientific disciplines, and societal actors will provide a basis for future transdisciplinary

projects to develop and implement complexity-informed interventions together with the involved actors. Second, this thesis contributes to the operationalisation of systems thinking methodology within the field of public health, in which the linear thinking model has remained dominant so far.

Chapter 3

Exploring the mechanisms behind HIV drug resistance in sub-Saharan Africa: conceptual mapping of a complex adaptive system based on multi-disciplinary expert insights

Research article

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This chapter is based on the published version of the article. Part of Supplementary Table 2 is also included in the published article but has been represented here only in Supplementary Table 2, to enhance readability of the chapter.

Abstract

HIV drug resistance (HIVDR) continues to threaten the effectiveness of worldwide antiretroviral therapy (ART). Emergence and transmission of HIVDR are driven by several interconnected factors. Though much has been done to uncover factors influencing HIVDR, overall interconnectedness between these factors remains unclear and African policy makers encounter difficulties setting priorities combating HIVDR. By viewing HIVDR as a complex adaptive system, through the eyes of multi-disciplinary HIVDR experts, we aimed to make a first attempt to linking different influencing factors and gaining a deeper understanding of the complexity of the system.

We designed a detailed systems map of factors influencing HIVDR based on semi-structured interviews with 15 international HIVDR experts from or with experience in sub-Saharan Africa, from different disciplinary backgrounds and affiliated with different types of institutions. The resulting detailed systems map was conceptualized into three main HIVDR feedback loops and further strengthened with literature evidence.

Factors influencing HIVDR in sub-Saharan Africa and their interactions were sorted in five categories: biology, individual, social context, healthcare system and 'overarching'. We identified three causal loops cross-cutting these layers, which relate to three interconnected subsystems of mechanisms influencing HIVDR. The 'adherence motivation' subsystem consists of opposite forces that ultimately create a balancing loop leading to a different set-point of adherence per individual which may vary over time. The 'healthcare burden' subsystem consists of a reinforcing loop leading to an increase in HIVDR at local population level. The 'ART overreliance' subsystem is a balancing feedback loop leading to complacency among program managers when there is overreliance on ART with a perceived low risk to drug resistance. The three subsystems are interconnected at different levels.

Interconnectedness of the three subsystems underlines the need to act on the entire system of factors surrounding HIVDR in sub-Saharan Africa in order to target interventions and to prevent unwanted effects on other parts of the system. The three theories that emerged while studying HIVDR as a complex adaptive system form a starting point for further qualitative and quantitative investigation.

Introduction

HIV drug resistance

HIV drug resistance (HIVDR) remains a threat to the effectiveness of antiretroviral therapy (ART). Over the last decade, major efforts have been made to achieve the global 90-90-90 goals by 2020 and to end the HIV epidemic as a public health threat by 2030 [97]. However, levels of HIVDR are rising, compromising the effectiveness of ART and potentially also the efforts to attain the last 90 goal [98]. In 2017, mathematical modelling predicted that if left unchecked, excess levels of pretreatment HIVDR to the non-nucleoside reverse transcriptase (NNRTI) drug class could directly lead to 890 000 AIDS deaths, 450 000 new infections, and 6.5 billion USD extra ART costs by 2030 in sub-Saharan Africa (SSA) [32]. Recently several cases of multi-drug class resistant HIV have been reported [99,100].

Several causes of both pretreatment HIVDR and acquired HIVDR have been described in the literature. Due to the high genetic variability of the virus, selective pressure stemming from a combination of incomplete adherence (defined here in the broader sense of not taking ART as prescribed, which can be influenced by a multitude of factors which are both within and out of the control of the clients themselves) and a low genetic barrier of ART may lead to the emergence of HIVDR [101]. In addition to biological and pharmacokinetic factors influencing the selection and emergence of HIVDR lie other, indirectly related factors. In a meta-analysis Shubber et al. identified diverse barriers to adherence such as forgetfulness, traveling, medication toxicity, stigmatization, food insecurity, alcohol or substance misuse [45]. Other crucial aspects to prevent HIVDR are for example sufficient ART availability and a well-functioning ART supply system [102]. These and other factors described in literature relate to several fields of science and in some cases also to other complex problems. For example, ART drugs have been reported to be used in a mixture of recreational drugs called whoonga in South Africa [103–105]. The complex problem of drug abuse, is therefore linked to HIVDR as this exposure to ART may have consequences for pretreatment drug resistance.

Despite the fact that most of the factors contributing to HIVDR are presumed to be known, and that models to mitigate these causes have been built, pretreatment HIVDR, especially in SSA, is still increasing [106].

HIVDR as a complex adaptive system

As the factors influencing the emergence of HIVDR are numerous, have roots in different fields of science and are interconnected with other complex problems, we argue that HIVDR should be approached as a complex adaptive system (CAS), combining knowledge of diverse experts and stakeholders. Such systems have been defined by Plsek et al as '*a collection of individual agents with the freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent's actions changes the context for other agents*' [77]. A successful intervention on one element of the system does not guarantee resolving the core problem. Rather, interventions should be planned keeping in mind the entire system, its particular dynamics and possible feedback loops and with the aim of reshaping the system in a favourable way [77,80]. Feedback loops can be reinforcing or balancing, meaning that a change in a certain direction will either evolve into more change or balance itself out by propagating an opposite effect. CASs have been studied in several other contexts such as ecosystem management, healthcare management and obesity [81,107,108]. Moreover, the importance of using systems thinking in health care has been widely described in the literature [77,80,82,109,110]. In 2017, Rutter et al. described the need of approaching public health problems as complex systems in order to identify, implement and evaluate effective interventions [80]. Such interventions should be done at leverage points in the systems. These are points where a small intervention can have a large impact on the system [87]. Identifying leverage points is difficult and sometimes counterintuitive. Gaining insights in subsystems or feedback loops may therefore facilitate the identification of leverage points [89].

With this study, we aimed to make a first attempt at understanding the complexity behind HIVDR by combining the expertise and viewpoints from different HIVDR experts. In this article we describe how we identified three interconnected feedback loops influencing HIVDR by developing a systems map that represents the CAS of HIVDR in sub-Saharan Africa based on the insights of international HIVDR experts from different disciplines. We discuss the insights gained from these feedback loops and possible applications for quantitative modelling, complexity-informed intervention design and policy development [111,112].

Methods

Recruitment, inclusion criteria and setting

The systems map was designed based on semi-structured interviews with international experts from or with experience in SSA. For the purpose of this study, international experts were defined as stakeholders from diverse disciplines and institutions, working at an international level on HIVDR related to SSA and with a minimum of five years of experience. The participants were selected based on their expertise concerning HIVDR and with the aim of creating a mix of backgrounds and institutions covering all aspects of HIVDR. Purposive sampling was done starting from the expertise and connections of the Rega Institute and the Institute for the Future in Leuven, Belgium. This was supplemented with snowball sampling, using the expertise and connections of participants, and theoretical sampling, looking for the missing perspectives based on the emergent findings. They were contacted through email or in person when an opportunity presented itself, for example at international conferences. The interviews were held face to face (n=6) or online over Skype or Zoom (n=9) and were conducted in English. Semi-structured interviews of approximately 60 minutes were conducted until data saturation was reached, aiming to cover all possible factors influencing HIVDR in SSA. For the purpose of this study we describe data saturation as the point at which no new elements were uncovered in new interviews and no new connections which significantly changed the final conceptual model, were uncovered.

Semi-structured interview guide

An interview guide was designed with the input of several HIVDR and social science experts and was adapted according to insights developed through analysis (Supplementary file 1). The guide contained three sections: the first section entailed sociodemographic questions concerning the interviewees gender, age and educational background. The questions of section two related to the interviewees professional and personal experience with HIV or HIVDR in SSA. The third and main section covered their perspectives on the factors influencing HIVDR. All experts were asked what, in their experience, were the main causes of HIVDR. As a general guideline, the interviewer aimed to cover the following four areas: causes related to 1) availability of ART at the healthcare centre, 2) PLHIV's ability to fetch ART, 3) PLHIV taking ART as

prescribed and 4) ART suppressing the viral load. Additionally, when causes outside these four areas came up, they were also further discussed. Subsequently, depending on the expertise of the participant, follow-up questions such as “What do you think is causing the situation you just mentioned?” aimed to clarify the deeper reasons behind some of those initially indicated causes.

Data analysis

Analysis of the semi-structured interviews was done by a grounded theory approach inspired by the QUAGOL method and done simultaneously with the data collection [95]. After each interview a technical report was written describing relevant characteristics of the participant and interview context, helpful for understanding the data in their specific context. The interviews were transcribed verbatim by an external firm and the quality of each transcription was verified by listening to the audio tapes and correcting possible errors in the transcripts. Each transcript was (re-)read until a list of factors influencing HIVDR as well as connections between those factors, mentioned either explicitly or implicitly by the interviewee, was extracted. Connections were assigned a positive, negative or dual polarity. A positive connection indicates that the influencing and influenced element evolve both in the same direction (e.g. A -> B: when factor A increases, B increases too). A negative connection indicates that both elements evolve in the opposite direction (e.g. A-> B: when factor A increases, B decreases and vice versa). A dual connection indicates that both effects are possible. Take the following paraphrased quote as an example: “You know, sometimes people form peer support groups so that each month someone will pick up the medication for the whole group. This way people have to go only once every six months instead of on a monthly basis.” This would be translated into a negative arrow from “peer support group” to “required frequency of hospital visits”. Subsequently for each of the first six interviews separately, these factors were visualized in a small systems map while re-reading the interview again in order to visualize all the mentioned connections between these factors. Afterwards the separate systems maps of the first six interviews were merged together into one and from that point onwards data from the following interviews was added to the map. Throughout the analysis newly discovered insights were constantly compared with previous findings resulting in an iterative process of re-reading interviews and reviewing the detailed systems map. For our clustered systems map, elements were assigned a theoretical cluster by one researcher, based on

qualitative analysis. Clusters were validated through discussions within the research team and with external stakeholders.

The model was visualized in Kumu, an online mapping tool which enables the user to save data such as interview quotes and memos for each element and connection [113]. In the first, confidential, version of the systems map, all interview quotes which mention a certain element or connection, are collected in the comment fields associated with the element or connection in the Kumu tool, facilitating our analysis. From this first draft systems map causal loops were identified manually as series of elements connected to each other in a circular way. Causal loops which contributed to the same mechanism were identified as a subsystem (this can be compared with a road map: all possible routs you could take to go from Brussels to Amsterdam would be classified together as the subsystem “routs from Brussels to Amsterdam”). Because the subsystems consisted of many elements and connections, they were conceptualized into one overall mechanism per subsystem which reflected the overall messages of interviews as good as possible. While each separate element and connection was mentioned in one or several interviews, the resulting feedback loops are based on the combination of knowledge from the different experts. The conceptualization of the subsystems was linked back to the original interviews, discussed with several stakeholders and strengthened with literature evidence.

Results

Systems map of factors influencing HIVDR as informed by the expertise of different HIVDR experts

In total 15 international experts were interviewed. Table 4 summarizes the scientific and institutional background of the interviewees. A diverse sample of experts with different expertise and institutional affiliation was reached, permitting us to gain insights in the various aspects of the CAS. Out of the 15 participants, 13 were researchers or had previous research experience in the field of HIVDR. Data saturation for elements (factors influencing HIVDR) was reached after about nine interviews and for connections (pathways of influence between two elements) after 12 interviews (Figure 8).

Table 4: *Participant characteristics: different backgrounds and institution types of the interview participants. Note that some participants had a background in several fields of science or were working for more than one institution.*

Scientific background	N	Institution type	N
Medicine (public health/tropical medicine)	5	Global policy-making institution	3
Virology	4	Local policy-making institution	2
Epidemiology and public health	4	Hospital	2
Psychology	2	NGO	5
Finance	1	Pharmaceutical company	1
Human rights law	1	Insurance company	1
Engineering	1	University	3
Nursing science	1		
Economy	1		
Business	1		
Anthropology	1		

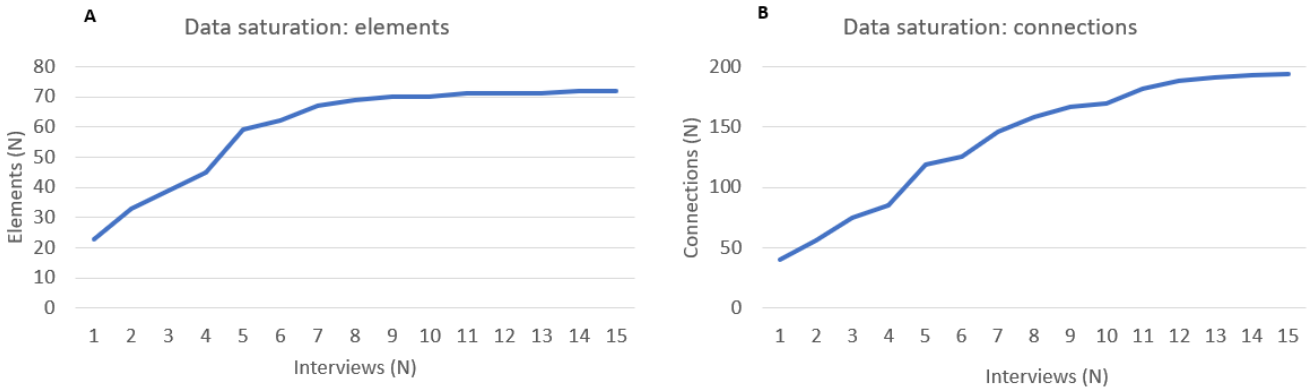


Figure 8: *Data saturation curves. A) Number of elements in the systems map after each consecutive interview. B) Number of connections in the systems map after each consecutive interview.*

The subsystems behind HIVDR

We visualized the system in two ways, based on the data collected from the semi-structured interviews [114]. The first visualization divides the elements in five layers according to their relation to biology (elements and processes happening inside the body), individual factors (psychology, personal factors and behaviour of adherence), social context (personal characteristics as a member of the community and baseline conditions in the community), healthcare system (treatment plan and healthcare organization), and 'overarching' factors (such as international policy, research and funding). The visualization and list of elements and connections can be found in Supplementary Figure 1 and Supplementary Table 2 and 3 respectively.

For the second visualization we grouped the same elements and connections in ten different thematic clusters (Figure 9). The clusters represent elements belonging to the same themes identified in the interview data, being adherence and retention in care, biology, clinical manifestations, complex problems, genetic barrier of the medication, global effort to tackle HIVDR, health literacy and empowerment, health system resources, psychosocial factors and quality of care. The elements included in each cluster are presented in Table 5. When visualizing these clusters and the connections between them, three major feedback loops or sub-systems emerge, indicated by the three circles in Figure 9.

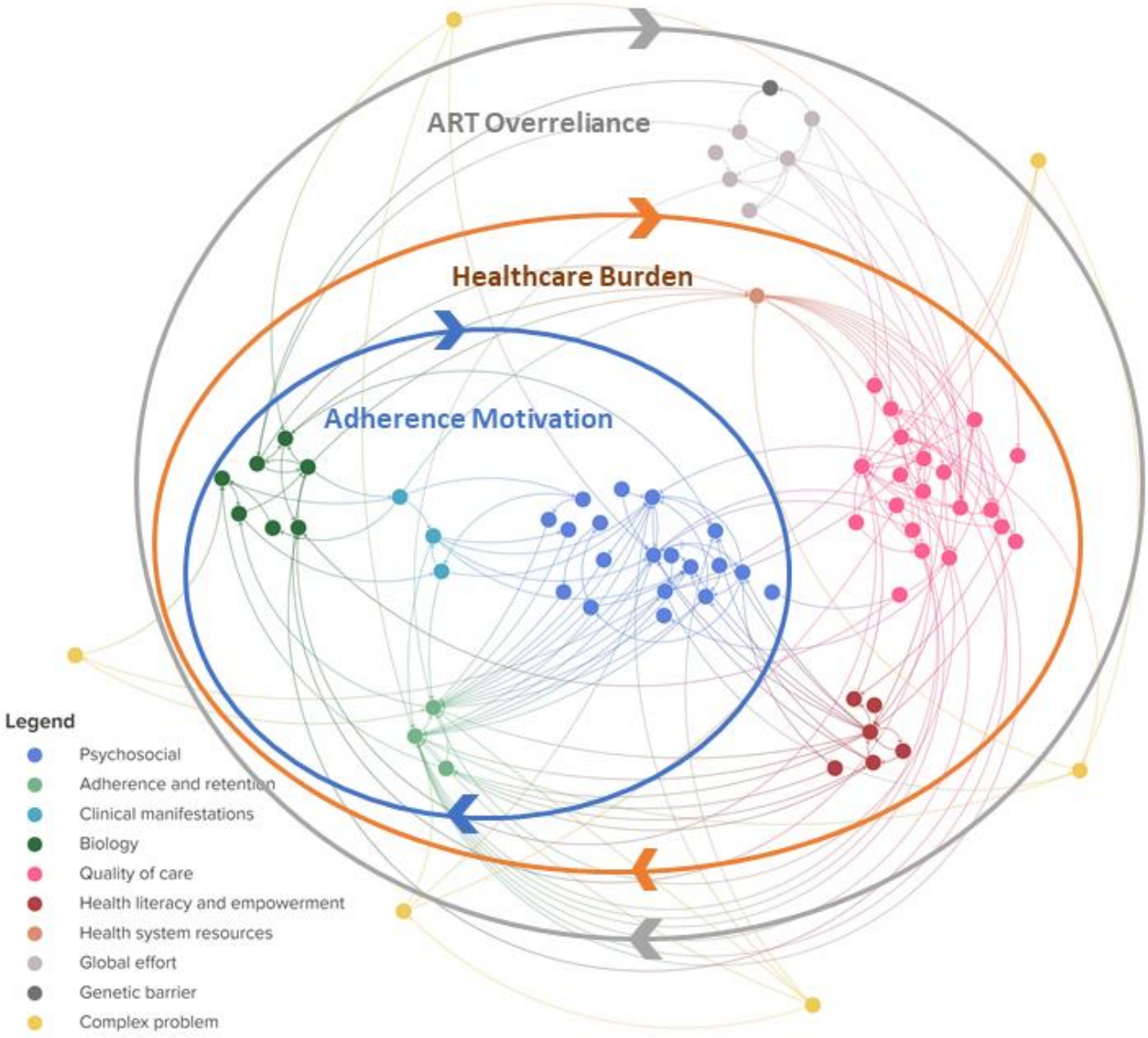


Figure 9: *Clustered systems map visualizing three interconnected subsystems. Each cluster of elements is represented in a different colour, corresponding to the colours used in Figure 10 and connects elements related to a certain theme. Note that all elements and connections represented here are the same as the ones presented in Supplementary Figure 1 but organized in clusters instead of in layers. Three main subsystems are indicated in the blue, orange and grey overlaying circles. An interactive overview this map, can be found on the interactive Kumu platform*[1] [114].

[1] https://Annemie.kumu.io/identifying-mechanisms-behind-hiv-drug-resistance-in-sub-saharan-africa-a-systems-approach?token=meUKVHYzmT1jrNse – page 1

Table 5: *Overview of elements included in each cluster of Figure 9.*

Adherence motivation subsystem		**Healthcare system burden**		**ART overreliance subsystem**	**Interconnected wicked problems**
Psychosocial	Social support	**Quality of care**	Timely acting on unsuppressed viral load	**Global effort to tackle HIVDR**	Food insecurity
Acceptance of HIV status	Substance abuse	Accessibility of health centre (including safety)	Tracing of PLHIV	Drug prices	Gender inequality
Community stigma and gossip	**Adherence and retention**	Adherence counselling	Well-functioning supply chain	Global effort to tackle HIVDR	Lower social status
Concerns about side effects of ART	Adherence	Administrative and political barriers	**Health literacy and empowerment**	HIVDR funding	Migration
Depression	Engagement and retention in care	ART treatment approach / policy	Individual and community empowerment	Need to show success of the ART programme	Punitive laws for MSM and sex workers
Engagement in risk behaviour	Engagement in alternative care	Assuring quality of ART	Individual education level	Research focus	War and disease outbreaks
Financial situation	**Clinical manifestations**	Availability and quality of equipment	Incentive to search for information	Resource allocation with focus on population	
Forgetfulness	Concurrent disease and opportunistic infections	Patient-provider relationship	Misinformation	**Availability of ART with a higher genetic barrier**	
Having examples of well-functioning ART	Feeling and looking healthy	Competence of healthcare workers	Religious beliefs	Availability of better drugs	
HIV status disclosure	Side effects of ART	Correct prescribing practices	Understanding of HIV infection and treatment		
Hospital design	**Biology**	Distance to the healthcare centre	**Health system resources**		
Linguistic issues	Drug levels in body	Healthcare provider stigma	Healthcare system workload		
Pill burden	Drug-drug interactions	Job satisfaction and motivation of healthcare workers			
Pill fatigue	Efficiency of drug combination	Peer support group			
Priority given to treatment	HIVDR selection	Quality of data systems			
Readiness to start taking ART	Optimal absorption of drug	Required frequency of hospital visits			
Self-stigmatisation	Transmission of HIV(DR)	Resistance (and subtype) testing			
Social obligations	VL suppression	Stock availability of ART and reagents			

1. Adherence motivation subsystem

The first subsystem suggests a mechanism at the personal level through which people living with HIV (PLHIV) may alternate between periods of optimal and suboptimal adherence. In different periods of their lives, PLHIV may give more or less priority to their treatment depending on several factors. When less priority is given to the ART and doses are missed, the viral load will not be suppressed and HIV related illness may develop. When feeling physically unwell, treatment may again be prioritized over other activities leading to a better adherence. When the viral load is suppressed and the individual feels better, other activities may take precedent and doses of ART may be skipped. When studying this subsystem, it is important to keep in mind that this alternating behaviour can occur only a limited number of times before HIVDR emerges, after which optimal adherence will not lead to a better physical condition anymore.

We also note that not all individuals follow the pathways of this subsystem. PLHIV may fail to adhere even when feeling physically ill, or on the contrary, may have a continuous optimal adherence. This interplay between factors influencing an individual's adherence has recently been described in a qualitative systematic review [115]. The authors describe how a combination of factors can lead to the decision of PLHIV to either adhere to ART or not and how this is a dynamic process of switching between adherence and non-adherence.

2. Healthcare burden subsystem

The second subsystem is situated at the programme level and relates to the burden on the healthcare system which, when too high, may jeopardize the quality of service delivery. Services provided at the healthcare centre, such as adherence counselling, viral load testing or pill pick-up are essential to sustain viral load suppression but may be compromised when the healthcare system is overburdened. This may lead to delayed acting on a detectable viral load which on its turn leads to emergence of HIVDR and/or transmission of HIV(DR), requiring additional counselling and viral load tests. This, on its turn, increases the healthcare system workload. In short, this loop represents a sequence of events through which a high burden on the healthcare system amplifies itself. On the programme level, a high burden on the healthcare system may lead to delays in acting on non-suppressed viral load as the testing itself may be delayed due to insufficient laboratory and sample transport capacity or the

healthcare workers may not have time to file reports or to return test results. HIVDR emergence resulting from a delay in acting on unsuppressed viral load in turn contributes to an increase in overall HIVDR burden at the personal and programme level. The World Health Organization reports that, though the African region carries the highest disease burden, they have the highest population/provider ratios [116]. In line with our findings, a study in Cameroon identified high health system workload as a possible risk factor for emerging HIVDR [117].

3. ART overreliance subsystem

At the population level, the availability of ART with a high potency and a high genetic barrier for resistance such as combinations including second generation integrase inhibitors offers a new and promising line of therapy. However, several interviewees expressed the concern that resistance against second generation integrase inhibitors such as Dolutegravir will eventually arise given that the first cases of resistance have already been reported [118–120]. With the introduction of integrase inhibitor-based ART in SSA, highly active treatment with a low risk to emergence of drug resistance, policy makers and in particular doctors, risk to overly rely on the effectiveness of the treatment. This shifts the healthcare focus to increasing the numbers of PLHIV on treatment at the cost of assuring high quality care for all. However, when adherence issues are left unsolved, the possibility of developing resistance against new ART regimens, despite their high genetic barrier, remains. This finding is supported by the review of Hamers et al. and by the findings of the ADVANCE trial that pretreatment HIVDR to NRTIs and/or NNRTIs predicts virologic failure for regimens containing Dolutegravir [121,122]. Altogether, this subsystem suggests that the use of ART with a higher genetic barrier to resistance alone may not be sufficient to prevent HIVDR and should always be supported by high quality service delivery. We currently see an interest in long-acting drugs with a high genetic barrier to drug resistance, which may facilitate adherence, but may again result in overconfidence, thereby increasing the risk of HIVDR in the long run if not implemented in the context of a systems approach. A similar reasoning has been made by Inzaule et al., who point out the challenges associated with the roll-out of dolutegravir such as reduced effectiveness of the therapy due to NRTI resistance and uncertainty about dolutegravir resistance due to insufficient access to viral load testing [44].

When interpreting the subsystems described above it is important to keep in mind that they are constantly influenced by each other and by other complex problems such as food insecurity, gender inequality or war and disease outbreaks. Figure 10 represents a summarized version of the three subsystems as presented in Figure 9.

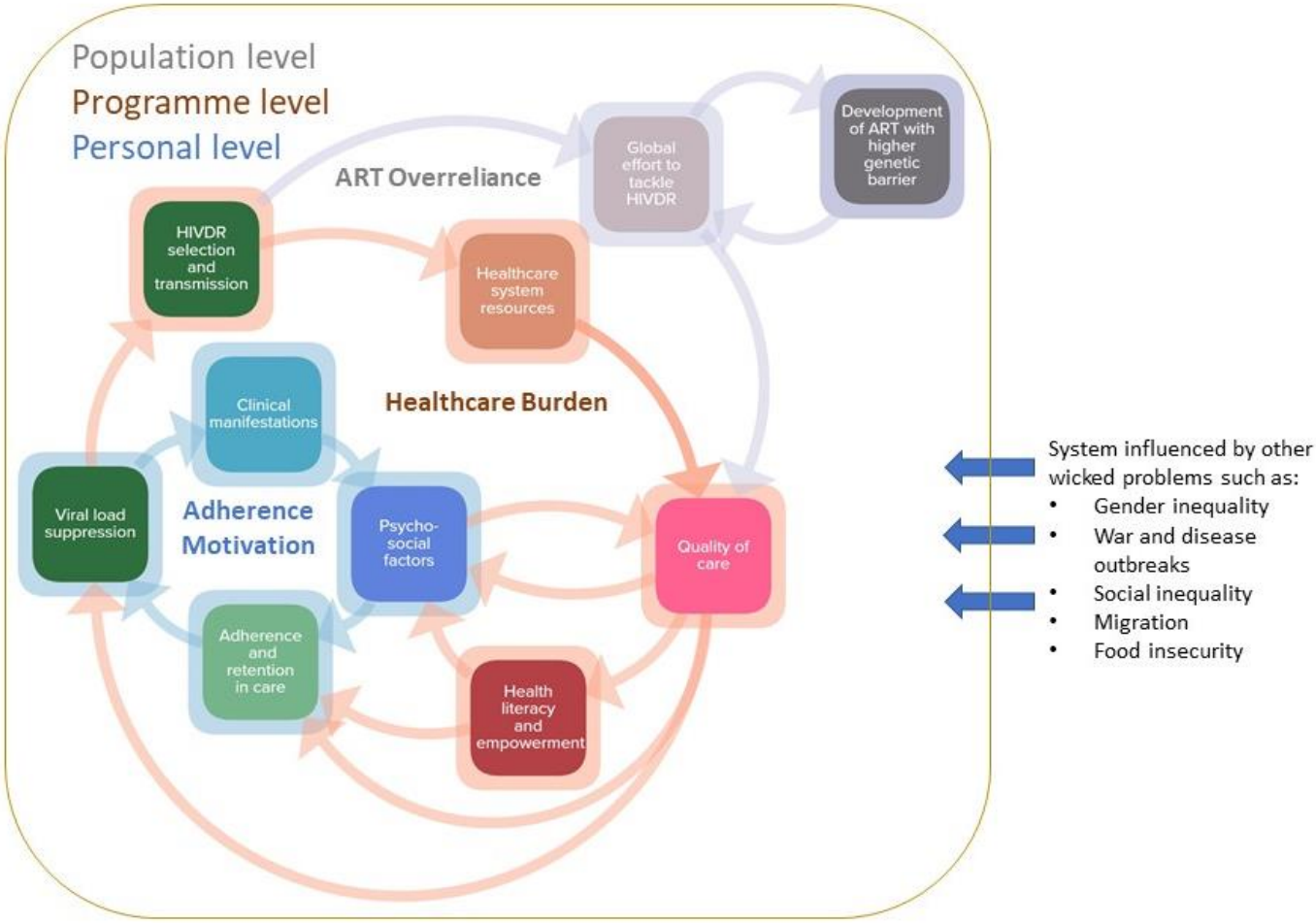


Figure 10: *Three identified interconnected subsystems driving HIVDR. The adherence motivation subsystem at the personal level, the healthcare burden subsystem at programme level and the ART overreliance subsystem at the population level. Each square in this map represents a cluster of Figure 9, indicated by the corresponding colours.*

Subsystem interactions

The three subsystems described above exist on different societal levels (personal, programme and population level) and are intrinsically linked with each other. The alternating adherence subsystem takes place on the personal level until HIVDR emerges, at which point the individual will add to the burden of the healthcare system.

The increased burden on the healthcare system may then impact the overall quality of care, which in turn may impact the adherence of PLHIV through a delayed switch in ART after detection of viral non-suppression, thus increasing the chances of personal- and population-level HIVDR emergence. Diminished quality of ART service delivery may also impact adherence counselling and support, thereby directly impacting the alternating adherence subsystem at the personal level. Both pathways will eventually lead to an increase in HIVDR, which is reacted upon at the population level by researching and developing new drugs that are more forgiving with respect to adherence (e.g. long-acting drugs) and that have higher genetic barriers to resistance. Policy makers overly relying on these new ART regimens may shift focus away from high quality service delivery and HIVDR prevention measures. As described above, decreased quality of care may then impact the healthcare system burden at the population level and/or alter personal-level adherence.

The HIVDR system is influenced by several other complex problems at different points in the three subsystems. Food insecurity for example, may negatively affect adherence considering PLHIV have to take the ART with a meal each day. Other examples are political instability and disease outbreaks (such as the COVID-19 pandemic), which may destabilize the healthcare system, increase the burden on healthcare personnel and may cause PLHIV to have priorities other than adherence to ART.

Discussion

In this paper, we, by our knowledge, approached HIVDR for the first time as a CAS by combining the perspectives of experts from diverse disciplines. We visualized the CAS of factors influencing HIVDR in two ways: a layered and a clustered view. We then summarized this detailed systems map into three interconnected subsystems influencing HIVDR emergence. We want to highlight that other ways of summarizing the detailed systems map are possible, but the three subsystems presented here were identified by the researchers as the most prominent ones throughout a process of analysis and stakeholder feedback.

The designed systems map provides insight in some properties of CASs such as emergence, adaptation and feedback and allowed to visualize the three interconnected subsystems [123]. The interplay between factors influencing adherence is an example of emergence, which indicates a phenomenon that cannot be predicted purely based

on the elements related to it but which rather emerges from a complex interplay between the factors. Adherence is influenced by factors stemming from each of the five layers and is influenced at both personal, programme and population level. Whether PLHIV adhere to treatment or not depends on the interplay between those surrounding factors which are constantly changing over time. Adaptation describes how interventions in the system can lead to behavioural changes. Our systems map shows that the implementation of second-generation integrase inhibitors could lead to a change in adherence as a result of the overreliance of policy makers and doctors and depending on how the new therapy is introduced to the community and whether education and other support is provided. The feedback loops summarized here in the three subsystems reveal the interconnectedness between subsystems at different population levels and between factors of different layers and disciplines. This also underlines the need to reflect on the entire system surrounding HIVDR when planning an intervention.

An important shortcoming of this study is that only expert viewpoints were included. To make up for this, we aimed to include experts who have close contact with PLHIV and thus have insights in their perspectives. However, in order to design locally tailored interventions, the systems maps should be strengthened with insights from PLHIV and local actors. In follow-up work that has in the meantime been published, a systems map based on the perspectives of local actors and PLHIV provided us with a better understanding of the personal and context dependent factors such as stigmatization or food insecurity [124]. This shifted the focus of the map with perspectives of local actors and PLHIV towards the “adherence motivation loop”, compared to the work presented here. For other study sites, perspectives of PLHIV and other local stakeholders such as local doctors or politicians, religious leaders, and other people of local influence could also help us better understand the differences in perspectives between those groups and identify possible gaps between science and practice. We also need to acknowledge that the mapping was done based on facts but also viewpoints and experiences of international experts. Combining the expertise of multidisciplinary HIVDR experts in a systems map has allowed us to identify three potentially interesting theories, represented by the three subsystems above, which may not have surfaced through disciplinary or purely quantitative research. This

qualitative approach was important to deepen our understanding of the CAS, before future quantitative efforts on specific parts of the system can be done [125].

Applications

Our study illustrates the added value of qualitative methodology to visualize the complexity and dynamics of a system. This may help decision makers to gain insight into the systems complexity and to identify leverage points in order to design targeted and complexity-informed interventions. This methodology can be transferred to study HIVDR in specific settings or could be used to gain insights into other complex problems. Moreover, the content of the model presented in this study may (partially) be extrapolated to other chronic diseases such as diabetes or obesity in order to understand their drivers and feedback loops.

The conceptual model presented here also lays the basis for quantitative mathematical modelling of the factors influencing HIVDR. This will allow quantitative modelers to collect data on relevant parameters in the system to monitor any changes, desired or not, in the entire system. An important advantage of basing a quantitative model on this conceptual map lies in the multidisciplinary manner this map was developed, therefore identifying mechanisms which might not have been identified using a monodisciplinary approach.

Conclusion

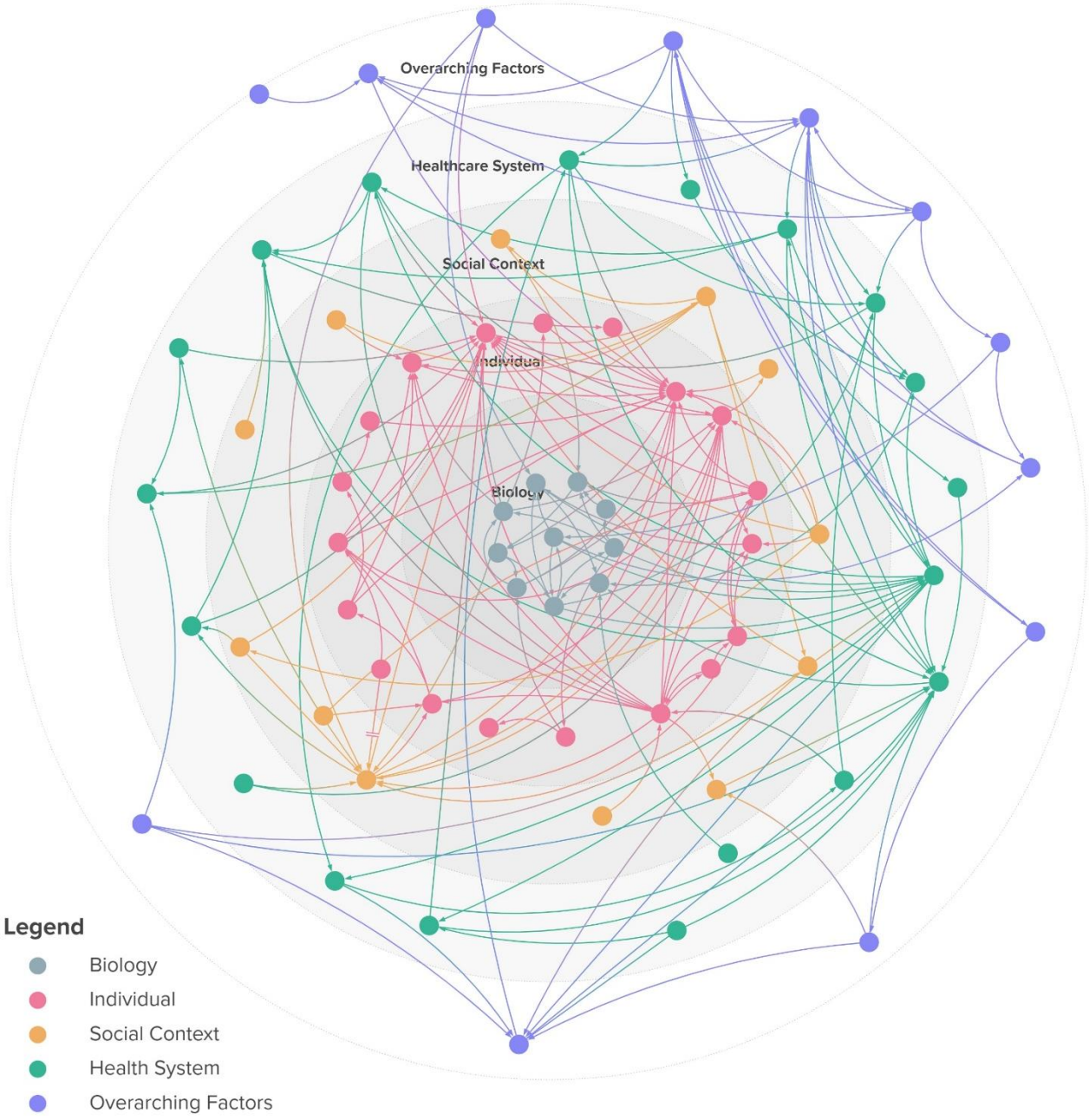
We successfully visualized the CAS surrounding HIVDR which is influenced by a complex and interconnected system of factors, transcending disciplines and population levels. This allows us for the first time to study the emergent and adaptive properties of the CAS and to distinguish feedback loops. The model suggests that i) overreliance on ART with a low risk to HIVDR emergence may be a driver for future HIVDR against those same ART; ii) when exceeding a certain threshold, the burden on the healthcare system amplifies itself; and iii) adherence tends to vary given that it is very individual- and context-dependent and might therefore be difficult to be influenced directly. A deeper understanding of the different aspects of this system will help decision makers to identify leverage points in order to design targeted and effective interventions in line with the complexity of the system.

Declarations

Ethics approval and consent to participate

This project is not within the scope of the Belgian Law regarding research on human subjects of 7/5/2004 [126]. This study did not involve patients and the interviews did not contain personal questions, but rather involved questions about expert opinions on an international scientific problem, therefore, ethics approval was not required. Before the interviews began, all experts were informed about the study aim and methods and provided informed verbal consent for participation in the study. Participation was voluntary and the experts were free to terminate the interview at any time. Data was collected between October 2018 and February 2020. Face to face interviews were done in Italy and South Africa. We obtained a statement of a local ethical committee confirming that ethical approval in Italy was not necessary. We also refer to the Italian law of 5 June 2019 “garante per la protezione dei dati personali”. None of the four experts interviewed during a conference in South Africa, had the South African nationality. Ethical approval was not needed for this research as the South African Health Act of 2003 covers only research done on South African citizens. The interviewees were not study subjects but rather provided their professional opinion about a complex public health problem. Moreover, both the researcher who conducted the interviews and the principal investigator followed a South African good clinical practice course.

Supplementary materials



Supplementary Figure 1: *HIVDR as a CAS, visualized in layers. Each element represents a factor influencing HIVDR and each line represents a connection between two factors. Factors are organized in five layers according to their connection with biology, the individual, the social context, the healthcare system and overarching factors. A detailed and interactive version of this map can be found on the Kumu platform*[2] [114].

[2] https://Annemie.kumu.io/identifying-mechanisms-behind-hiv-drug-resistance-in-sub-saharan-africa-a-systems-approach?token=meUKVHYzmT1jrNse – page 2

Supplementary Table 1: *Overview of the elements as represented in Figure 9 and Supplementary Figure 1. Each element is described for coding purposes, to clarify what can or cannot be coded under this element. For each element, the layer, subsystem and cluster are indicated.*

Label	Description	Layer	Subsystem	Cluster
Acceptance of HIV status	Includes (not) coming to terms with the HIV infection and feeling (un)comfortable with it but also denying the infection and refusing to believe being HIV-positive.	Individual	Motivation	Psychosocial
Accessibility of health centre	Includes road access, public transportation, safety on the road, etc. It does not include distance as this is a separate category. Health centres may not be reachable in situations of war or disease outbreak where the health system is destabilised, people are living in refugee camps with little access to care etc. The health centre may also be less accessible for some people for financial reasons when someone is not able to pay the transportation costs, or for practical reasons such as opening times. When a pharmacy is only open during working hours this may be a barrier for some people to pick up their medication. This also includes offering treatment or testing outside the hospital for example in youth educational centres.	Healthcare system	Healthcare burden	Quality of care

Adherence	Adherence is defined as taking the correct dose of the prescribed ART at the correct time, every day. This can be influenced by individual related factors but also by factors which are outside of the patients control (such as drug stock-out).	Individual	Motivation	Adherence and retention
Adherence counselling	Includes explaining the individual anything there is to know about ART and HIV but also the time spent to understand the personal situation and help search for the best way to live with HIV.	Healthcare system	Healthcare burden	Quality of care
Administrative and political barriers	Includes administrative barriers for all kinds of actions such as ART supply chain and general healthcare centre functioning.	Overarching	Healthcare burden	Quality of care
ART treatment approach / policy	Includes all aspects of the ART treatment approach such as which persons receive which treatment, when are VL and HIVDR tests done, etc.	Overarching	Healthcare burden	Quality of care
Assuring quality of ART	This includes (both voluntary or involuntary) storage problems, or unavailability of high-quality ART for certain sub-populations.	Healthcare system	Healthcare burden	Quality of care
Availability and quality of equipment	Includes the availability of equipment for viral load testing but also any other basic but necessary equipment such as ventilators etc.	Healthcare system	Healthcare burden	Quality of care
Availability of better drugs	Including ART with a higher genetic barrier but also for example long acting drugs.	Overarching	ART overreliance	Genetic barrier
Community stigma and gossip	Includes any segregating act of community members or spreading of rumours, based on the HIV status of the person. This includes also "double stigmatisation" of PLHIV who are also gay or sex workers. Community stigma includes also stigmatisation by family members.	Social Context	Motivation	Psychosocial

Competence of healthcare workers	Includes the healthcare workers skills, both technical and soft skills and the trainings they follow.	Healthcare system	Healthcare burden	Quality of care
Concerns about side effects of ART	Fears or concerns that PLHIV may have about ART especially when they feel healthy before starting treatment or whether they have seen the side effects in other people.	Individual	Motivation	Psychosocial
Concurrent disease and opportunistic infections	Includes any disease or infection a PLHIV may have. This may either be a result of lowered immunity because of HIV infection or be unrelated to HIV infection. Does not include side effects related to ART treatment.	Biology	Motivation	Clinical manifestations
Correct prescribing practices	Includes both drug combination and dosage.	Healthcare system	Healthcare burden	Quality of care
Depression	Includes mental health issues both related or unrelated to HIV and ART.	Individual	Motivation	Psychosocial
Distance to the healthcare centre	The physical distance between the individual's home and the healthcare centre they choose to enrol in.	Healthcare system	Healthcare burden	Quality of care
Drug levels in body	This is not the dosage but the level of functional ART in the body (which may differ after drug interactions etc.).	Biology	Motivation	Biology
Drug prices	The price at which drugs are sold to governments (assuming ART is distributed to patients for free).	Overarching	ART overreliance	Global effort
Drug-drug interactions	Does not include interactions with traditional medicines (see "engagement in alternative care").	Biology	Motivation	Biology

Efficiency of drug combination	Includes altered or suboptimal efficiency because of the dosage (whether prescribed correctly or not, or affected by for example crushing of pills), therapy combination, storage issues etc.	Biology	Motivation	Biology
Engagement and retention in care	This covers linkage to care after a positive HIV test and after that, the presence of the patient at every follow-up visit or pill pick-up.	Individual	Motivation	Adherence and retention
Engagement in alternative care	Includes all types of unconventional treatment such as traditional healthcare, cure through religious prayers, etc.	Individual	Motivation	Adherence and retention
Engagement in risk behaviour	Includes all behaviour that may result in transmission of HIV or HIVDR, both consciously or unconsciously.	Individual	Motivation	Psychosocial
Feeling and looking ill	Feeling physically ill related to HIV infection, HIVDR emergence or opportunistic infections. Feeling ill because of side effects of ART does not belong in this category but in the category "side effects of ART".	Biology	Motivation	Clinical manifestations
Financial situation	This describes whether an individual has the financial means available to pay the direct (e.g. medication) and indirect (e.g. transportation, food) costs of HIV care.	Social Context	Motivation	Psychosocial
Food insecurity	Some ART needs to be taken with a meal in order to be absorbed correctly which may be a problem for individuals who do not always have a meal available. They may then choose to skip a dose of ART in order to avoid side effects. Some individuals also experience an increase in appetite when taking ART.	Social Context	Interconnected complex problem	Complex problem
Forgetfulness	Simply forgetting to take one’s medication (when none of the other here described factors are involved).	Individual	Motivation	Psychosocial

Gender inequality	Include any gender related issue which can impact adherence or retention in care. For example: women not being able to make decisions about their own health because of financial dependence on their husbands or non-disclosure because of fear of violence. But also gender related issues for men fall under this category.	Social Context	Interconnected complex problem	Complex problem
Global effort to tackle HIVDR	This includes the general global priority given to HIVDR research, funds allocation, resource allocation etc.	Overarching	ART overreliance	Global effort
Having examples of well-functioning ART	For example, community members or public figures who are adhering to ART and who are healthy.	Individual	Motivation	Psychosocial
Healthcare provider stigma	Including the stigmatizing attitude a healthcare provider may have against PLHIV but also against vulnerable populations such as MSM and sex workers.	Healthcare system	Healthcare burden	Quality of care
Healthcare system workload	Includes both understaffing, increasing the workload for the staff that is present, and on the other hand an overload of HIV patients.	Healthcare system	Healthcare burden	Health system resources
HIV status disclosure	Includes informing family, friends, community, healthcare staff, employer, etc. of the HIV status. Either voluntary or involuntary, by the patient him/herself or by another person.	Individual	Motivation	Psychosocial
HIVDR Funding	This covers funding for any expenses related to HIV drug resistance at the healthcare system but also concerning research projects.	Overarching	ART overreliance	Global effort

HIVDR Research focus	Including developing ART with less side effects, ART with a high genetic barrier and long acting therapy in order to reduce the amount of hospital visits needed. But next to pharmaceutical research, knowledge is also needed on the barriers of adherence, specific for certain populations and the interplay between them in order to develop high quality frameworks and encourage the global effort to tackle HIVDR. This includes also interdisciplinary collaboration in research.	Overarching	ART overreliance	Global effort
HIVDR selection	Definition as written in WHO HIV drug resistance report 2019 "HIV drug resistance (HIVDR) is caused by one or more changes (mutation/s) in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus. All current antiretroviral (ARV) drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus. People receiving ART can acquire HIVDR, and people can also be infected with HIV that is already drug resistant." [98]	Biology	Motivation	Biology

Hospital design	Includes the separation versus integration of the HIV clinic but also the privacy level at the hospital (leaving the door open during consultation etc.).	Healthcare system	Motivation	Psychosocial
Incentive to search for information	The active search for information on HIV infection resulting in either a better understanding or misinformation.	Individual	Healthcare burden	Health literacy and empowerment
Individual and community empowerment	WHO defines empowerment as "a process in which patients understand their role, are given the knowledge and skills by their health-care provider to perform a task in an environment that recognizes community and cultural differences and encourages patient participation." [127]	Social Context	Healthcare burden	Health literacy and empowerment
Individual education level	Includes literacy but also general education level.	Social Context	Healthcare burden	Health literacy and empowerment
Job satisfaction and motivation of healthcare workers	Includes the motivation of healthcare workers to provide high quality care, maintain equipment, implement new projects and policy changes and to keep their job. Also includes reasons for being satisfied (or not) with their job and feeling ownership about one's job.	Healthcare system	Healthcare burden	Quality of care
Linguistic issues	In sub-Saharan Africa many different languages are spoken and not everyone may have adherence counselling available in his or her own language and may have problems to fully understand the counselling in another language. Moreover, one hypothesis is that language can shape the way people view the HIV infection because of some cultural linguistic factors involved.	Social Context	Motivation	Psychosocial
Lower social status	Who is seen as having a lower social status depends on the community but may include MSM (men who have sex with men), sex workers, children, women, etc.	Social Context	Interconnected complex problem	Complex problem

Migration	Includes migration for any kind of reason, for example due to political instability, disease outbreak or job searching.	Social Context	Interconnected complex problem	Complex problem
Misinformation	Includes misunderstandings about HIV and treatment on both the individual and population level. Does not include religious beliefs.	Individual	Healthcare burden	Health literacy and empowerment
Need to show success of the ART programme	Donors often require conditions (numbers, rather than quality of care) to be met in order to hand out the next round of funding. They need to do this to keep an oversight of their money. On the other hand, this can be a barrier for the country itself which might ignore some existing problems in order to be able to write a better report.	Overarching	ART overreliance	Global effort
Optimal absorption of drug	Several factors such as diarrhoea disease or drug-drug interactions may affect the correct absorption of ART in the body. Absorption can also be compromised when the ART is not taken with food.	Biology	Motivation	Biology
Patient-provider relationship	Includes the trust the patient has in the provider, whether the patient feels comfortable to ask questions, whether the healthcare provider is friendly etc.	Healthcare system	Healthcare burden	Quality of care
Peer support group	Includes peer support in all its forms (psychological support, peer education, logistic support, etc.).	Healthcare system	Healthcare burden	Quality of care
Pill burden	Includes pills for HIV treatment but also pills taken to treat other diseases.	Individual	Motivation	Psychosocial
Pill fatigue	Being tired of having to take medication every day for the rest of one’s life.	Individual	Motivation	Psychosocial
Priority given to treatment	Includes the priority given by the individual to ART treatment compared to other things such as social events.	Individual	Motivation	Psychosocial

Punitive laws for MSM and sex workers	Includes all reasons for which the legal environment can impact adherence, retention or HIVDR emergence and transmission for certain populations.	Overarching	Interconnected complex problem	Complex problem
Quality of data systems	Including whether the system is paper based or electronic, whether systems are synchronised between facilities, whether reports can be found back easily, whether data entry can be done fast etc.	Healthcare system	Healthcare burden	Quality of care
Readiness to start taking ART	Includes mental preparedness to start taking ART.	Individual	Motivation	Psychosocial
Religious beliefs	Including the believe that HIV is a punishment of God etc.	Social Context		Health literacy and empowerment
Required frequency of hospital visits	Includes how often the individual has to visit the healthcare centre for all kinds of HIV related check-ups. Does not include peer support meetings.	Healthcare system	Healthcare burden	Quality of care
Resistance (and subtype) testing	Includes testing of HIVDR mutations and also testing of the HIV virus subtype.	Healthcare system	Healthcare burden	Quality of care
Resource allocation with focus on population	This covers the difficult ethical decisions that may need to be taken when limited resources are available, about which ART to provide and for whom, so that as many people as possible benefit from them.	Overarching	ART overreliance	Global effort
Self-stigmatisation	Stigmatizing feelings towards oneself including self-blame, the feeling to be punished by god, etc.	Individual	Motivation	Psychosocial
Side effects of ART	Includes fatigue, hallucinations, feeling hungry, etc.	Biology	Motivation	Clinical manifestations
Social obligations	Includes cultural events such as weddings and funerals but also other work obligations.	Social Context	Motivation	Psychosocial
Social support	Includes psychological, practical and financial support community or family members may give to a PLHIV.	Social Context	Motivation	Psychosocial

Stock availability of ART and reagents	Includes having a sufficient stock of ART and other reagents for viral load tests etc. at the healthcare centre. Does not include possible supply chain issues as these are categorized under "well-functioning supply chain". Does however include issues which are not dependent on the supply chain such as a lack of funding.	Healthcare system	Healthcare burden	Quality of care
Substance abuse	Includes alcohol abuse and other substance abuse.	Individual	Motivation	Psychosocial
Timely acting on unsuppressed viral load	Includes both healthcare system related reasons and individual related reasons. Timely acting on unsuppressed viral load (VL) includes the detection of unsuppressed VL and thus access to VL testing and tracing individuals to encourage them to take VL tests but also making sure the samples arrive timely in the laboratory, having enough laboratory capacity to analyse the tests and good quality equipment to do so. Moreover, reagent stock-outs can be an issue preventing the timely analysis of a blood sample. Once analysed, a good data system needs to be in place for the results to arrive back at the health centre.	Healthcare system	Healthcare burden	Quality of care
Tracing of PLHIV	Tracing of individuals who are lost to follow up and who missed appointments.	Healthcare system	Healthcare burden	Quality of care
Transmission of HIV(DR)	When HIV is transmitted between people (for example by unprotected sex, mother-to-child transmission, etc.). This includes transmission of HIV to a previously uninfected person, but also the transmission of a drug resistant virus to someone who was previously infected only with a non-resistant virus.	Biology	Motivation	Biology

Understanding of HIV infection and treatment	Includes understanding how and when to take the ART, why it is important to take the ART as prescribed, what happens when ART is not taken as prescribed etc., both on the individual and population level.	Individual	Healthcare burden	Health literacy and empowerment
Viral load suppression	Defined in several low-and middle-income countries as having viral load levels of under 1000 copies/ml or as being undetectable for the viral load essay used.	Biology	Motivation	Biology
War and disease outbreaks	Includes all reasons for which wars and disease outbreaks can influence HIVDR emergence and spread both on healthcare system level and on the individual level.	Overarching	Interconnected complex problem	Complex problem
Well-functioning supply chain	Includes everything from keeping track of the amount of ART needed to ordering the correct amount of ART and all the steps the order has to go through before it arrives in the clinic.	Overarching	Healthcare burden	Quality of care

Supplementary Table 2: *Connections as presented in Figure 9 and Supplementary Figure 1. The connection type represents the polarity of the connection. A positive connection type indicates that both elements evolve in the same direction (when element A increases, element B will increase too, and vice versa). A negative connection type indicates that both elements will evolve in the opposite direction (when element A increases, element B will decrease, and vice versa).*

From	To	Type	Description
Acceptance of HIV status	Adherence	+	Denial of HIV status may cause people to pick up their medication but then throw it away or not take it. This includes denial at diagnosis but also situations in which PLHIV feel well and after a few years start doubting whether they are really HIV+.
Acceptance of HIV status	Engagement and retention in care	+	Includes denial at diagnosis but also situations in which PLHIV feel well and after a few years start doubting whether they are really HIV+.
Acceptance of HIV status	HIV status disclosure	+	Includes situations in which people consider themselves not infected with HIV and therefore don't disclose their status to others.
Acceptance of HIV status	Priority given to treatment	+	When HIV status is not accepted, ART treatment is likely to be less prioritised.
Accessibility of health centre	Engagement and retention in care	+	Retention in care may be easier when the healthcare system is easier accessible. Accessibility includes road access, public transportation, safety on the road, etc. It does not include distance as this is a separate category.
Adherence	Drug levels in body	+	Skipping doses of ART leads to lower levels of ART in the body.
Adherence counselling	Readiness to start taking ART	+	Counselling and psychological support can help prepare the client to start taking ART.
Adherence counselling	Understanding of HIV infection and treatment	+	Adherence counselling can help clients understand how to take the ART, what to do when they forget, what could be the consequences, and everything there is to know about ART treatment.
Administrative and political barriers	Individual and community empowerment	-	In order for communities to be empowered, policy makers have to recognise the issues they raise about possible flaws in the healthcare system.

Administrative and political barriers	Timely acting on unsuppressed viral load	-	This includes having to consult a 3rd line committee before switching which may take a lot of time.
Administrative and political barriers	Well-functioning supply chain	-	Includes burocratic or political barriers which may influence the supply chain.
ART treatment approach / policy	Competence of healthcare workers	+/-	This includes how the training of healthcare workers (and thus also their competence) can be influenced by the ART treatment approach and also what they are allowed to do and what not.
ART treatment approach / policy	Correct prescribing practices	+/-	Even if the healthcare worker prescribes according to the guideline, the guideline may be suboptimal in terms of drug combination, dosage, etc.
ART treatment approach / policy	Healthcare system workload	+/-	Includes several ways in which the ART treatment approach influences the workload such as task shifting to community health workers, how often VL tests should be done, etc.
ART treatment approach / policy	Required frequency of hospital visits	+/-	Frequency of hospital visits depends on ART treatment approach and may be less for stable clients.
ART treatment approach / policy	Timely acting on unsuppressed viral load	+/-	The ART treatment approach determines when a high VL is acted upon. How many VL tests have to be taken before a switch can be made? Should a switch in ART be approved by a special committee?
Assuring quality of ART	Efficiency of drug combination	+	The quality of ART may affect the efficiency of the drug combination because of production issues (both voluntary or involuntary), storage problems, or unavailability of high-quality ART for certain sub-populations.
Availability and quality of equipment	Timely acting on unsuppressed viral load	+	Includes the availability of equipment for viral load testing but also any other basic but necessary equipment such as ventilators etc.
Availability of better drugs	Global effort to tackle HIVDR	-	Describes how the availability of ART with a higher genetic barrier may put policy makers at ease, shifting their focus away from HIVDR.
Availability of better drugs	HIVDR selection	-	ART with a higher genetic barrier to resistance or long acting ART are expected lower the chances of developing HIVDR.
Community stigma and gossip	Adherence	-	Includes any impact community stigma and gossip may have on adherence. For example, clients who experience or are afraid of community stigma may refrain from taking their ART when then are in a public place or have visitors at the time they need to take their medication, to avoid others finding out about their status.

Community stigma and gossip	Distance to the healthcare centre	+	Clients who fear community stigma or gossip may choose to enrol in a healthcare centre which is further away from home.
Community stigma and gossip	Engagement and retention in care	-	Clients may refrain from engaging in care or returning for their appointments when they fear being recognized at the healthcare centre by community members.
Community stigma and gossip	Healthcare provider stigma	+	This link indicates that prejudices healthcare workers may have towards PLHIV or other vulnerable populations such as sex workers stem from the influence of the communities they grew up in/make part of.
Community stigma and gossip	HIV status disclosure	-	Includes situations in which non-disclosure of HIV status stems from the fear of community stigma and gossip.
Community stigma and gossip	Self-stigmatisation	+	Self-stigmatisation may be influenced by the stigmatising behaviour of community members surrounding the PLHIV (either towards the client or towards other people).
Competence of healthcare workers	Adherence counselling	+	This includes healthcare workers having the right skills and trainings but also how friendly they are etc.
Competence of healthcare workers	Correct prescribing practices	+	Includes the skills of the healthcare worker to prescribe the correct medication but also how to recognise that therapy is failing etc.
Competence of healthcare workers	Patient-provider relationship	+	Includes the skills of the healthcare worker which enables him or her to form a good relationship with the client.
Competence of healthcare workers	Timely acting on unsuppressed viral load	+	Includes skills such as recognising failing therapy but also the competence to enter data in the data system, to find back reports etc.
Concerns about side effects of ART	Adherence	-	Includes skipping doses of ART to avoid negative side effects.
Concurrent disease and opportunistic infections	Drug-drug interactions	+	Medication taken for concurrent diseases (such as TB medication) can interact with ART and therefore interfere with the correct absorption of ART.
Concurrent disease and opportunistic infections	Feeling and looking ill	+	Includes feeling and looking ill due to any type of illness.
Concurrent disease and opportunistic infections	Healthcare system workload	+	Opportunistic infections and other diseases increase the workload of the healthcare system, next to the regular HIV care.
Concurrent disease and opportunistic infections	Optimal absorption of drug	-	Concurrent diseases (such as diarrheal diseases) can interfere with the correct absorption of ART.
Concurrent disease and opportunistic infections	Pill burden	+	Includes ART therapy and any other pills the client may have to take for other illnesses, increasing the pill burden.

Correct prescribing practices	Efficiency of drug combination	+	Includes both a correct prescription of the dose and the correct therapy for the HIV subtype or possible resistance.
Depression	Adherence	-	Includes skipping doses of ART due to mental health issues (whether linked to HIV status or not).
Depression	Priority given to treatment	-	Includes situations in which ART treatment is reprioritised due to depression.
Depression	Substance abuse	+	Includes depression (both because of HIV diagnosis or for other reasons) leading to substance abuse (alcohol and other products).
Distance to the healthcare centre	Accessibility of health centre	-	The closer the healthcare centre is to home, the easier reachable it may be.
Distance to the healthcare centre	Engagement and retention in care	+/-	A long distance to the healthcare centre (both because there are no other options, or because the client chose to enrol far from home) may lead to disengagement from care or skipping appointments.
Drug levels in body	Side effects of ART	+	A higher dose of ART may lead to more side effects.
Drug levels in body	Viral load suppression	+	When a client stops taking ART the concentration in the blood declines slowly and there is a period of time where the virus is starting to replicate again, whereas the ART concentration takes longer to decline. This can lead to resistance.
Drug prices	Resource allocation with focus on population	-	High prices and big differences in prices between drugs may lead to difficult ethical decisions on which ART to provide and for whom.
Drug-drug interactions	Optimal absorption of drug	-	Interactions between drugs (such as TB drugs and ART) can affect correct absorption of ART.
Efficiency of drug combination	Viral load suppression	+	Better viral load suppression when the used drug combination is efficient.
Engagement and retention in care	Adherence	+	Retention in care here relates mainly to the appointments for pill pick up. Skipping other check-ups may not have an impact on adherence as long as ART are picked up timely.
Engagement and retention in care	Financial situation	-	Includes reasons for which engagement in care could lead to loss of income.
Engagement in alternative care	Adherence	+/-	Alternative healers (traditional or religious) may discourage or encourage PLHIV to adhere to ART.
Engagement in alternative care	Engagement and retention in care	+/-	Alternative healers (traditional or religious) may discourage or encourage PLHIV to retain in the conventional HIV care.

Engagement in alternative care	Misinformation	+/-	How engagement in alternative care (traditional healers, religious activities) may result in misinformation or believes about HIV. On the other hand, depending on the care given, it may also decrease misinformation.
Engagement in alternative care	Optimal absorption of drug	-	Traditional healers may prescribe roots or herbs which can interact with the ART and therefore affect drug absorption. (Traditional medicines are here not categorized as "drugs"; therefore, these interactions do not fall under drug-drug interactions.)
Engagement in risk behaviour	Transmission of HIV(DR)	+	Includes unprotected sex or other blood-blood contact resulting in transmission of HIV(DR).
Feeling and looking ill	Community stigma and gossip	+	Bing sick and therefore not being able to contribute to society may be a driver of community stigma.
Feeling and looking ill	Concerns about side effects of ART	+	When feeling healthy, the idea of facing possible side effects of ART may be a barrier to adherence.
Feeling and looking ill	Engagement and retention in care	+/-	Clients may stop engaging in care when feeling better and return only when they start feeling sick again. On the other hand, when feeling sick they may not be able to come to the healthcare centre without help. On again another note, visibly looking sick may enable clients to take time off work without disclosing their HIV status.
Feeling and looking ill	HIV status disclosure	+	On the one hand, when people look ill, the community may recognize the symptoms of HIV infection and therefore start to stigmatize them. On the other hand, when someone does not look ill but is seen collecting or taking ART, the community may understand that the person is HIV positive. Both are examples of involuntary status disclosure.
Feeling and looking ill	Priority given to treatment	+	When feeling healthy, clients may prioritise other things (such as food) over their ART treatment, or they may believe ART is not necessary anymore. On the other hand, having a previous experience of feeling ill before the start of ART treatment, may motivate the client to keep adhering, even when feeling healthy.
Financial situation	Accessibility of health centre	+	Includes financial reasons because of which the healthcare centre could be less accessible. For example: the price of transportation, but also the price of hospital food vs food made at home or not being able to take a day off work because of financial reasons.

Financial situation	Food insecurity	-	Not having the financial means to buy food to take with ART.
Financial situation	Migration	-	Lack of a stable income and the search of a job drives migration.
Financial situation	Priority given to treatment	+	Due to a poor financial situation clients may prioritize other things (like searching food for the family) over the ART. On the other hand, improving one's financial situation by getting healthy may be a driver for prioritizing treatment.
Financial situation	Timely acting on unsuppressed viral load	+	Includes for example not being able to pay for viral load tests. Does not include not being able to pay the bus ticket (this is reflected in the link Financial situation - > accessibility of health centre).
Food insecurity	Adherence	-	When clients don't have a meal available to take with the ART they may opt to skip a dose of ART.
Food insecurity	Optimal absorption of drug	-	Absorption can be compromised by not taking the ART with a meal.
Forgetfulness	Adherence	-	Includes skipping doses of ART because of simply forgetting to take the dose (and when none of the other factors here described applies).
Gender inequality	Adherence	-	Includes any way gender inequality may impact the adherence to ART of both men and women.
Gender inequality	Engagement and retention in care	-	Includes any way gender inequality may impact the engagement and retention in care of both men and women.
Gender inequality	Engagement in risk behaviour	+	Includes any way through which gender inequality could influence the participation in acts which may contain a risk of transmission of HIV.
Gender inequality	HIV status disclosure	-	Includes ways through which gender inequality can impact HIV status disclosure for both men and women.
Gender inequality	Lower social status	+	In some environments women are seen as having a lower social status.
Global effort to tackle HIVDR	ART treatment approach / policy	+	The general global tendency to focus on HIVDR or not influences ART treatment approaches in the sense that focus may shift from "getting as many people as possible on ART" to improving quality of care and adherence levels etc.
Global effort to tackle HIVDR	HIVDR Funding	+	The level of funding that goes to HIVDR issues, depends on the global effort towards tackling HIVDR.
Having examples of well-functioning ART	Acceptance of HIV status	+	How having an example of a family or community member taking ART and feeling healthy can facilitate the acceptance of HIV status.

Having examples of well-functioning ART	Community stigma and gossip	-	Knowing people (either public figures or personal contacts) who are taking ART and who are healthy, may reduce community stigma and gossip about PLHIV.
Healthcare provider stigma	Adherence counselling	-	Stigma the healthcare provider may have may influence the adherence message or healthcare provider may simply refuse to provide adherence counselling to certain populations.
Healthcare provider stigma	Engagement and retention in care	-	Retention in care may be influenced by stigmatisation by healthcare workers due to HIV status or other reasons.
Healthcare system workload	Adherence counselling	-	There may be very little time for adherence counselling when there is a high workload. Moreover, adherence counselling may be done by a health provider who doesn't have the right skills or knowledge.
Healthcare system workload	Competence of healthcare workers	-	Understaffing may mean that no medical doctor is present in the hospital or that healthcare workers don't have time to take extra courses or read new guidelines.
Healthcare system workload	Correct prescribing practices	-	Includes mistakes made because of the lack of time and high workload, but also healthcare staff having to write prescriptions without receiving the necessary training.
Healthcare system workload	Job satisfaction and motivation of healthcare workers	-	High work pressure can impact job satisfaction of the healthcare workers.
Healthcare system workload	Patient-provider relationship	-	There is a lack of time for the client and the provider to build up a good relationship because of the high workload.
Healthcare system workload	Timely acting on unsuppressed viral load	-	Includes all examples of why a high workload could delay the acting on high VL.
Healthcare system workload	Tracing of PLHIV	-	Including lack of human resources preventing the tracing of PLHIV, and other reasons.
Healthcare system workload	Well-functioning supply chain	-	Healthcare workers may not have time to make difficult calculations to order the right amount of ART.
HIV status disclosure	Adherence	+/-	Includes any impact HIV status disclosure may have on adherence. A positive impact could be not having to hide the ART from family members anymore. A negative impact could be the family members trying to discourage the client to take ART.
HIV status disclosure	Community stigma and gossip	+	(In)voluntary HIV status disclosure (such as visible side effects of ART or visible illness) can lead to community stigma and gossip.

HIV status disclosure	Engagement and retention in care	+	Includes reasons for which HIV status disclosure can facilitate engagement and retention in care. For example, that the client doesn't have to worry about hiding at the facility. Social support resulting from HIV status disclosure doesn't fall under this category because it has a separate pathway.
HIV status disclosure	Engagement in risk behaviour	-	When the HIV status is not disclosed it may be difficult to motivate to partners why protection should be used. Also other examples fall under this category.
HIV status disclosure	Social support	+/-	Includes examples of how social support can increase after HIV status disclosure but also how there can be less social support when for example the HIV status is disclosed involuntarily or how fear for a loss of social support can prevent people from disclosing their HIV status.
HIVDR Funding	Availability and quality of equipment	+	Availability and quality of equipment depending on HIVDR funding.
HIVDR Funding	HIVDR Research focus	+	Focus of research projects depending on the funder's priorities.
HIVDR Funding	Need to show success of the ART programme	+	Programmes need to show success to their funder in order to ensure future funding.
HIVDR Funding	Resistance (and subtype) testing	+	Includes the availability of HIVDR testing equipment but also their maintenance, salaries of staff etc.
HIVDR Funding	Resource allocation with focus on population	+/-	Limited funding and resources may lead to the need to make difficult ethical decisions on which ART to provide and for whom.
HIVDR Funding	Stock availability of ART and reagents	+	Availability of ART and reagents depending on HIVDR funding.
HIVDR Research focus	ART treatment approach / policy	+	How research focus and results influence the ART treatment approach. This includes developing new drugs but also information on which level of adherence is needed, how often VL should ideally be done etc.
HIVDR Research focus	Availability of better drugs	+	Including ART with a higher genetic barrier, long acting ART and ART with less side effects.
HIVDR Research focus	Required frequency of hospital visits	-	Includes research in different area's such as development of long acting ART but also the testing of decentralised care etc.
HIVDR Research focus	Resource allocation with focus on population	+	Research (with interdisciplinary collaboration) may help to make better decisions on how to allocate resources so that the most people benefit from them.
HIVDR selection	Global effort to tackle HIVDR	+	The global effort to tackle HIVDR may increase again only after HIVDR against new drugs (such as DTG) has risen.

HIVDR selection	Healthcare system workload	+	Clients with HIVDR have to come more often to the healthcare centre, will have extra counselling sessions before switching therapy and may need extra care if they have opportunistic infections, all leading to increased workload.
HIVDR selection	Transmission of HIV(DR)	+	HIVDR can be transmitted if the client is on failing therapy, has suboptimal adherence or is not on therapy.
HIVDR selection	Viral load suppression	-	HIVDR development may lead to viral load failure.
Hospital design	Community stigma and gossip	+/-	The hospital design may be stigmatising in several ways, for example if the ART clinic is separated, in a far corner of the hospital. On the other hand, an ART clinic inside the hospital which is clearly indicated to be the ART clinic, and where clients do not have privacy may also be stigmatising.
Hospital design	HIV status disclosure	+/-	Includes ways the hospital design could reveal the status of PLHIV coming to their appointment. For example, when the ART clinic is in a separate building with clear indication of the purpose of the building, HIV status may be involuntary disclosed.
Incentive to search for information	Misinformation	+	How the active search for information on HIV infection can result in misconceptions and misunderstandings of HIV infection and treatment.
Incentive to search for information	Understanding of HIV infection and treatment	+	How the active search for information on HIV infection can result in a better understanding of HIV infection and treatment.
Individual and community empowerment	Timely acting on unsuppressed viral load	+	Reduced patient empowerment leads to a delayed acting on high VL through a lower probability of attending visits but also less demand of testing, follow up etc.
Individual education level	Understanding of HIV infection and treatment	+	The literacy and general education level of a client may impact the level of understanding of HIV infection and treatment.
Job satisfaction and motivation of healthcare workers	Timely acting on unsuppressed viral load		This includes the ways the job satisfaction and motivation of healthcare workers can impact the timely acting on high VL.
Job satisfaction and motivation of healthcare workers	Well-functioning supply chain	+	Includes healthcare workers who are motivated to make correct calculations and order in time but also who take the effort to drive to other clinics when they run out of ART etc.
Linguistic issues	Adherence counselling	-	Including not being counselled in the client's mother language but also the difference in nuances between different translations.

Lower social status	Community stigma and gossip	+	People with a "lower social status" may be more prone to stigmatisation as the will concern both being HIV+ and being a MSM, a sex worker, …. Etc.
Lower social status	Engagement and retention in care	-	This covers population groups for whom it may be more difficult to retain in care (such as children).
Lower social status	Healthcare provider stigma	+	Healthcare workers may stigmatize people who according to them belong to a lower social class (such as MSM, sex workers etc.)
Migration	Engagement and retention in care	-	When constantly on the move it is difficult to retain in care. Also in refugee camps (quality) care may not be available.
Migration	Healthcare system workload	+	When the immigration in a certain city (for example due to job opportunity) is bigger than foreseen, it may cause an increase in the healthcare system workload.
Migration	Well-functioning supply chain	-	When the immigration in a certain city (for example due to job opportunity) is bigger than foreseen, there may be difficulties in predicting the amount of ART to order.
Misinformation	Community stigma and gossip	+	Stigmatisation can be driven by misinformation such as the fear of being infected by drinking from the same cup.
Misinformation	Engagement in alternative care	+	How different illness believes, misunderstanding or religious believes may drive people to enrol in alternative care (either combined with or instead of the conventional health care).
Misinformation	Engagement in risk behaviour	+	How certain believes and misunderstandings may be a driver for engagement in risk behaviour (mainly unsafe sex).
Misinformation	Understanding of HIV infection and treatment	-	In the context of this map, this link shows that misinformation automatically contributes to a lesser understanding of HIV infection and treatment.
Need to show success of the ART programme	Administrative and political barriers	+	How the need to show success of the ART programme to funders may prevent actions to be taken towards possible issues in the system.
Need to show success of the ART programme	HIVDR Funding	+	Programmes need to show success to their funder in order to ensure future funding.
Optimal absorption of drug	Drug levels in body	+	Absorption influences the levels of effective ART in the body.
Patient-provider relationship	Adherence counselling	+	Includes the ways in which the patient provider relationship can influence the adherence counselling (trust of the client, feeling comfortable to ask questions etc.).

Patient-provider relationship	Engagement and retention in care	+	For example, how a good relationship between the client and the provider may motivate them to stay in care.
Patient-provider relationship	HIV status disclosure	+	Ways the patient provider relationship caninfluence HIV status disclosure.
Patient-provider relationship	Understanding of HIV infection and treatment	+	A better relationship can directly help the client to gain a better understanding of the HIV infection and treatment.
Peer support group	Required frequency of hospital visits	-	For example, when each month another group member collects ART for all.
Peer support group	Understanding of HIV infection and treatment	+	Includes all the ways peer education can improve understanding of HIV infection and treatment.
Pill burden	Pill fatigue	+	Higher pill burden leads to more pill fatigue.
Pill burden	Side effects of ART	+	Includes the pill burden of ART and other therapies.
Pill fatigue	Adherence	-	When clients are discouraged from adhering to ART due to the fact that they need to take the medication every day for the rest of their lives (sometimes in combination with other medication).
Priority given to treatment	Adherence	+	Higher priority given to ART treatment leads to better adherence.
Priority given to treatment	Engagement and retention in care	+	Higher priority given to ART treatment leads to more engagement and retention in care.
Punitive laws for MSM and sex workers	ART treatment approach / policy	-	This implies that the legal environment for some vulnerable populations could influence the treatment they receive.
Punitive laws for MSM and sex workers	Community stigma and gossip	+	The illegal status of certain population groups contributes to the stigma surrounding them.
Punitive laws for MSM and sex workers	Engagement and retention in care	-	The legal situation may make it extra difficult for certain populations to engage in care or to keep their appointments.
Punitive laws for MSM and sex workers	Transmission of HIV(DR)	+	Punitive laws against MSM or sex workers discourage these people from seeking health services. If they have unprotected sex and their viral load is not suppressed they can transmit the virus.
Quality of data systems	Timely acting on unsuppressed viral load	+	Including whether the system is paper based or electronic, whether systems are synchronised between facilities, whether reports can be found back easily, whether data entry can be done fast etc.
Quality of data systems	Tracing of PLHIV	+	Including whether the system is paper based or electronic, whether systems are synchronised between facilities, whether reports can be found back easily, whether data entry can be done fast etc.

Quality of data systems	Well-functioning supply chain	+	Including mainly the difficulty of forecasting the correct amount of ART needed with a paper-based system, but other data system issues can also be included.
Readiness to start taking ART	Adherence	+	Being mentally prepared to start taking ART may improve adherence to ART.
Religious beliefs	Engagement in alternative care	+	Religious beliefs may drive PLHIV to search for alternative care options.
Religious beliefs	Self-stigmatisation	+	Self-stigmatisation may stem from misconceptions such as the believe that HIV is a punishment of God.
Required frequency of hospital visits	Engagement and retention in care	-	How a higher frequency of hospital visits may both improve or decrease retention in care depending on the client's preference.
Required frequency of hospital visits	Healthcare system workload	+	Includes all reasons for which the workload would increase if clients need to do more hospital visits and vice versa.
Resistance (and subtype) testing	Correct prescribing practices	+	Resistance testing allows to prescribe a more suitable treatment for the client.
Resource allocation with focus on population	Adherence	+	Includes all possible ways in which resources can be spent with a focus on improving adherence rather than developing new drugs.
Resource allocation with focus on population	ART treatment approach / policy	+	How the need to make difficult ethical decisions (because of limited resources) may influence the ART treatment approach. In the field of HIV but also concerning other health issues.
Self-stigmatisation	Acceptance of HIV status	-	Self-stigmatisation can hinder the acceptance of HIV status.
Self-stigmatisation	Depression	+	Self-stigmatisation may contribute to depression.
Self-stigmatisation	HIV status disclosure	-	The negative believes one has about their own HIV status may prevent them from disclosing to others.
Side effects of ART	Adherence	-	The side effects of ART including hallucinations or increased appetite can be a barrier to adherence.
Side effects of ART	Feeling and looking ill	+	Includes feeling and looking ill due to side effects of ART.
Side effects of ART	HIV status disclosure	+	Some ART can result in physical manifestations and therefore people may be recognised as being HIV positive. (Involuntary disclosure)
Social obligations	Financial situation	-	Some social events such as funerals are costly and can make a family "temporarily poor".
Social obligations	Priority given to treatment	-	Includes both family obligations such as funerals etc, and not being able to take time off work.

Social support	Adherence	+	Includes any type of social support which may improve adherence. For example: reminders to take ART, explaining why it is important to adhere etc.
Stock availability of ART and reagents	Adherence	+	This includes situations in which clients receive less ART or are not able to receive extra ART when they go travelling.
Stock availability of ART and reagents	ART treatment approach / policy	+	Limited resources (and ART availability) may lead to difficult ethical questions and decisions on which groups should be prioritized for receiving treatment.
Stock availability of ART and reagents	Job satisfaction and motivation of healthcare workers	+	Stock-outs for both ART and other medicines can impact job dissatisfaction of the healthcare workers as they are not able to help their clients.
Stock availability of ART and reagents	Required frequency of hospital visits	-	Including situations in which the ART stock is low and clients receive treatment for a limited number of days before they have to return to the healthcare centre.
Stock availability of ART and reagents	Timely acting on unsuppressed viral load	+	Including reagent stock outs for ART, reagents for viral load tests or other tests.
Substance abuse	Forgetfulness	+	Forgetting to take ART due to alcohol consumption.
Timely acting on unsuppressed viral load	Efficiency of drug combination	+	When keeping clients on a failing regimen the HIVDR can increase, making the current therapy less efficient.
Tracing of PLHIV	Engagement and retention in care	+	Tracing PLHIV who were lost to follow up can help them to reengage in care.
Tracing of PLHIV	Timely acting on unsuppressed viral load	+	When PLHIV (who were lost to follow up) are traced, acting on high viral load can be done timelier.
Transmission of HIV(DR)	Efficiency of drug combination	-	Superinfection with a drug resistant strain may render the client's current therapy ineffective.
Transmission of HIV(DR)	Healthcare system workload	+	Transmission of HIV increases the workload of the healthcare system as new people will have to enrol in HIV care. Transmission of HIVDR to either new clients or clients who were already HIV positive also increases the workload as these clients will need extra care.
Understanding of HIV infection and treatment	Acceptance of HIV status	+	Knowledge about HIV and treatment may help acceptance of HIV status, for example by understanding that ART is able to suppress the virus lifelong.

Understanding of HIV infection and treatment	Adherence	+	Includes understanding how and when to take the ART, why it is important to take the ART as prescribed, what happens when ART is not taken as prescribed etc.
Understanding of HIV infection and treatment	Community stigma and gossip	-	Stigmatising acts can be based on a lack of knowledge on the transmission of HIV such as the fear of being infected by sharing the same cup.
Understanding of HIV infection and treatment	Engagement and retention in care	+	Includes the understanding of the importance of engaging and retaining in care.
Understanding of HIV infection and treatment	Engagement in alternative care	-	Includes that clients who understand the transmission and treatment of HIV may be less inclined to search for alternative care options.
Understanding of HIV infection and treatment	Engagement in risk behaviour	-	Includes not knowing how HIV is transmitted and therefore not being careful in situations that may result in transmission.
Understanding of HIV infection and treatment	Incentive to search for information	-	Includes how people wo have questions about HIV start their own search for answers on social media, in the community etc.
Understanding of HIV infection and treatment	Individual and community empowerment	+	The more clients and communities in general understand about HIV, the transmission and the treatment, the more they are empowered to educate each other but also to take their care in their own hands and for example demand viral load tests.
Understanding of HIV infection and treatment	Priority given to treatment	+	The better the importance of adherence to ART is understood, the more priority is given to the treatment.
Understanding of HIV infection and treatment	Self-stigmatisation	-	Self-stigmatisation may stem from a lack of understanding and believing for example that HIV is a death sentence.
Viral load suppression	Concurrent disease and opportunistic infections	-	Lower susceptibility for opportunistic infections when viral load is suppressed.
Viral load suppression	Healthcare system workload	-	When the viral load is not suppressed clients have to visit the hospital more often, take extra counselling sessions etc. This increases the workload of the healthcare system.
Viral load suppression	HIVDR selection	-	When the viral load is not suppressed and adherence is sub-optimal, HIVDR can be selected.
Viral load suppression	Required frequency of hospital visits	-	In several cases when viral load is not suppressed, clients have to visit the hospital every month instead of every two or three months.
Viral load suppression	Transmission of HIV(DR)	-	When viral load is not suppressed, HIV can be transmitted. When viral load is undetectable however, the virus cannot be transmitted.

War and disease outbreaks	Accessibility of health centre	-	Health centres may not be reachable in situations of war or disease outbreak where the health system is destabilised, people are living in refugee camps with little access to care etc.
War and disease outbreaks	Migration	+	War and disease outbreaks drive migration.
War and disease outbreaks	Timely acting on unsuppressed viral load	-	Includes situations in which the health system is focused on other issues and therefore VL tests are delayed or not done. This does not include clients not reaching the healthcare system and ART stock outs as this is included in other categories.
War and disease outbreaks	Well-functioning supply chain	-	Includes all the ways in which the supply chain may be influenced by war or disease outbreaks.
Well-functioning supply chain	Peer support group	+	For the well-functioning of peer support groups, a well-functioning supply chain should be in place as it will include the extra step of getting the ART from the hospital to the peer support group.
Well-functioning supply chain	Stock availability of ART and reagents	+	Includes all the ways in which the supply chain influences the ART stock availability.

Supplementary file 1

Interview guide – International experts

1. Instructions to the interviewer

Instructions to the interviewer are in italics.

Text to be read is in bold.

If a respondent declines to answer a question, please write 'declined to answer' in the margin.

2. Information of the study

Hello, I am …. from …. working on a research project concerning HIV drug resistance. By interviewing experts from several fields, I aim to construct a broad overview of all possible factors leading to HIV drug resistance and possible solutions to these problems.

You have been selected for this interview because of your expertise in X. Before we start I would like to remind you that the information you provide is completely confidential. Your responses are recorded but this questionnaire does not have your name on it and is only identified by a number. If you have questions after we are finished, you can always contact me.

3. Interview information

Interview number:

Date of interview:

Interviewer name:

Location:

Time of start:

Language:

Part 1: Sociodemographic information

1.1 Gender of respondent

□ Male

□ Female

□ Other

If you don't mind, I would like to start by asking you some questions about your age, educational background and work.

1.2 What is your age?

1.3 What did you study?

1.4 When did you graduate?

Part 2: HIV related experience

2.1 Which work are you doing at the moment and how is it related to HIV or HIV drug resistance?

2.2 In which sub-Saharan African countries have you worked before and are you working at the moment?

2.3 Are you active in an association concerning sub-Saharan Africa or HIV beyond your job or intersecting with your job?

Part 3:

3.3 In your experience, what are the main causes of HIV drug resistance?

The following four areas should be covered:

 Availability of ART at local healthcare centre

 PLHIV fetches / is able to fetch his/her ART

 PLHIV takes the ART as prescribed

 ART suppresses the viral load

Reasons outside these four areas:

3.4 What do you think is causing the problems/situations you just mentioned?

3.5 Can you think of some solutions for the problems you have just mentioned? These can be your personal ideas or solutions that have already been studied and implemented.

3.6 Is there anything else important for this conversation that you would like to share?

This concludes our interview. Thank you very much for your participation.

Time of conclusion:

Additional interviewer notes:

Chapter 4

Factors associated with HIV drug resistance in Dar es Salaam, Tanzania: analysis of a complex adaptive system

Research Article

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Abstract

HIV drug resistance (HIVDR) is a complex problem with multiple interconnected and context dependent causes. Although the factors influencing HIVDR are known and well-studied, HIVDR remains a threat to the effectiveness of antiretroviral therapy. To understand the complexity of HIVDR, a comprehensive, systems approach is needed. Therefore, a local systems map was developed integrating all reported factors influencing HIVDR in the Dar es Salaam Urban Cohort Study area in Tanzania. The map was designed based on semi-structured interviews and workshops with people living with HIV and local actors who encounter people living with HIV during their daily activities. We visualized the feedback loops driving HIVDR, compared the local map with a systems map for sub-Saharan Africa, previously constructed from interviews with international HIVDR experts, and suggest potential interventions to prevent HIVDR. We found several interconnected balancing and reinforcing feedback loops related to poverty, stigmatization, status disclosure, self-esteem, knowledge about HIVDR and healthcare system workload, among others, and identified three potential leverage points. Insights from this local systems map were complementary to the insights from the sub-Saharan systems map showing that both viewpoints are needed to fully understand the system. This study provides a strong baseline for quantitative modelling, and for the identification of context-dependent, complexity-informed leverage points.

Introduction

Over the past years, Tanzania has made considerable progress towards reaching the global 95-95-95 goals [128]. In August 2020, an estimated 83% of people living with HIV (PLHIV) in Tanzania were aware of their HIV status, of which 90% were on HIV treatment. Of those on treatment, 92% were virally suppressed. In 2019, the HIV prevalence in Tanzania was estimated to be 4.8%. The Tanzanian epidemic consists entirely of the HIV-1 type as no HIV-2 infections have been reported so far [56,61]. In 2019 the WHO reported alarming increases in pretreatment HIV drug resistance (PDR) with 12 out of 18 reporting countries exceeding the 10% non-nucleoside reverse transcriptase inhibitor (NNRTI) PDR threshold, triggering immediate national action [98]. A recently published study conducted between 2013 and 2019 found a prevalence of 11% PDR among the 801 antiretroviral therapy (ART)-naïve participants from

Tanzania, Kenya, Uganda and Nigeria [68]. Among the ART-experienced participants with unsuppressed viral load (VL), resistance rates of 82.5%, 66.7% and 1.8% were reported for NNRTI, nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) mutations, respectively. Another study in Dar es Salaam from 2010, although with a small sample size, found drug resistance mutations in 82.6% of the included therapy-experienced participants [70]. A systematic literature review published by the WHO showed that the prevalence of pretreatment NNRTI resistance has been increasing the fastest in Eastern Africa, compared to other low- and middle-income regions [129]. These results underline the importance of addressing HIV drug resistance (HIVDR) in order to sustain the progress towards the goal of ending the epidemic by 2030.

HIVDR is influenced by a multitude of factors which transcend single disciplines and population levels, and which, together, form a complex, multi-layered and interconnected system [130]. Several individual, socio-economic, structural and health care system related factors influencing HIVDR in Tanzania have been described in a literature review by Msongole et al. [131]. Although the diverse factors influencing HIVDR are relatively well studied, preventing HIVDR (including acquired and transmitted drug resistance) in the real world remains difficult [45,98,101,115]. In order to understand and address the underlying challenges of HIVDR there is a need to shift away from the reductionist, linear cause-effect models towards a comprehensive systems approach and study the factors associated with HIVDR as a complex adaptive system (CAS) [80]. A core characteristic of such CASs lies in the understanding that successfully intervening on one element of a system does not guarantee resolving the central problem due to influences of other aspects of the system [77]. Interventions in a complex system ideally require a small shift in one place which has the potential to positively change the whole system. Such places to intervene on are called leverage points and can be divided into shallow and deep leverage points [86,87]. Shallow leverage points, such as parameters and feedbacks, are relatively easy to intervene on, but have a limited effect on the system, whereas interventions at deep leverage points are difficult to accomplish but can result in an extensive change of the system. Interventions at deep leverage points are aimed at changing the underlying structure, goal, or paradigm of the system. Achieving this requires a joint understanding of the system by scientists, stakeholders (including PLHIV) and societal actors, as well as a

joint commitment towards supporting the envisioned change. With this study we took a first step in this direction and studied HIVDR in its totality as a CAS of interconnected and interacting factors. Concretely, we aimed to understand how these factors are interconnected with and embedded in the local context of our study area in the Ukonga and Gongolamboto areas of Dar es Salaam, Tanzania [55,77]. We compare this local systems map with one constructed from the knowledge of international experts, developed in a previous study, and discuss the differences and similarities [130]. We also provide a first assessment of potential intervention points.

Materials and methods

Study design

An iterative systems mapping design was used to visualize and analyse the CAS of factors associated with HIVDR in our case study site in Dar es Salaam, Tanzania. Qualitative methods rooted in grounded theory were used for data collection and analysis. The systems analysis and identification of leverage points were based on a systems thinking inspired analysis guide [83].

Study site and participants

The study was conducted at the Dar es Salaam Urban Cohort Study (DUCS) site in the Ukonga and Gongolamboto administrative wards, Illala district, Dar es Salaam region, Tanzania. The DUCS follows more than 100,000 residents from more than 20,000 households and collects sociodemographic and other data on a six-monthly basis [55]. This study site was chosen because of the rich data available which may support future intervention designs. We included three types of stakeholders in this study, each representing a different perspective: local experts, local actors, and PLHIV. Local experts were people with professional expertise on HIVDR, based in Tanzania. For the purpose of this study, local actors are defined as people who have good insights in the daily lives of the local citizens and who, through their job, status or daily activities come into contact with PLHIV. The local actors were selected with the aim of including a range of people who could provide us with insights about HIV in the community from diverse angles in order to create an overview that is as comprehensive as possible. PLHIV in several stages of their treatment, on different therapy regimens

and with varying treatment-adherence levels were selected purposefully and recruited by research assistants of the DUCS.

Data collection procedures

The systems map was developed in four phases (Table 6). During the preparation phase we organized a workshop with local experts to discuss factors influencing HIVDR in our study site. During this meeting we started from a sub-Saharan systems map based on knowledge from international experts, developed in previous research and adapted this map to the local situation. This adapted map served as a basis to design the semi-structured interview guides and was not used further in data analysis. This way, the CAS of HIVDR in our study site was constructed anew from the interview data, truly allowing the perspectives and mental models of the local inhabitants to form the map, without the influence of previous research.

Semi-structured interviews

The first draft of the systems map was designed based on semi-structured interviews with PLHIV and local actors at DUCS in the Ukonga and Gongolamboto areas in Dar es Salaam, Tanzania. Semi-structured interviews do not consist of a set of rigorous questions but rather use a set of common themes to be explored with all the participants. This type of interview allows new themes to come up and be explored, based on the interviewee's answers.

The participants were called on their cell-phone and invited for a face-to-face interview at the DUCS office in the local community centre located in the Ukonga area. This location is neutral and not linked to any activities involving PLHIV and was therefore chosen to avoid stigmatization of the participants. The interviews were held in Kiswahili by IM, a local social scientist and participants were reimbursed for their transportation costs. Each interview session lasted for about forty-five minutes. The interviews were audio recorded after seeking consent from study participants, transcribed verbatim and translated into English.

Table 6: *Overview of the different activities and participants in the project.*

Phase	Activity	Participants	Purpose
Preparation	Expert meeting + field visit (June 2019)	10 Tanzanian HIVDR experts	Discussion on factors influencing HIVDR in the Tanzanian context, informed by a systems map previously developed with sub-Saharan African HIVDR experts. This meeting informed our semi-structured interview guide.
Data collection	Semi-structured interviews (June 2019–February 2020)	12 PLHIV and 10 Local actors	Forming a detailed understanding of the perspectives of PLHIV and local actors on the CAS of factors influencing HIVDR in the study site.
Data analysis and interpretation	Coding, mapping, regular meetings between the researchers	No external participants	Developing a systems map of factors influencing HIVDR in the study site based on the semi-structured interview data.
Validation	Workshops (February–March 2021)	10 PLHIV and 9 Local actors	Validating the systems map developed based on the semi-structured interviews and brainstorming about possible interventions for preventing HIVDR.

The semi-structured interview guide was informed by the expert meeting and designed by AK, AV and IM with the aim of capturing the deeper factors influencing HIVDR in the DUCS area (Supplementary file 2 and 3). After each interview day IM, AK and AV met to debrief the interviews and the interview guide was adapted according to the insights gained. After a first analysis of the interviews, a selection bias was noted as only participants enrolled in care were interviewed. In order to have a more diverse perspective on the factors influencing HIVDR in the study area, two additional

participants who had not been attending healthcare services regularly in the past months were recruited and interviewed during a phone conversation. Interviews were conducted until data saturation was reached. For the purpose of this study, data saturation was defined as the moment in which no new elements or connections are discovered in two consecutive interviews.

Data analysis

The analysis of the semi-structured interviews was conducted by two researchers (LZ) and (AK) with a combined background in psychology, biomedical science and systems thinking. The method used was inspired by the qualitative analysis guide of Leuven (QUAGOL) method [95]. After each interview, a technical report was written, containing all the specifics needed for a full comprehension of the data in their specific context. In order to ascertain a correct interpretation and cultural understanding of the transcripts, they were each individually discussed in a series of meetings between AK, LZ and IM.

For each transcript, a respective systems map was made, visualizing the factors influencing HIVDR mentioned in the interview and the connections between those factors. Seven interviews with PLHIV and five local actor interviews were schematized and coded by AK. The other five interviews with PLHIV and five local actor interviews were schematized by both AK and LZ and the interviews were coded by LZ. The schemes were compared as a verification of our analysis and possible differences were discussed until a consensus was found. In a next phase the separate schemes were merged together into one comprehensive systems map containing all the codes extracted from the interviews. The systems map was designed with the online mapping tool KUMU, which facilitates the visualization and analysis of the map, as different types of data can be stored behind the elements and connections [113]. Though here described linearly, the coding and mapping was an iterative process in which the interviews were re-read at several points in time, codes were revised throughout discussions between the researchers and findings were constantly compared with insights from previously analysed interviews.

Validation

A validation round of the systems map was held in two workshops, one with PLHIV and one with local actors, organized in February and March 2021. The discussion was organized around six central areas of the systems map. The participants discussed the model, changes in the model since the first data collection, and possible interventions. The workshops were organized in the form of a focus group discussion, conducted in Kiswahili. The workshops were recorded, transcribed, and translated into English and they were coded and analysed following the same method as for the semi-structured interviews above.

Results

We interviewed 12 PLHIV and 10 local actors in the DUCS located in the Ukonga and Gongolamboto areas of Dar es Salaam. Of the PLHIV, two were lost to follow-up and ten were engaged in care. Another 10 PLHIV and nine local actors engaged in the validation workshops. The sociodemographic and therapy data of the participants are described in Table 7.

Not surprisingly, the majority of participating PLHIV were female, which can be explained by the higher HIV prevalence in women, as well as the lower linkage to care rates in men. Of the 22 PLHIV involved, 18 were on first line dolutegravir-based treatment. The other four were on first-line NVP or EFV-based regimens. Overall, we reached a diverse sample of participants which allowed us to study the factors influencing HIVDR from different angles. Data saturation for the factors influencing HIVDR (elements) was reached after 16 interviews and after about 19 interviews for the connections between those factors (Supplementary Figure 2 and 3).

Based on the collected data, we developed a systems map representing the factors influencing HIVDR in the Ukonga and Gongolamboto areas in Dar es Salaam as experienced by the local population. The map consists of several interconnected feedback loops which we will describe step by step. In Figure 11 to 15, parts of the system are shown, whereas the complete system is presented in Figure 16.

Table 7: *Sociodemographic and therapy data of the participants of the interviews and validation workshops.*

	PLHIV (N = 22)	**Local actors (N = 19)**
Average age (year)	40 (21–56)	49 (33–73)
Gender		
Male	18% (4)	63% (12)
Female	82% (18)	37% (7)
Education		
No degree	14% (3)	16% (3)
Primary education	77% (17)	26% (5)
Secondary education	9% (2)	16% (3)
Higher education	0% (0)	42% (8)
Occupation		
Employed	64% (14)	100% (19)
Unemployed	36% (8)	0% (0)
Years of experience in local actor role		
<5	/	16% (3)
5–10	/	21% (4)
≥10	/	58% (11)
Time since first positive HIV test		
≤1 year	14% (3)	/
2–5 years	36% (8)	/
>5 years	50% (11)	/
Time since start of treatment		
≤1 year	18% (4)	/
2–5 years	36% (8)	/
>5 years	45% (10)	/

The purple section of Figure 11 represents the biological mechanism of HIVDR selection. HIVDR is selected under selective pressure caused by incomplete VL suppression. A major cause of incomplete VL suppression is suboptimal adherence, here defined as the compliance of PLHIV with their therapy as well as the possibility for them to take their medication daily, thus including both factors that are within and out of their own control. Selection of HIVDR will lead to an increase in opportunistic infections and generally poorer health as a result of an unsuppressed VL. The interviewees described situations in which clients do not believe they are HIV-positive when they do not experience symptoms after testing or who believe they are cured when their health improves and therefore do not see the need to adhere anymore.

These clients then re-start taking their ART when they develop symptoms. This may be fuelled by a lack of knowledge about HIV, by the influence of traditional healers or religious leaders who claim to cure HIV, or by the client not accepting their HIV status. A major barrier to adherence in the study site is poverty (Figure 11, green colour). Clients who cannot afford a meal each day, may skip their medication, out of fear of side effects. Clients living in poverty may also have difficulties picking up medication when they do not have money to pay for transportation or when they are offered an employment opportunity on the day of their refill and have to choose between income and medication. One participant described this as follows:

"When I say that money is more important than health, it's not that health is not important but they depend on each other. It happens that you stayed hungry for three days and failed to take your medication because of the food insecurity. The fourth day someone calls you to go to work and get money, tell me if it were you, what would you do? Would you go to the clinic or to work?"

-PLHIV (Female, 48 years old)

Clients migrating to other parts of Tanzania in search of an income or for other purposes may also experience difficulties remaining in care. The socio-economic aspects of HIVDR are very prominent in the study site as barriers to adherence but also as motivators. The knowledge that when adhering to therapy, one will be in good health, able to work and provide income for the family, drives clients to adhere well, a motivational strategy which is also used by the healthcare workers. The yellow arrows in Figure 11 illustrate an issue caused by the stigmatized nature of HIV in the community. When joining social activities or travelling for work, some clients do not take their medication with them out of fear of involuntary status disclosure, subsequent stigmatization, and the possibility of losing employment opportunities.

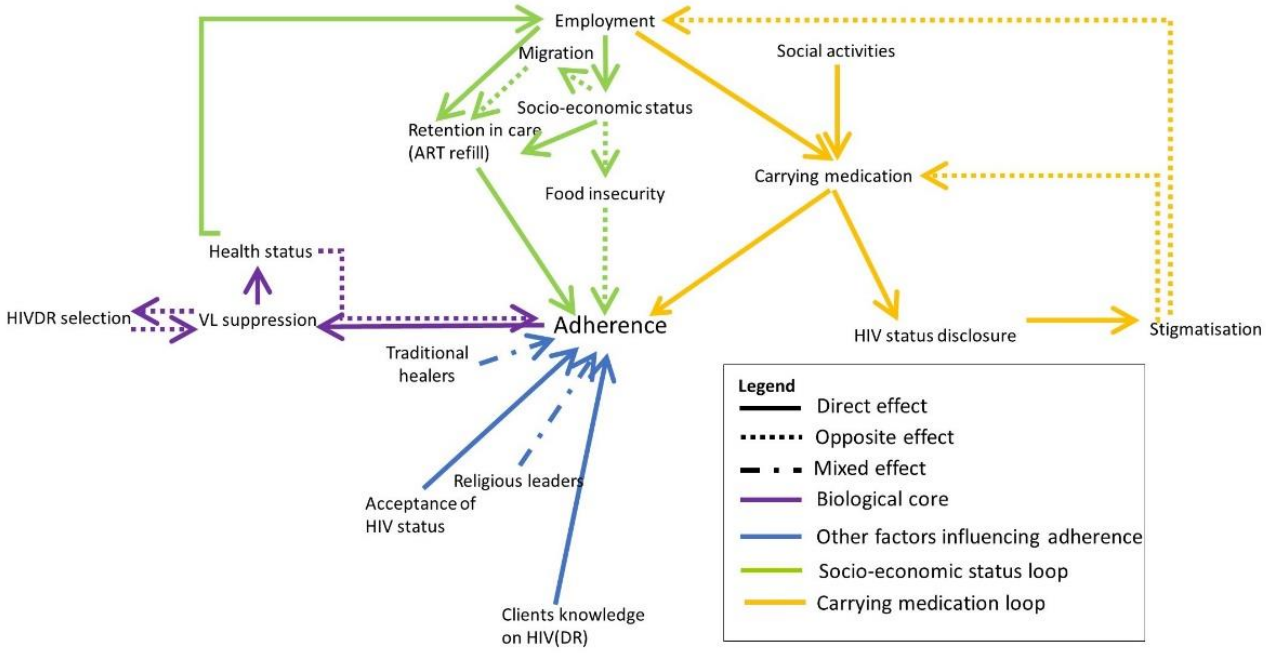


Figure 11: *The participants' perspectives on HIV drug resistance in the study site, reflected in three core loops related to the health status (purple), socio-economic situation (green) and involuntary status disclosure when carrying medication (yellow). Some additional factors influencing HIVDR are indicated in blue. Full arrows indicate that both elements are evolving in the same direction (e.g., A->B: when A increases, B increases as well). Dotted arrows indicate an opposite effect (when A increases, B decreases). Mixed arrows indicate that the effect can be either direct or opposite.*

Participants indicated that stigma and discrimination can have a profound effect on PLHIV's lives, reflected by the dark red and brown loop in Figure 12. Next to the risk of losing employment, the participants reported that stigma and discrimination can be the cause of marital or familial conflicts, discrimination at social gatherings and general discomfort due to gossip or being treated differently. Moreover, the impact on people's self-esteem can cause them to self-stigmatise. To avoid that, they often choose not to disclose their status, drop out of care, or become nonadherent. Some even go as far as to give fake contact details to the healthcare staff in order not to be traceable. Others prefer to go to a healthcare centre far from home in order not to be recognised. However, this may come with the challenge of sustainably accessing this healthcare centre for each refill and check-up due to for example financial constraints. The participants indicated that stigma and discrimination can be prevented by educating the community on HIV, its modes of transmission, prevention, treatment and required

support. They also expressed the need to encourage the community to appreciate and support PLHIV who disclose their HIV health status. This can be achieved through the media, brochures, and seminars given by NGOs, or for example by religious leaders who have a wide reach. Over time, the more PLHIV disclose their status and openly talk about HIV, the more the community will learn about HIV. This increased community education is expected to decrease the stigma surrounding HIV, encouraging more PLHIV to disclose their status and adhere to ART. This is a delayed reinforcing loop.

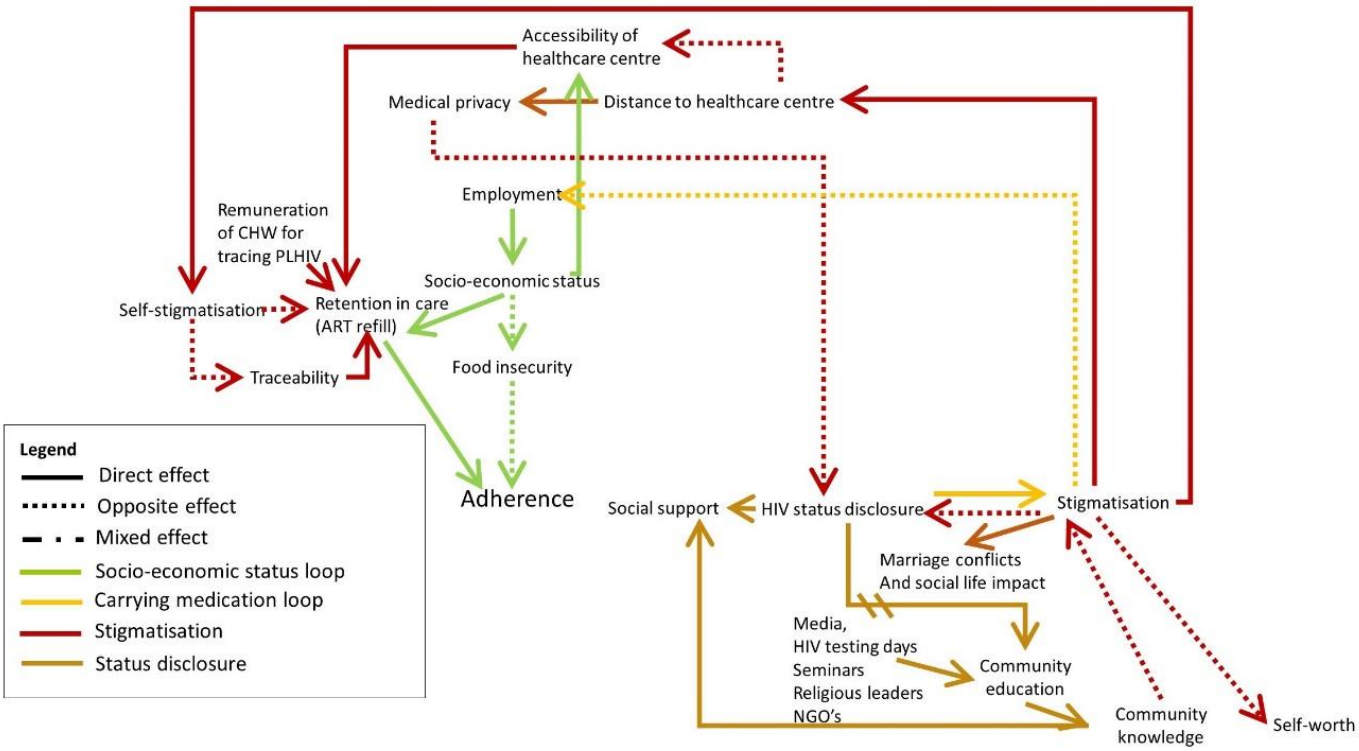


Figure 12: *The causes and effects of stigmatisation and HIV status disclosure are indicated in dark red and brown. The arrow with double strikethrough indicates a relationship with a delayed effect. Full arrows indicate that both elements are evolving in the same direction (e.g., A->B: when A increases, B increases as well). Dotted arrows indicate an opposite effect (when A increases, B decreases). Mixed arrows indicate that the effect can be either direct or opposite.*

HIV status disclosure can have positive and negative consequences: on the one hand, stigmatisation can have a profound effect on social life as discussed above. On the other hand, people may receive social support from their family who can help them to adhere and accept their status, or who can help them financially or by providing meals (Figure 13, beige arrows). A person living with HIV may experience both positive and negative consequences and may therefore choose to disclose their status only to a select group of people. Counselling can help to prepare PLHIV to disclose their status. Some participants reported not disclosing their status in order to spare their loved ones from worrying about them. However, the will to protect others may also motivate PLHIV to disclose their status in order to engage in safer sex and to adhere to their medication in order not to infect others.

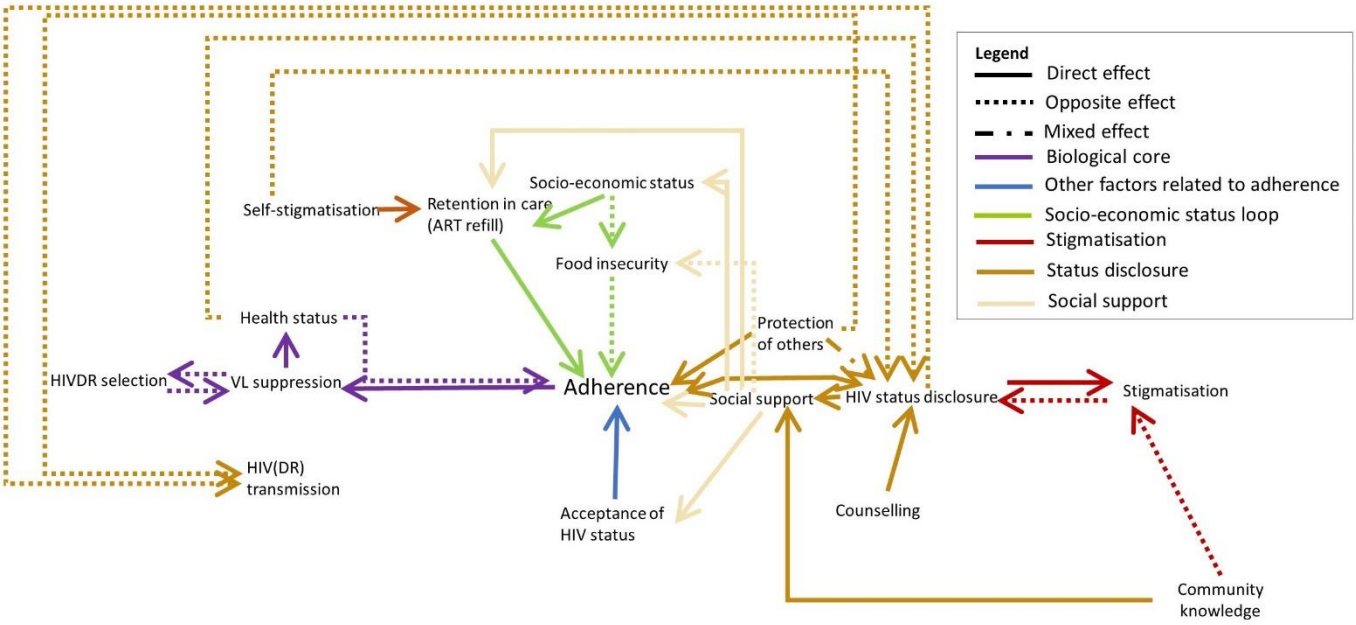


Figure 13: *The influences of social support are indicated in beige. Full arrows indicate that both elements are evolving in the same direction (e.g., A->B: when A increases, B increases as well). Dotted arrows indicate an opposite effect (when A increases, B decreases). Mixed arrows indicate that the effect can be either direct or opposite.*

Counselling can help PLHIV to accept their HIV status, gain a deeper understanding about HIV and ART and feel socially empowered to ask questions or demand VL tests for instance. In some cases, the health care provider gives very strict guidelines (such as dietary information or the guideline to take the medication strictly at a certain time)

which may discourage the client to take the ART when they cannot meet these requirements.

"… However, we shouldn't miss the nutrients they recommended in our foods. … I don't know things like finger millet and others, we are missing them in our foods because we can't afford to get them, we are missing the nutrients. … For instance, the ones with [financial] ability. Vegetables, small fried fishes aren't bad. They told us not to use beef, it isn't good that's what they said. For instance, they told me an old man like me what I should eat is like pig's meat, chicken and fishes. Now things I am able to get in most cases are green vegetables and stiff porridge. You see how it is hard. … They told me so, but they didn't tell me the reasons. They told me that I shouldn't prefer using beef."

-PLHIV (Male, 34 years old)

Elements important for good counselling sessions that arose from the interviews include: medical privacy (in some cases, there are multiple clients in the doctor's office or the door is left open), well-trained healthcare workers and community health workers (CHW) who are able to answer the clients' questions and who have a caring attitude, and a good client-provider relationship (Figure 14, dark blue). Participants also indicated that this could help clients to accept their HIV status.

Another important factor is the workload of the healthcare centre. Both PLHIV and local actors indicated that at times the healthcare centre is overburdened, and healthcare providers do not have enough time to provide thorough counselling for all clients, which may impact its efficiency.

The healthcare system workload increases when PLHIV have to visit the hospital more frequently because they have an unsuppressed VL or developed drug resistance, or when HIV(DR) is transmitted in the community and more people have to enrol in care. When healthcare staff are not sufficiently trained to handle certain cases or answer all questions of the client, they may have to refer the client to other colleagues, therefore also increasing their workload.

Next to decreased counselling efficiency, a high healthcare system workload also increases the waiting time at the healthcare centre which may lead to PLHIV not picking up their medication as they are afraid of being recognised by other people at

the healthcare centre. The healthcare system workload loop (Figure 14, dark green) is a reinforcing loop in which the consequences of high workload (decreased counselling quality and therefore a decreased adherence) will eventually lead to an even higher workload.

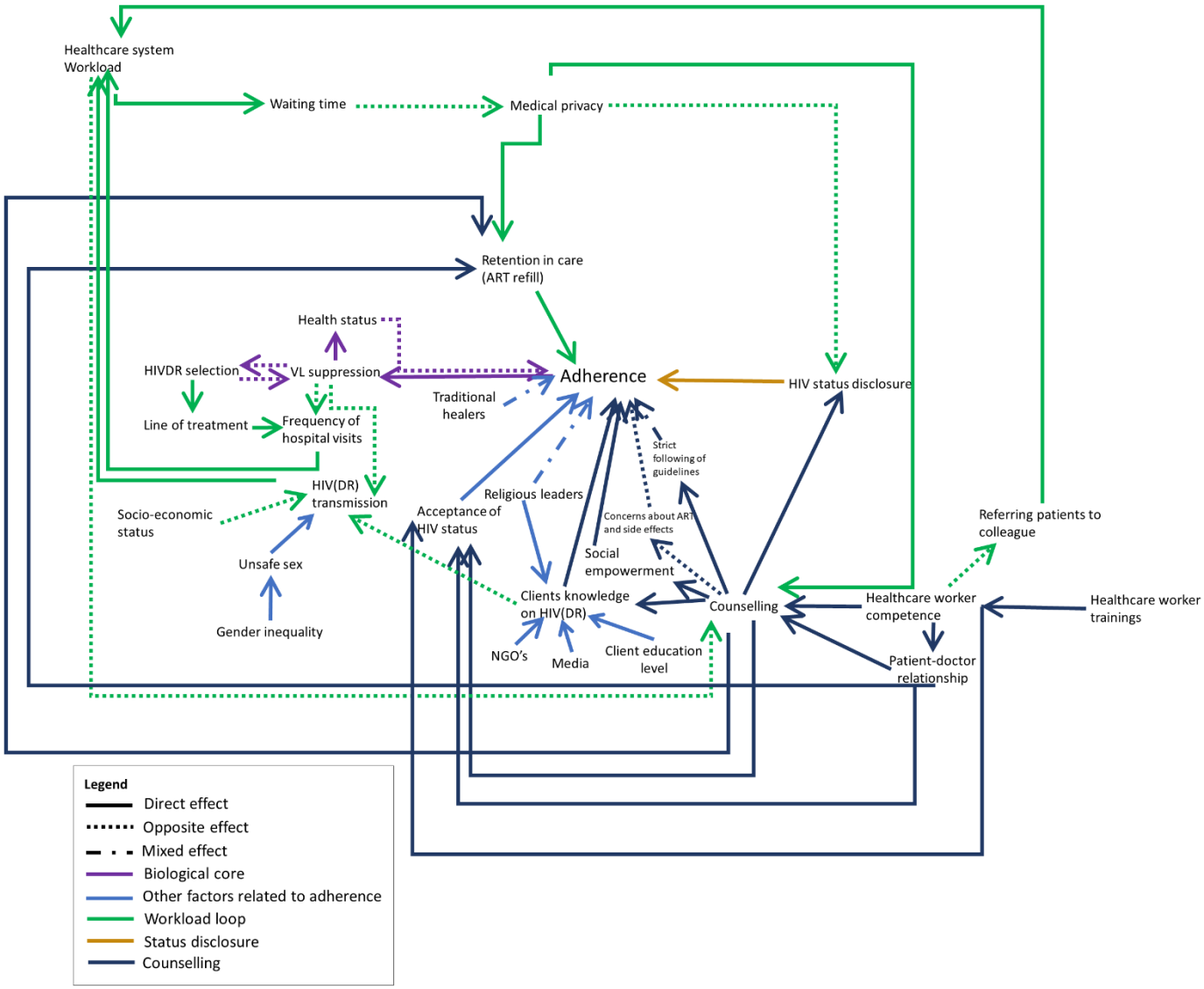


Figure 14: *The reinforcing workload loop is indicated in dark green. Full arrows indicate that both elements are evolving in the same direction (e.g., A->B: when A increases, B increases as well). Dotted arrows indicate an opposite effect (when A increases, B decreases). Mixed arrows indicate that the effect can be either direct or opposite.*

The following reinforcing loop is indicated in red in Figure 15. Having access to information about one's health status, such as VL and CD4 count information, especially when the client is doing well, contributes to the client's feeling of self-esteem. Clients are proud of their good health and are congratulated by healthcare staff, which motivates them to continue adhering. In black, we indicated the impact of the VL testing organization on the system. Test results sometimes arrive with a delay, or not at all because of which the test has to be repeated, further increasing workload. Possible causes of this are a lack of equipment for testing and a lack of uniform electronic data systems to facilitate sharing the results.

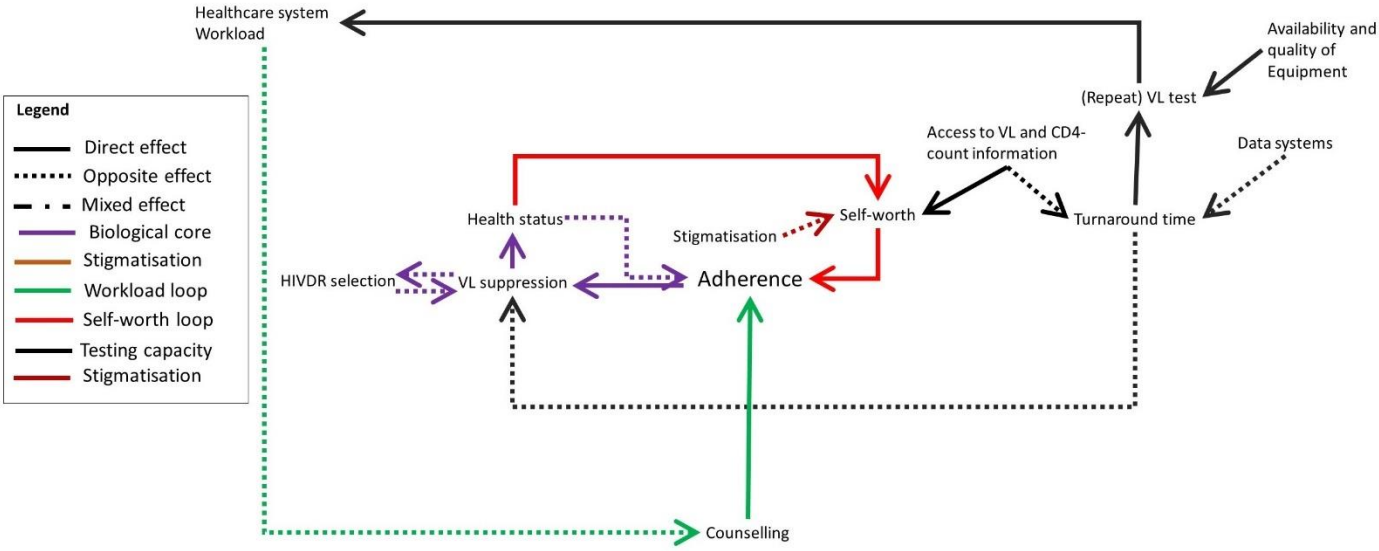


Figure 15: *The importance of linking back testing results to the clients, and related practical requirements are indicated in red and black, respectively. Full arrows indicate that both elements are evolving in the same direction (e.g., A->B: when A increases, B increases as well). Dotted arrows indicate an opposite effect (when A increases, B decreases). Mixed arrows indicate that the effect can be either direct or opposite.*

Figure 16 shows the full system of all identified factors influencing HIVDR in the study site. Additional to what is described above, other factors influencing adherence are substance abuse (possibly stemming from poor acceptance of one's HIV status), forgetfulness or pill fatigue as illustrated by the interview quote below. The burden of having to take medication each day for the rest of one's life may contribute to self-stigmatisation and may on its own be a reason to skip the medication from time to time.

Although the first line ART in the study site consists of one pill per day, usually more medication needs to be taken such as medication for opportunistic infections.

"Truly, you can swallow the drugs and there are times you get tired of taking them and say let me skip them today. You can stop for a day; you just say today I am resting. … Only one day, I am scared to skip them for two days because that's when you are told viruses increase in one day if you skip. … Honestly, for instance for the drugs which I was given for three months. I can rest for one day. … Ahh per three months I only rest once".

-PLHIV (Female, 39 years old)

In light grey, two elements are added which are no longer applicable for the adult population in our study site. The participants reported relatively little supply issues in the study area and if needed the healthcare centres reorganize themselves and give half supplies to the clients so that everyone can be served until they have restocked. Additionally, the side effects are of lesser concern since first line treatment has been switched from tenofovir/lamivudine/efavirenz (TLE) to tenofovir/lamivudine/-dolutegravir (TLD). It is important to note that side effects can demotivate clients from adhering to therapy directly, but clients can also experience being hungry after taking the medication and therefore skip the medication when they know they will not be able to satisfy their increased appetite. Some clients also report an increased libido after taking the medication and indicated that this increases the transmission risk.

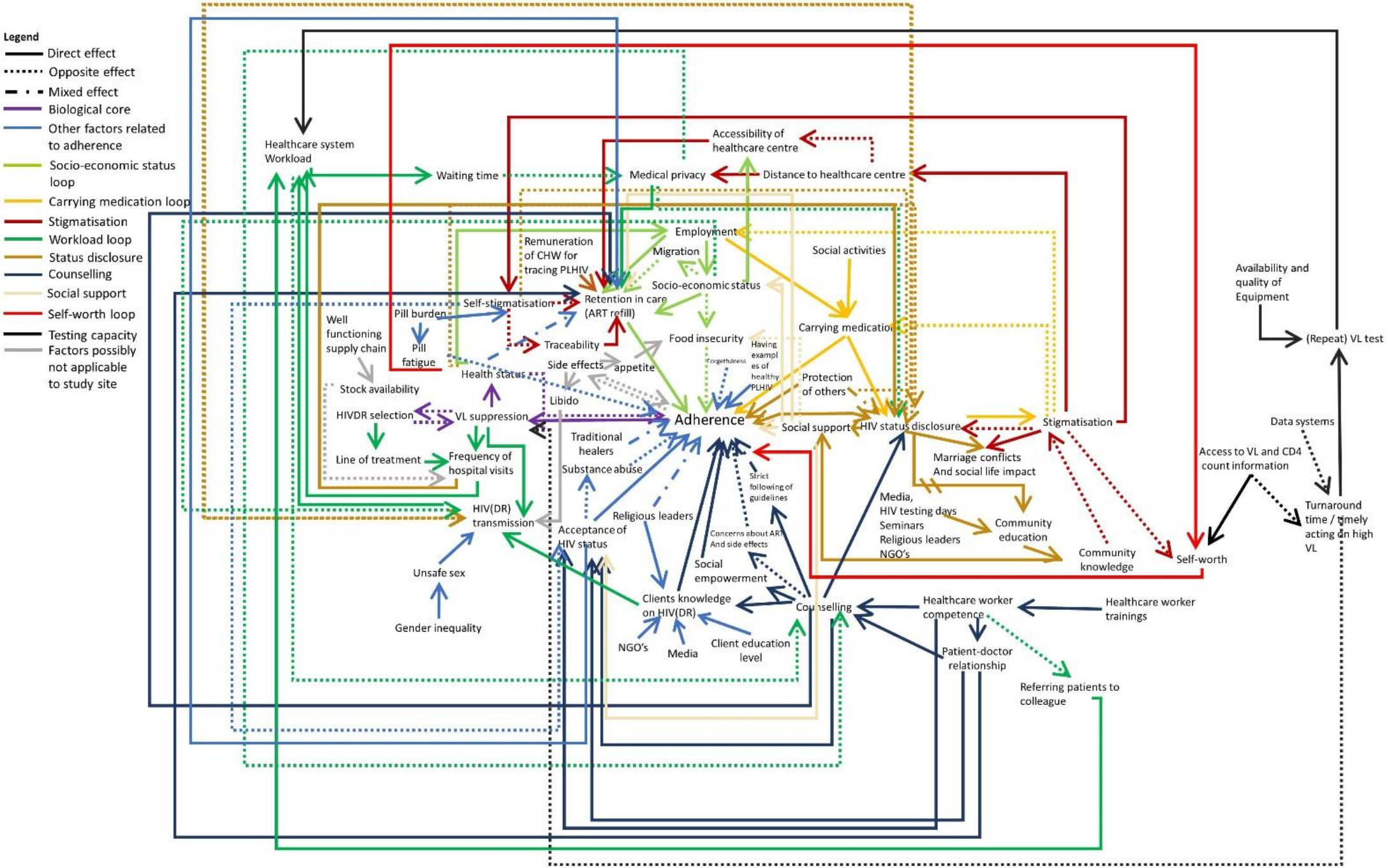

Legend
Direct effect
Opposite effect
Mixed effect
Biological core
Other factors related to adherence
Socio-economic status loop
Carrying medication loop
Stigmatisation
Workload loop
Status disclosure
Counselling
Social support
Self-worth loop
Testing capacity
Factors possibly not applicable to study site
Healthcare system Workload
Waiting time
Accessibility of healthcare centre
Medical privacy
Distance to healthcare centre
Employment
Remuneration of CHW for tracing PLHIV
Migration
Social activities
Socio-economic status
Availability and quality of Equipment
(Repeat) VL test
Self-stigmatisation
Retention in care (ART refill)
Pill burden
Well functioning supply chain
Pill fatigue
Traceability
Food insecurity
Carrying medication
Having examples of healthy PLHIV
Forgetfulness
Side effects
appetite
Health status
Protection of others
Stock availability
Libido
HIVDR selection
VL suppression
Adherence
Social support
HIV status disclosure
Stigmatisation
Data systems
Traditional healers
Line of treatment
Frequency of hospital visits
Substance abuse
Marriage conflicts And social life impact
Access to VL and CD4 count information
Strict following of guidelines
Media, HIV testing days Seminars Religious leaders NGO's
Community education
Turnaround time / timely acting on high VL
HIV(DR) transmission
Religious leaders
Acceptance of HIV status
Concerns about ART And side effects
Community knowledge
Self-worth
Unsafe sex
Social empowerment
Clients knowledge on HIV(DR)
Counselling
Healthcare worker competence
Healthcare worker trainings
Gender inequality
NGO's
Media
Client education level
Patient-doctor relationship
Referring patients to colleague

Figure 16: *The full system of factors influencing HIVDR in the study site. Additional factors influencing adherence and some elements which are no longer applicable are indicated in blue and grey, respectively. Full arrows indicate that both elements are evolving in the same direction (e.g., A->B: when A increases, B increases as well). Dotted arrows indicate an opposite effect (when A increases, B decreases). Mixed arrows indicate that the effect can be either direct or opposite.*

While the above systems map represents the CAS in detail, Figure 17 summarizes the system into seven core loops representing the main mechanisms behind HIVDR in the study site. In the following paragraph the core loops and three identified leverage points are discussed. R1.1 is a reinforcing loop through which PLHIV are motivated to keep adhering to the ART because of their improved health status. The first, shallow level leverage point identified is the strengthening of this loop, for example through motivation by healthcare workers. Reinforcement of R1.1 will automatically weaken R2.1 and 2.2 which represent the effects of an increased healthcare system workload when adherence levels are not sufficient. The decreased time for counselling and other support for PLHIV will lead to a further decrease in adherence levels. Furthermore, R1.1 reinforcement would strengthen R1.2, which results in improved adherence through increased socio-economic opportunities. It would also decrease R1.3 as healthy looking PLHIV tend to be less stigmatized by others and by themselves. The second, also shallow leverage point is to weaken R2.3 and R2.4 which represent a decreased adherence through stigmatization and decreased socio-economic opportunities, respectively. This could be done by providing community education, potentially through religious leaders, community leaders or traditional healers, who have a wide range.

The third leverage point is identified at the design level and is therefore considered a deep leverage point. Based on the combined needs for economic support, education on HIV(DR) and improving the mental well-being of PLHIV, we propose the organization of microfinance groups specifically for PLHIV. Microfinance groups are informal financial support groups where members are educated on entrepreneurship, contribute a monthly amount of money and have the opportunity to request a loan from the group. These groups may be a platform for PLHIV to combine their economic support group with peer support-like activities such as education sessions on HIV(DR) and practical and psychological support [132]. Although the economics of microfinance

groups for PLHIV have been described in the literature, more research remains to be conducted on the effect on health outcomes [133,134].

The summary system in Figure 17 is influenced by several other factors which are here considered external and therefore not represented. These are, for example, supply chain related factors, testing capacity and ART properties.

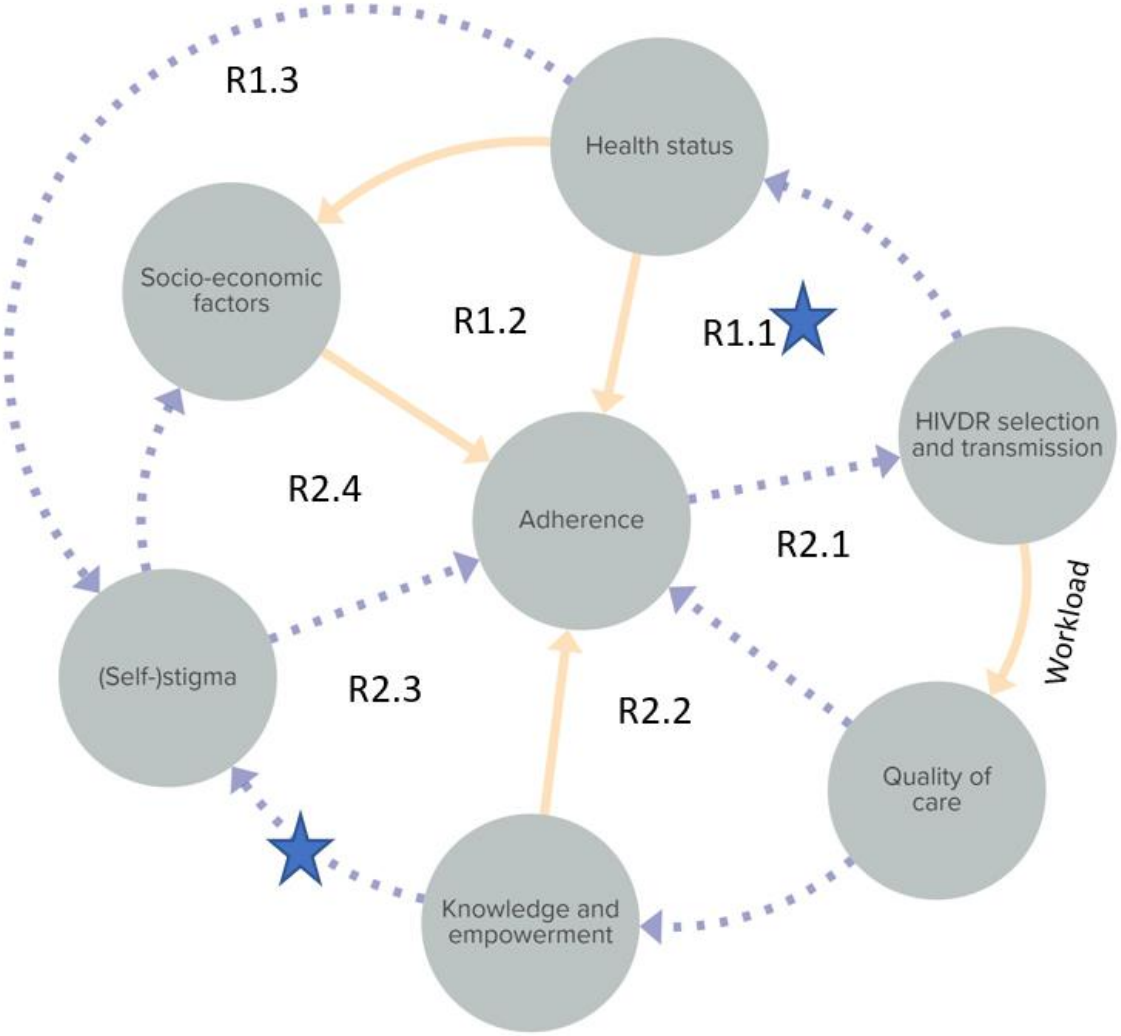


Figure 17: *Summary figure of the CAS of factors associated with HIVDR in the study area. Seven reinforcing loops and two leverage points (blue stars) are indicated. The third leverage point is at the structural level and is therefore not visualised here. Individual reinforcing loops are indicated as R1.1 to R2.4. Full arrows indicate that both elements are evolving in the same direction (e.g., A->B: when A increases, B increases as well). Dotted arrows indicate an opposite effect (when A increases, B decreases).*

Discussion

In this study, we gained insight into the complexity of HIVDR in the Ukonga and Gongolamboto areas of Dar es Salaam by developing a model representing the CAS of its interconnected factors, together with local actors and PLHIV. It is important to note that our aim was to understand the CAS of factors influencing HIVDR through the mental models of the people most affected by it. Therefore, the model does not represent one fixed reality but rather an interconnected network of elements influencing HIVDR, which are constantly evolving over time, and which are highly dependent on context.

Three leverage points were identified based on the insights provided by our systems map. The first, shallow, leverage point aims at reinforcing the motivation to adhere to therapy, for instance through the encouragement of positive health outcomes. The second also shallow one, aims at decreasing stigmatization by strengthening community education. The third identified leverage point is at a deeper level and requires the restructuring of certain aspects of care through combining microfinance and peer support groups for PLHIV. Our work provides valuable insights at the systems level which, after strengthening of the healthcare system viewpoint, can be used to design and test interventions at these leverage points.

In addition to the identified leverage points, we obtained some other system-level insights. First, our data clearly showed the impact of psychological wellbeing on the dynamics of the HIVDR system as also described extensively by Zlatić (2020) [135]. In particular, stigmatization was found to be the driver of several important feedback loops. Second, at the healthcare system level, we found that some counsellors give very strict guidelines to their clients which are ill-adapted to their life circumstances. These are failing to convey their purpose, and therefore sometimes work counterproductively. Clients may refrain from taking their medication if they do not find the advised type of food or if they come home one hour late. Future seminars on HIVDR for healthcare workers may need to be revised to refocus on the objective of the counselling sessions (preventing HIVDR and ensuring good health of PLHIV) rather than on the individual rules they have to follow. Third, our map visualizes the importance of several material factors and their impact on HIVDR, such as money, food, transportation modalities, the healthcare centre environment and related privacy

and the medication needing to be physically carried around. The importance of studying such material markers has recently been highlighted in a review by Hendricks et al [136].

Fourth, at the community level, we found a delayed reinforcing feedback loop, indicating that PLHIV openly disclosing and discussing their HIV status are conducting a type of community education. This can reduce community stigmatization over time, encouraging more PLHIV to disclose their status. Previous studies have shown the correlation between knowledge and HIV related stigma [137,138]. One study in South Africa found that a decrease in stigma was associated with an increase in knowledge over a period of four years [137]. To identify the tipping point at which this reinforcing loop is kicked into action additional research is needed.

To explore the contents of our systems map beyond the local level, we compared it with a systems map of factors influencing HIVDR for sub-Saharan Africa, which was informed by experts and developed using the same methodology [130]. Overall, the content of the systems maps remains largely similar. As can be expected, however, the expert systems map contained more extensive information at the healthcare system level and the local map goes into more detail at the personal level. A notable difference is that, whereas in the expert map the economic factor food insecurity was considered to be important but external to the system, it became clear that at the local level those factors were at the very core of the system, forming daily barriers to adherence for PLHIV. This shows that in order to fully understand the CAS of HIVDR, the viewpoints of PLHIV, actors and experts, as well as those groups at the local and broader geographical level need to be integrated.

A shortcoming of this study is its timeframe as two important events happened: 1) at the time of data collection the healthcare centres in the study site had just switched their ART regimens from TLE to TLD, a therapy which evokes less side-effects and which has a lower chance of provoking mutations in the virus and 2) between the data collection and validation the world was hit by the COVID-19 pandemic which, for a period of time brought a number of changes to the system. From March until July 2020, all PLHIV in the study area were given ART for six months instead of the usual one or three months, wearing face masks was obligatory in the healthcare centre, which caused problems for clients who could not afford them and transportation fees increased due to strict rules for seat capacity of commuter buses. While further

research is needed to clarify the impact of these interruptions on the HIVDR prevalence in the population, our systems map can help to understand how these measures may have impacted the adherence level of PLHIV. Moreover, the systems mapping method described can be used to study the impact of the COVID-19 pandemic on other aspects of the healthcare system, to study other public health problems, or to be transferred to study HIVDR in other study sites.

Conclusions

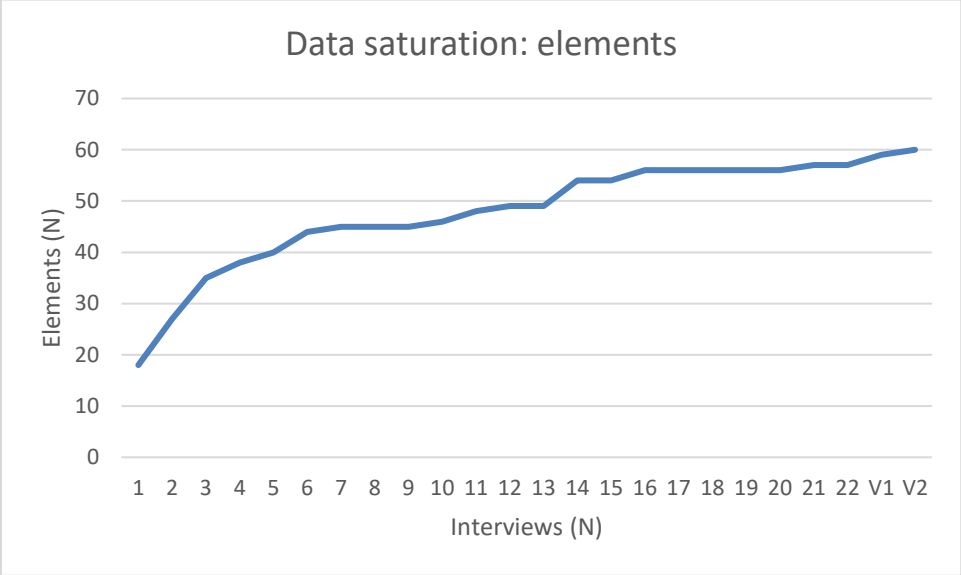
We successfully modelled the CAS of factors influencing HIVDR in the Ukonga and Gongolamboto areas of Dar es Salaam, Tanzania. The model provides a detailed understanding of the mechanisms that locally drive HIVDR, based on which we suggested three local leverage points: 1) strengthening an adherence-driven reinforcing loop, 2) weakening the feedback loops driven by stigmatisation and 3) linking psychological, adherence and financial services for PLHIV. We described that the last, deep leverage point could be intervened upon by organizing combined microfinance and peer support groups for PLHIV. Together this forms a strong basis for the design of sustainable, complexity-informed interventions, tailored to the local context of the study site.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of MUHIMBILI UNIVERSITY FOR HEALTH AND ALLIED SCIENCES (protocol code No.DA.282/293/03/ C/69, approved on 24 May 2019).

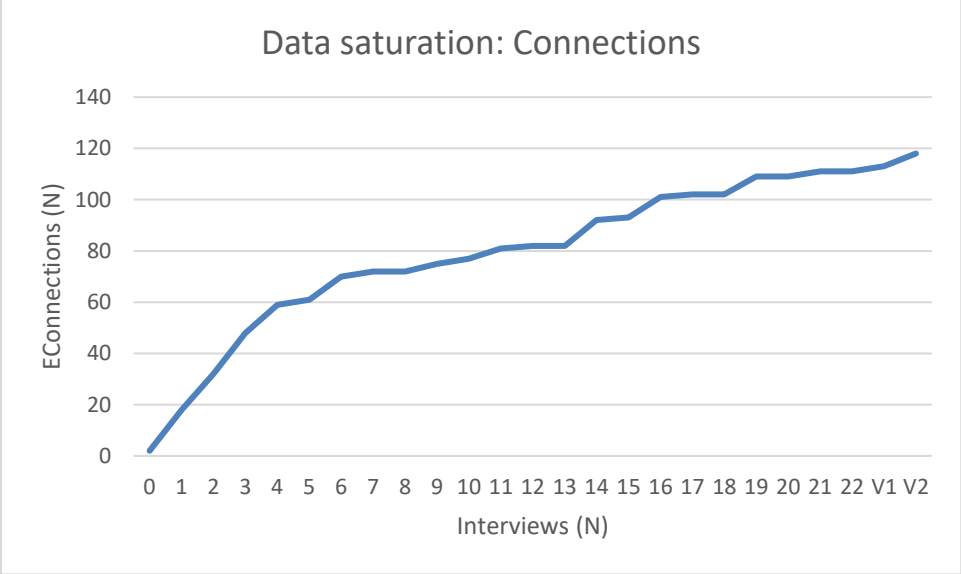
Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data generated or analyzed during this study is included in this published article and its supplementary information files.

Supplementary material



Supplementary Figure 2: *Data saturation: elements. Data saturation curve of the number of elements after each interview and workshop. V1 and V2 stand for the validation workshops.*



Supplementary Figure 3*: Data saturation: connections. Data saturation curve of the number of connections after each interview and workshop. V1 and V2 stand for the validation workshops.*

Supplementary file 2

Interview guide for PLHIV

English Version

Instructions to the interviewer

Instructions to the interviewer are in italics.

Text to be read is in bold.

If a respondent declines to answer a question, please write 'declined to answer' in the margin.

Information of the study

Hello, my name is ….. I am coming from ….. working in a collaborative project with ….. working on a research project concerning HIV drug resistance. By interviewing people living with HIV, this research will construct a broad overview of all possible factors leading to HIV drug resistance and possible solutions to these problems.

You have been selected for this interview because you are living with HIV. Before we start I would like to repeat some items from the informed consent form:

The information you provide is completely confidential. Your responses are recorded but this questionnaire does not have your name on it and is only identified by a number.

If you have questions after we are finished you can always contact me.

Interview information

Interview number:

Date of interview:

Interviewer name:

Location:

Time of start:

Language:

Part 1: Sociodemographic information

I. Baseline interviewee profile:

A1	Sex (Gender) of interviewee: [ ] Male [ ] Female
A2	Age (in years).....
A3	Religion:
A4	Marital status:

A5	Job:
A6	Level of education or degrees:
A7	Year when highest level of education was completed
A7	May we contact you if we have any additional questions in the weeks/months ahead? [ ] Yes [ ] No If not, why?
A8	If yes, contact information: Phone: Email:

Part 2: HIV related background

2.1 When did you first learn about your HIV positive status?

And when did you start taking antiretroviral therapy?

2.2 Which medication are you taking?

And which line of treatment are you on?

2.2.1 Do you use other types of HIV treatment, next to the medication you are taking? If yes, can you explain about them?

2.3 How often do you have to visit the healthcare centre in relation to your HIV status?

2.3.1 Do you feel like you get the necessary counselling from your healthcare provider? Please explain.

2.4 Are you a member of any peer support group or another organization concerning HIV support or advocacy? If yes, please explain.

Part 3:

3.1 Could you describe some of the challenges you face concerning your HIV treatment?

The following four areas should be covered:

 Availability of ART at your local healthcare centre (*this aims to cover for example drug stock-outs*)

 Your ability to fetch your ART supplies (*this aims to cover all the reasons people would not be able to / want to go to the healthcare centre for ART pick up or follow-up visits*)

 Your adherence in taking the ART as prescribed *(this aims to cover all the reasons why people don't always take their medication daily and as prescribed)*

3.1.1 Do you think the HIV drugs you are taking is helping you? If yes explain, if no, explain.

Reasons outside these four areas:

3.2 What do you think are the causes of the problems/situations you just mentioned?

Go deeper into some of the issues indicated by the interviewee in the previous questions.

3.3 What would help you to take your treatment daily as prescribed?

Here other solution-oriented questions can be asked depending on the previous course of the interview. For example: "What would be the best way to overcome stigma?".

3.4 Is there anything else you think is relevant for our discussion that we haven't discussed so far?

This concludes our interview. Thank you very much for your participation.

Time of conclusion:

Additional interviewer notes:

Supplementary file 3

English Version

Instructions to the interviewer

Instructions to the interviewer are in italics.

Text to be read is in bold.

If a respondent declines to answer a question, please write 'declined to answer' in the margin.

Information of the study

Hello, my name is … I am coming from … working in a collaborative project with … working on a research project concerning HIV drug resistance. By interviewing experts from several fields, this research will construct a broad overview of all possible factors leading to HIV drug resistance and possible solutions to these problems.

You have been selected for this interview because of your role in [study site] as a X. Before we start I would like to repeat some items from the informed consent form:

The information you provide is completely confidential. Your responses are recorded but this questionnaire does not have your name on it and is only identified by a number.

If you have questions after we are finish the interview you can always contact me.

Interview information

Interview number:

Date of interview:

Interviewer name:

Location:

Time of start:

Language:

Part 1: Sociodemographic information

I. Baseline interviewee profile:

A1	Job:
A2	Sex (Gender) of interviewee: [ ] Male [ ] Female
A3	Age (in years).....
A4	Months/years of experience in current job:
A5	Level of education:
A6	Where were you born?

A7	Where do you live at the moment?
A8	May we contact you if we have any additional questions in the weeks/months ahead? [ ] Yes [ ] No If not, why?
A9	If yes, contact information: Phone: Email:

Part 2: HIV related experience

2.1 Could you describe what you are doing in your work? What are your daily activities and responsibilities?

2.2 Do you encounter PLHIV at your work?

2.2.1 If yes, how often are you in contact with them?

2.2.2 What is the nature of your contact with PLHIV? *(e.g. logistic, medical, psychosocial, …)*

2.2.3 Do you give assistance to PLHIV? If yes, which type of assistance? If no, please explain

Part 3:

3.1 In your experience, what are the issues PLHIV face in their daily life?

The following four areas should be covered:

 Concerning the availability of ART at the local healthcare centre

 Concerning picking up their ART at the healthcare centre

 Concerning the ability to take the ART every day as prescribed

 Concerning the effect of the medication (*capturing side effects but also believes about the medication)*

Reasons outside these four areas:

3.2 What do you think is the cause of ……..?

(Go deeper into some of the problems described above)

3.3 Have you ever heard about HIV drug resistance?

3.3.1 If yes, what do you know about HIV drug resistance?

3.3.2 Where did you hear this information?

3.4 What do you think the people living with HIV in your community need?

(Adapt the question based on the previous discussion. E.g. What do you think the PLHIV in your community need to overcome stigma? What do you think would help them to take their medication correctly? …)

3.5 Do you have anything important to add to our discussion that you want to share with us?

This concludes our interview. Thank you very much for your participation.

Time of conclusion:

Additional interviewer notes:

Chapter 5

Qualitative systems mapping for complex public health problems: a practical guide

Research Article

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Kiekens, A.; Dierckx de Casterlé, B.; Vandamme, AM.

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PMID: 35213648

This chapter is based on the published version of the article.

Abstract

Systems mapping methods are increasingly used to study complex public health issues. Visualizing the causal relationships within a complex adaptive system allows for more than developing a holistic and multi-perspective overview of the situation. It is also a way of understanding the emergent, self-organizing dynamics of a system and how they can be influenced. This article describes a concrete approach for developing and analysing a systems map of a complex public health issue drawing on well-accepted methods from the field of social science while incorporating the principles of systems thinking and transdisciplinarity. Using our case study on HIV drug resistance in sub-Saharan Africa as an example, this article provides a practical guideline on how to map a public health problem as a complex adaptive system in order to uncover the drivers, feedback-loops and other dynamics behind the problem. Qualitative systems mapping can help researchers and policy makers to gain deeper insights in the root causes of the problem and identify complexity-informed intervention points.

Introduction

In recent years, systems thinking methodology is increasingly used to study health systems and complex public health problems [82,139]. Researchers and policy makers around the globe are more and more aware of the need to shift away from reductionist cause-effect approaches towards a systemic understanding of public health issues [80]. Health systems may be conceptualised as complex adaptive systems (CASs), which entail a set of diverse, interrelated factors and which are characterized by dynamic behaviours such as emergence, self-organization and the formation of feedback-loops [77,112,140]. In a CAS, positive interventions in one part of a system, may have undesired effects in other parts of the system, depending on the paths that exist in the system and choices and events that happen along the way. This phenomenon is called path dependence.

Despite the rising interest in systems approaches, literature on the topic remains dispersed and a common jargon is yet to be developed [82]. Moreover, the available literature on complex systems approaches in the field of public health has remained largely theoretical. A commonly used method to visualise, understand and analyse a

CAS is systems mapping. Systems mapping has been used to study diverse public health problems such as obesity, vaccine hesitancy and neglected tropical diseases [109,141,142]. The term systems mapping comprises a set of different methods for visualising and analysing complex adaptive systems. Depending on the exact nature of the research question, a different type, or combinations of types, of mapping can be used. One of the most used types of systems mapping is causal loop diagramming [82]. This is a qualitative approach in which the causal relationships between factors are represented. Connections between elements are directed and can be positive (both elements evolve in the same direction) or negative (both elements evolve in the opposite direction). An often-used example of a causal loop diagram is that of the heating and the thermostat (Figure 18). When the room temperature drops to a certain point, the thermostat will automatically increase the heating (negative causality). When the heating is on, the room temperature will increase (positive causality) up until the point in which the desired temperature is reached.

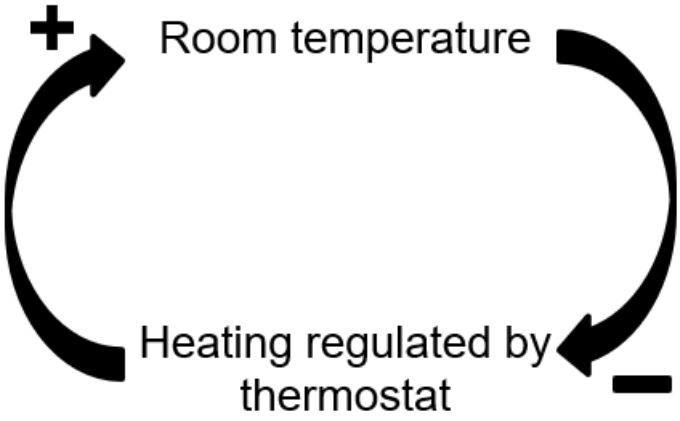

Figure 18: *Causal loop diagram example. Thermostat room temperature regulation as a (simplified) example of a causal loop diagram.*

While in this manuscript we primarily focus on the mapping of causal loop diagrams, there are also other types of mapping such as stock and flow diagrams, which is a more quantitative approach to systems mapping and can be used to study the dynamic behaviour of a system over time, or social network analysis which aims at visualising and studying the relationships between social actors [84,85]. Such visualisations of CASs help to gain deeper insights into the dynamics of complex problems and to develop a shared understanding between different stakeholders in order to come to a

nuanced understanding of the complexity of the situation. Systems dynamics and types of modelling have been thoroughly described by Sterman (2000) [143]. Systems mapping aims to do more than integrating the perspectives of different stakeholders. It uncovers emerging dynamics which are built up of more than the sum of the elements involved and which would likely have remained uncovered if a linear approach were adopted. In some cases, the process of developing a systems map may be more valuable than the final product itself. In such cases, participatory practices such as group model building sessions may be used. Different stakeholders then come together to jointly develop insights and search for solutions while mapping the system. [144–146]. However, group model building sessions are not always the most desirable or feasible option. For example, the topic under investigation might be highly stigmatised in the community, therefore not allowing participants to speak freely during a group model building session, the participants perspectives on the topic may be too diverse to organize a common discussion (e.g. technical experts vs family and friends), or participants might live in different parts of the world, making a physical meeting organizationally challenging [147,148]. In some cases, individual interviews are also preferred when one aims to understand the individual mental models of stakeholders separately before generating an integrated overview of the combined viewpoints [149]. In this article we provide some practical guidelines and reflections on how to use systems mapping as a means to collect and investigate rich, complex data on public health challenges in order to integrate different perspectives and gain a deeper understanding of the complex systems dynamics. We use a case study concerning HIV drug resistance in sub-Saharan Africa as a practical example to clarify how complex data can systematically be collected, mapped and analysed while incorporating the principles of transdisciplinarity every step of the way (Figure 19) (Table 8).

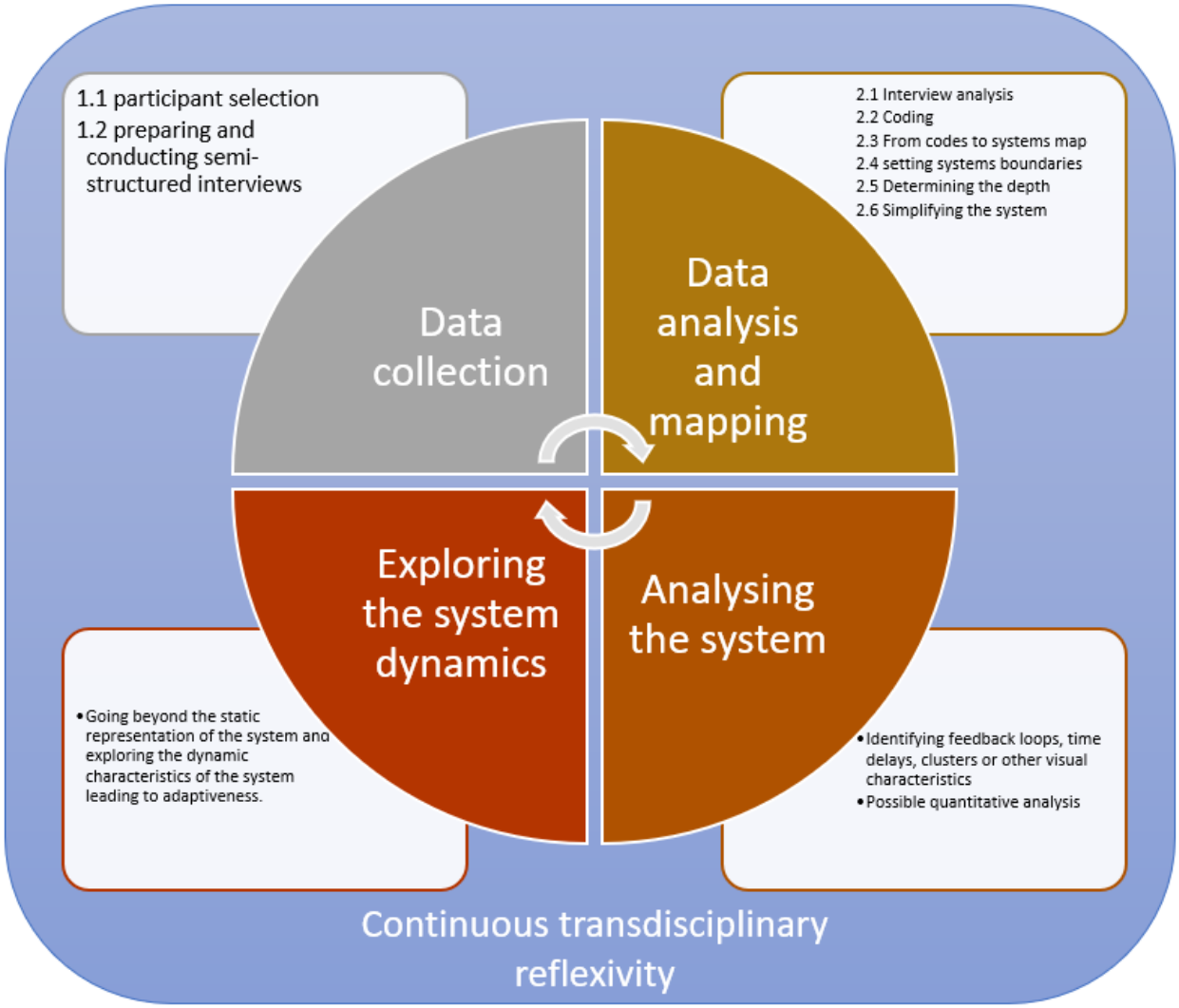

Figure 19: *Overview of the described methodology, consisting of four iterative building blocks and continuously requiring the researchers to adopt a transdisciplinary approach and to be aware of their disciplinary biases.*

Case study

The methodology discussed in this paper is illustrated by a study on the complex adaptive system of factors influencing HIV drug resistance (HIVDR) in sub-Saharan Africa [124,130]. Although antiretroviral therapy (ART) is available, allowing people living with HIV to live a long and healthy life, the increase in HIVDR is threatening the success of the available therapies. HIVDR arises when the ART present in the body is insufficient to suppress the viral load, creating selective pressure which allows the virus to mutate in order to escape the effect of the therapy. This situation can be due to

irregular adherence of PLHIV to their therapy which on its turn has many other possible causes. The aim of the study was to gain detailed insights in the underlying dynamics of factors influencing HIVDR and to identify suitable intervention points. To this purpose two systems maps were developed: one visualising the complex adaptive system of factors influencing HIVDR as understood by experts on an international level and one visualising the system at local level for a study site in Dar es Salaam in Tanzania. These systems maps were informed by interviews with 15 international experts, 12 PLHIV in Dar es Salaam and 10 local actors, who through their daily activities regularly come into contact with PLHIV in the study site. The findings of these studies are described in two separate publications [124,130]. In the next sections we use examples from this case study to illustrate our guide.

Guidelines

Table 8: *Overview of the guideline and the timing of each step throughout the process.*

Step	Description	Timing
1	Data collection	
1.1	Participant selection	
1.2	Preparing and conducting semi-structured interviews	May lead back to 1.1
2	Data analysis and mapping	
2.1	Interview analysis	May lead back to 1.1 and 1.2
2.2	Coding	May be in parallel with 2.1
2.3	From codes to systems map	After 2.2
2.4	Setting systems boundaries	After 2.3, though one can reflect about this throughout the data analysis
2.5	Determining the depth of the system	After 2.4, though one can reflect about this throughout the data analysis
2.6	Simplifying the system	After 2.5
3	Analysing the system	In parallel with 4
4	Exploring the system dynamics	In parallel with 3
5	Continuous transdisciplinary reflexivity	Throughout the whole process

Data collection

Choosing a data collection method and participant selection

The first consideration to make is which way of collecting data is most suitable for the topic under investigation. As already explained in the introduction, there are different reasons (both methodological and practical) to opt for either group modelling sessions or individual interviews. This guide focusses specifically on the mapping and analysing of complex data collected by semi-structured interviews. Participants should be recruited with the aim of obtaining a full picture of all aspects of the system. Next to interviewing patients and healthcare workers, one might therefore also consider interviewing people who are somewhat further removed from the core problem but are still in touch with certain parts of it. For example, architects designing certain hospital area's relevant for the topic under investigation or religious leaders who provide spiritual support to patients could contribute unique insights into the topic. Next to the interviews themselves, other types of data such as participant observation and document analysis could also be used to triangulate the data and increase the validity of the results.

In our case study we opted for collecting the data for our systems map through individual semi-structured interviews. This had a dual reason. First, for our mapping at international level, we wanted to obtain broad insights in all possible factors influencing HIVDR. Individual interviews were chosen to give us the opportunity to collect deep insights in the specific expertise of the interviewee while verifying or building further on information obtained from previous interviews. For our local map, individual interviews were preferred for another reason. As people living with HIV still face strong stigmatisation, we wanted to create a safe environment for them to speak their mind, without other community members present. Moreover, a workshop would likely only have attracted PLHIV who felt comfortable with their HIV status and were facing less difficulties adhering to the therapy, while for the interviews we also managed to recruit PLHIV who had dropped out of care.

Preparing and conducting semi-structured interviews

A semi-structured interview guide should be developed based on the available scientific literature or already existing and validated guides on the topic, and adapted throughout the data collection process when new insights are developed (Supplementary file 1-3). In order not to bias the data collection towards certain assumptions the researcher may have, it is advised to start the interview with a broad, open question about the complex problem, rather than asking a question about a single aspect of the problem. This way, the participants are inclined to start by expressing the aspect of the complex problem most important to them and the interviewer can explore the main believes and experiences the participant has to share about the topic. For example, an initial question like “how do you experience being HIV positive” may reveal to the interviewer that the patient’s whole perception of his or her HIV infection is based on the believe that it is a punishment of God. This information is important for the interpretation of the rest of the interview and may not have come up if the interview had started with a focus on a certain aspect of the system, such as the question “how do you perceive the healthcare service you receive?”. After this first question, the interviewer may continue covering a list of specific topics, retrieved from the literature or which came up in previous interviews. When a question is answered by “A happens because of B” the interviewer can ask for specific examples or experiences that support this claim and subsequently delve deeper into other possible underlying causes aiming to obtain the structure “A happens because of B, which is caused by C, D and E, etc.” This continues until a sufficient level of depth is reached or until the insights of the interviewee are exhausted, at which point the chain of causality may be built up further during interviews with other participants. Such chain of causality is built several times within one interview, each time starting from an open question. To further reduce bias, the interview circumstances should be well thought-through in order to create trust between the interviewer and interviewee. For example, interviews with PLHIV are best done in their native language and in a location that cannot be perceived as stigmatizing.

Data analysis and mapping

When developing a systems map based on the interview data, the first steps are largely similar to conventional interview analysis methods used in a grounded theory design.

The first steps of our data analysis method are inspired by the Qualitative Analysis Guide of Leuven (QUAGOL) which provides clear steps for capturing the rich insights in complex qualitative data [95,150].

Interview analysis

Interviews should be recorded and transcribed verbatim. Throughout the interview process, the research team should have regular debriefing sessions to allow for modifications of the interview guide if needed. This can for example be the case when a new relevant topic comes up, which needs to be further investigated in the following interviews. Ideally, technical reports are written after each interview, describing the context of the interview, possible technical issues, characteristics of the participant and possible cultural clarifications important for the full comprehension of the data in their specific context. After thoroughly reading the transcripts, a series of meetings is organized between the research team in order to discuss the interpretation of the interviews and to make sure cultural elements are well-understood. It is advised to include researchers from different disciplinary backgrounds in the team, in order to prevent disciplinary bias in the analysis of the data.

Coding

Once an interview and its core messages are well understood, the coding process can start. Coding can be done with professional programmes such as NVivo or in an excel table. The researcher keeps a list of all elements that were mentioned as a direct or indirect cause of the problem under investigation and of each link between two of those elements. Ideally this coding process is done simultaneously by multiple researchers to avoid researcher specific outcomes. When after comparison, the coding is different, the reason should be identified and resolved. For further analysis purposes, other types of data can be stored behind each element or connection. In Table 9 we explain the types of data that can be stored behind one element, using the element “accessibility of healthcare centre” as an example

Table 9: *Coding examples. Examples of types of data which could be retrieved during the coding process and stored behind elements and connections of the systems map. We illustrate with an example of our study on HIVDR.*

Data type	Explanation	***Example***	Note
Element Name	The factor directly or indirectly influencing the problem under investigation.	*Accessibility of healthcare centre*	
Definition	It is important to define the element and what is included or excluded in order to facilitate the interview coding.	*Accessibility refers to road access, public transportation, road safety, transport costs, limited opening time, poor access due to other disease outbreaks or wars etc. Distance to healthcare centre is considered a separate element.*	
Number of Interviews	The number of interviews a certain element or connection was mentioned in.	*7*	This element has been discussed in 7 out of 22 interviews.
Interview Identification Number	The identification number of the interviews in which a certain element or connection was discussed.	*For example: I01, I03, I04, I08, I09, I13, I15*	(Fictive identification numbers are used due to confidentiality reasons).
Quote	The interview quotes in which the element or connection was described. Storing this information in the systems map	*"Sometimes I don't get a bus fare but I borrow somewhere because I must go for refill. When few drugs for two or three days remain, that is when I go to refill my drugs. I must go the same date*	This is one quote given as an example. During data collection, all quotes relevant to this element would be collected here.

	will facilitate the analysis as all the quotes linked to a certain element can easily be revisited.	*written on my card by the health care providers so as I may not confuse them. If it is written fifth I must go to refill, so even if it is from my neighbour I borrow one thousand shillings so as I go to the facility to refill my drugs"*	
Tag	The opportunity to categorise elements.	Healthcare system related	This allows the researcher to easily filter out all elements related to a certain topic, in this case healthcare system related factors.
Other…	Several other types of data (for example: degree of importance) can be stored, depending on what may be useful during the analysis process.		For example, a degree of importance as judged by the interviewee could be given to elements based on how the elements or connections were described in the interviews. However, as this is a subjective indicator, it is advised to always use this parameter in combination with other ones when drawing conclusions.

From codes to systems map

While keeping the codebook updated after analysing each interview, it can also be of interest to make a separate systems map of each transcript, visualizing the mental model of the interviewee in order to understand how he or she perceives the system (Figure 20). Mental models are graphical representations of how people internally understand causal relationships between elements to make sense of a complex problem [151,152]. They often unconsciously affect our behaviour or decision making and are useful for the researcher to gain a deeper understanding of the interviewees way of thinking about the problem [153].

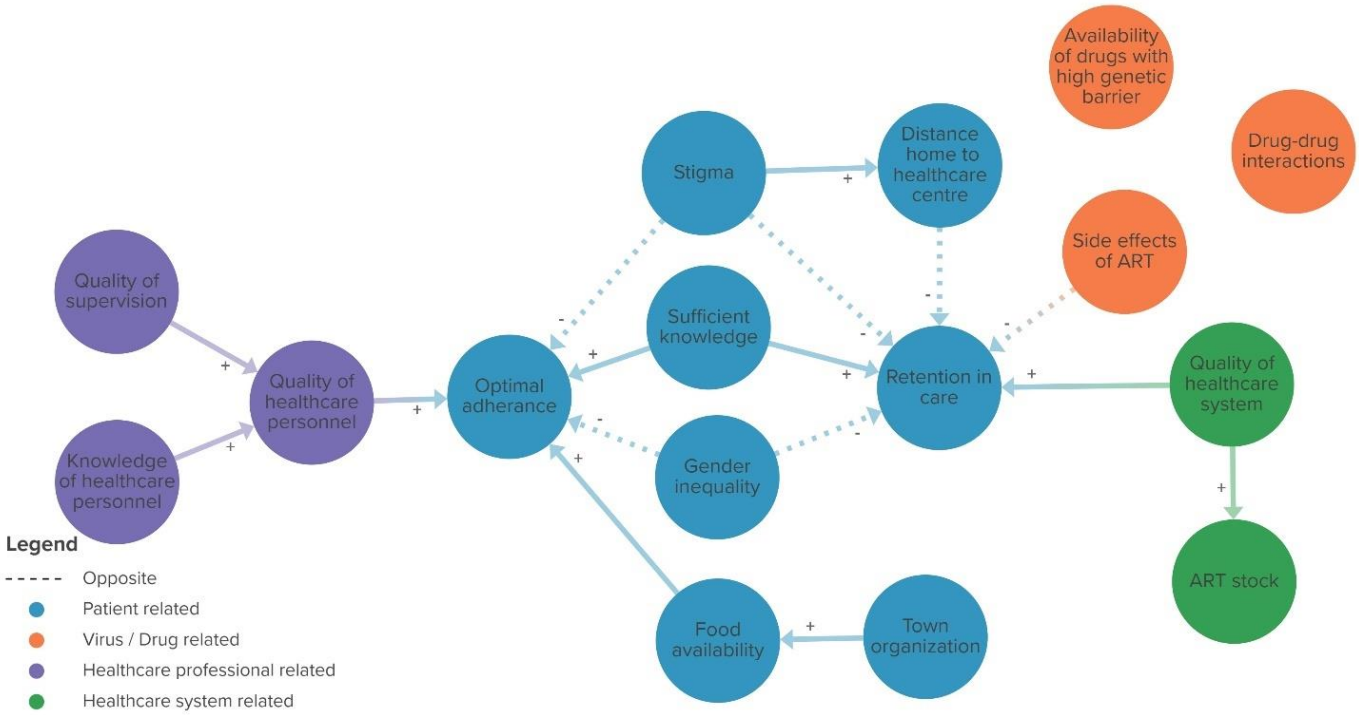

Figure 20: *Example of a mental model. Example of a mental model of an interviewee, visualizing the elements and connections which came up during the interview and which are perceived to be true by the interviewee. The researcher tried to bring some first structure in the model by using a colour code.*

In a next phase these schemes can be merged manually or automatically by simply uploading the codebook in the used mapping tool. In our case study we used Kumu, a user-friendly online mapping tool which allows the storage of different types of data behind each element and connection and which has some built in analysis tools [113].

Once the codebook is imported, some immediate structure can be brought into the map by for example colouring or grouping the elements according to a common parameter or sizing the elements by number of occurrences. This structure will most likely be changed at a later stage in the analysis process when new insights are gained. Eventually, the researchers may opt to retain different visualizations of the model to highlight different structures. In the case of HIV drug resistance in sub-Saharan Africa, we developed one visualization showing how the elements relate to different societal layers, whereas the second visualization highlights the main dynamics of the system (Figure 21). In both visualizations each element is a factor influencing HIVDR as mentioned in the interviews and each connection indicated the relationship between those factors. An interactive version of the systems maps where the reader can zoom in and click on elements and connections is available on the Kumu platform[3] [154].

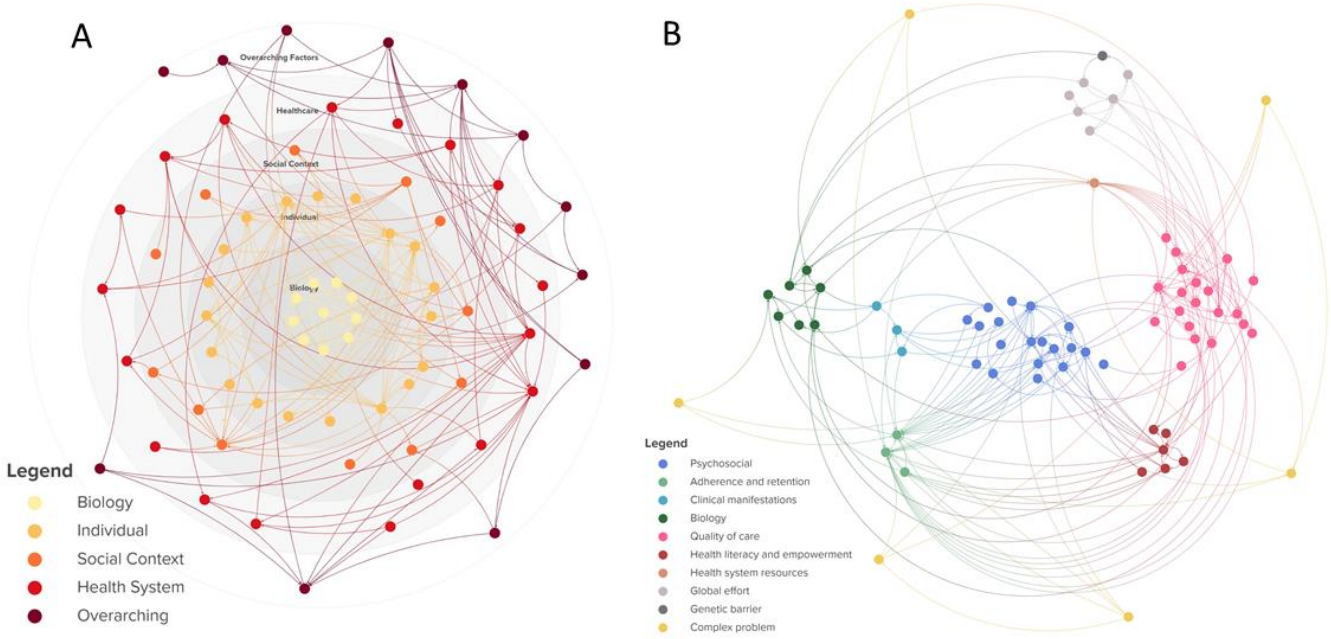

Figure 21*: Different ways of visualizing a system. The elements and connections in A and B are exactly the same. In A the system is organized according to the different layers ranging from biology on the micro level to the individual level, the social context, the healthcare system and overarching factors at the macro level. In B, the elements are divided in thematic clusters and the relationships between clusters are visualized. Figure adapted from Kiekens et al.* [130] *and for illustrative purposes only.*

[3] https://annemie.kumu.io/qualitative-systems-mapping-for-complex-public-health-problems-a-practical-guide

When a first basic structure is reached, we suggest to revise all elements and connections in order to avoid the same concept being visualized in different ways inside the map. For example, a pathway representing the difficulties PLHIV may face reaching the clinic due to their economic status may be represented as “economic status -> retention in care” or as “economic status -> ability to pay transportation -> retention in care”. Especially when the coding is done by more than one researcher, the codebook may contain such double pathways. To resolve this, the research team has to come to a common agreement on how to visualize such concepts.

Setting systems boundaries

Throughout this process the researcher can also start to set system boundaries, determine the level of depth the CAS will be represented in and simplify the system. In reality, the boundaries of CASs are often blurry as different CASs are interlinked and systems are constantly evolving [77]. For example, while our case study aimed at covering a public health issue (HIVDR), we realized throughout the study that our system is strongly interlinked with other complex systems such as poverty (e.g. having financial means to reach the healthcare centre and food insecurity influencing adherence as medication needs to be taken with a meal). However, when visualizing a system, some choice in what to include in the system and what not, needs to be made. Though it might seem tempting to set boundaries at the beginning of the project, the authors recommend starting without boundaries in mind and representing the CAS as detailed as possible. While more time consuming, the advantage is that the possibility of excluding important factors due to pre-set limits is reduced and the researchers gain deep insights in all aspects of the system before analysing it or reducing it to its essence if needed. Boundaries can be set in different ways depending on the information the map needs to transmit. For example, one can decide to consider the factors which are not part of a closed system as being exogenous, meaning they only have influence on the system but are not influenced by the system. For example, in Figure 21B, all endogenous elements are part of a closed feedback loop (they influence and are influenced by the system), whereas the exogenous factors (indicated in yellow), are exerting an influence on the system but are not influenced by the system (e.g. “gender inequality” influences “HIV status disclosure” and “HIV transmission” but is not influenced by any element in the system). Another way of determining the boundaries of the system could be to view all elements that form the core of a different

CAS as exogenous factors (for example: gender inequality, poverty and war and disease outbreaks are all complex problems on their own, which are interlinked with our complex problem).

Determining the depth of the system

The depth of the system refers to the level of detail a system is represented in. Issues surrounding stigmatization of PLHIV could be separately represented as “stigmatization”, “self-stigmatization”, “gossip and discrimination” or as one common term such as “stigma and discrimination” (Figure 22). Again, this depends on the research question and purpose of the systems map.

Figure 22: *In-degree. Illustration of mapping choices to be made by the researchers and the consequences for the in-degree metric.*

Simplifying the system

Additionally, the systems map might need to be reduced or simplified to a smaller, more manageable system that is understandable for external stakeholders. In the rest of this paragraph we suggest some strategies for the simplification of systems maps. Other strategies (possibly topic dependent) could also be used. More important is to consequently apply the strategy to the whole systems map. When in doubt whether two elements should be merged or not, we suggest the researcher asks two questions: 1) are there significant differences in nuance between the content of both elements? And 2) do both elements have different connections to other elements? If the answer to both questions is “No”, the elements can be merged into one. Moreover, elements

that have only one incoming and one outgoing connection (A->B->C) might be deleted and taken up into one connection from A to C (A->C), unless element B is crucial for the understanding of the system. When several loops are present, loops sharing a same broader theme can be summarized into one. This can be compared with a route on a roadmap [130]. When one wants to know the route from Paris to Brussels, there are several options. All the options pass by different towns but they all have one common theme: they represent ways to go from Paris to Brussels. Bundling these loops or pathways between two elements, may help to drastically simplify the map and to visualize only the core essence. Figure 23 is an example of a holistic, detailed system (A), summarized into its core feedback loops (B)

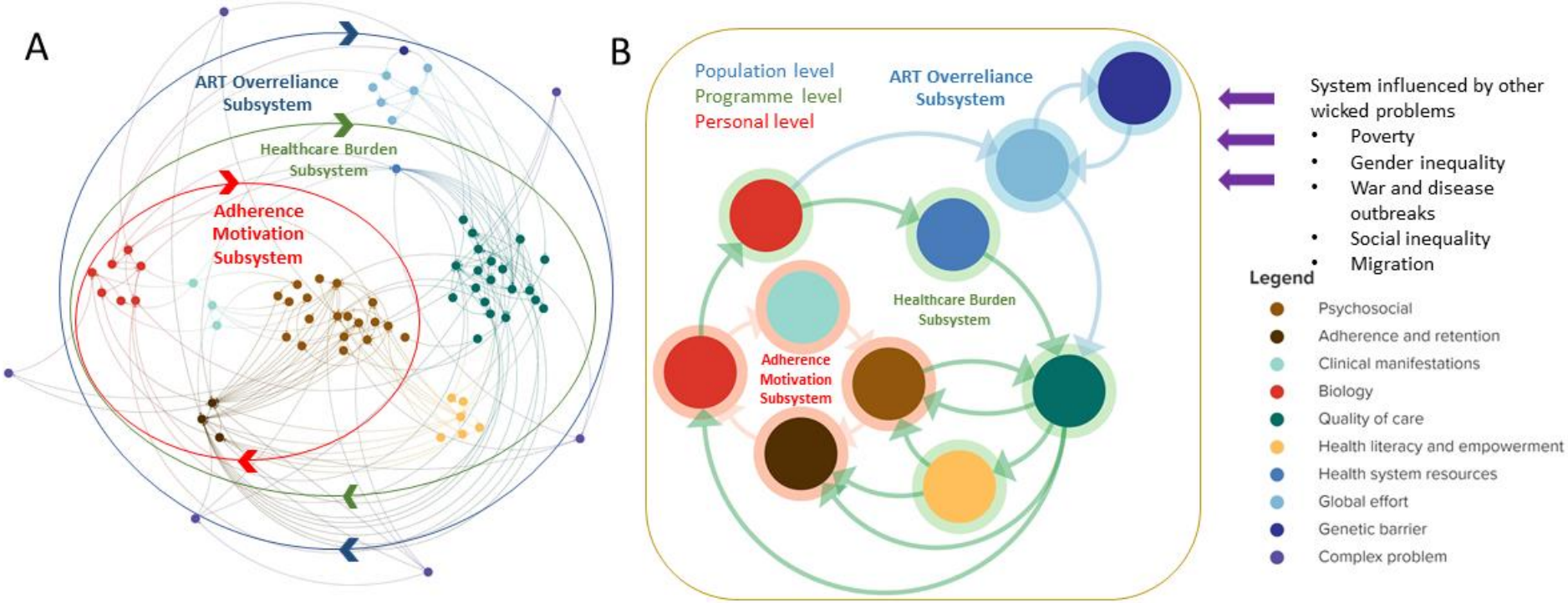

Figure 23: *Summarizing a complex system. A) Detailed system of factors influencing HIVDR. The main feedback loops or subsystems are highlighted with coloured circles. B) The same system, condensed into the main feedback loops and with the main exogenous factors represented on the outside. Each cluster in panel A is represented as a single element in panel B, represented with the same colour in the core of the element. All connections between two clusters in panel A are represented as one connection in panel B. This way, the main dynamics of the system are represented in a more condensed and comprehensible format. Figure adapted from Kiekens et al.* [130] *and for illustrative purposes only.*

Analysing the system

In fact, the analysis of the CAS starts during the mapping process itself. Throughout the mapping process, the researcher will start to identify certain characteristics of the system. These could be for example reinforcing or balancing loops, time delays or clusters of elements or connections sharing the same characteristics. Though the analysis is foremost qualitative, involving a continuous (re)-reading of interview quotes or relevant literature, some quantitative elements may support the interpretation. McGlashan et al. propose some quantitative network analysis metrics and describe how to interpret them when applied to systems maps [111]. The in-degree describes the number of incoming connections (the number of elements influencing the element of interest). The higher the in-degree, the more the element is directly influenced by other elements of the system. In our case study, the element with the highest in-degree was “adherence”, which is not surprising because adherence is a well-studied factor with a known correlation to HIVDR and many influencing variables [37,45]. The out-degree describes the number of outgoing connections (the number of elements thought to be influenced by the element of interest). In our case study, “understanding of HIV infection and treatment” had the highest out-degree, indicating that this element is perceived to exert the most influence on the rest of the system. Elements with a high out-degree but a low in-degree might be good candidates for leverage points in a system as they impact several parts of the system but are not influenced by many other elements. For example, social support is influenced by the status disclosure of the patient and the knowledge the family members have about HIV, while it has a direct impact on five different factors in the system, such as acceptance of HIV status and help with adherence. Another quantitative method by Finegood et al. can be used to quantitatively compare two systems maps visualizing the same system but from different points of view [155]. In the Finegood method, elements (based on the same thematic coding for both maps) are divided into clusters and inter- and intra-cluster relationships are compared. However, an important note has to be made concerning both methods. When interpreting these metrics, one needs to consider the coding choices made earlier in the process. Coming back to the example used before, psychological wellbeing can have an in-degree of four as it is influenced by stigmatisation, self-stigmatisation, discrimination and gossip, or it can have an in-degree of one if the researcher has decided to group all four elements in one. In both

cases, the content of the map is the same, but the in-degree metric will be different (Figure 22). The authors therefore advise to be cautious when using such metrics as a supportive tool during analysis and always ground findings in qualitative evidence. Other methods to quantify causal loop diagrams and to select desirable future scenarios have been described in the literature [84,156].

After analysis, it is advised to link back to the stakeholders and population in order to validate the findings. This is an important step in order to verify whether data was correctly interpreted and whether no major elements were overlooked. This can be done during participation in a conference if the target population are experts, or through a workshop, peer debriefings or member checks.

Exploring the system dynamics

While a systems map is a static representation of a CAS, in reality systems are constantly evolving and reorganizing when changes occur. Uncovering the potential for adaptiveness in a CAS requires an understanding of what is contributing to such dynamics. Once the system is mapped, one therefore needs to explore the characteristics that have the potential to lead to adaptiveness [112,140]. These characteristics may be difficult to represent in a static systems map, which makes it all the more important to study them separately. In Table 10 we illustrate some of these characteristics with an example of our case study.

Table 10: *Dynamic characteristics of CASs. Elements that contribute to the dynamics of a CAS, illustrated with an example of our case study.*

Characteristic	Explanation	Example
Emergence	Spontaneous behaviour which arises when individual actors or elements reorganize themselves into a bigger whole.	In order to prevent HIVDR, it is important that PLHIV take their medication on a daily basis. When there is a stock-out, healthcare workers organize themselves in WhatsApp groups in order to re-divide the stock and provide all patients with their doses.
Path dependence	Events that started in the same point, can lead to different outcomes, depending on the choices that are made during the process.	When a patient discloses their HIV status to family members it can lead to an increased social support and a better adherence, but also to stigmatisation, a decreased self-image or for example loss of employment opportunities.
Feedback loop	A series of elements that influence each other in a circular motion.	PLHIV need to take their medication with a meal in order to avoid side effects. When medication is taken daily, the patient will feel healthy and will be able to work and have access to daily meals as well as provide for their family. This reinforcing feedback loop is also used by healthcare workers to motivate PLHIV.
Tipping point	A point at which the system will rapidly change and eventually settle into a new balanced state.	Stigmatisation of PLHIV is for a large part caused by a lack of information and knowledge on the nature of the infection and the transmission modalities. When the point is reached where enough people have sufficient knowledge, and

		community stigmatisation decreases, it is possible that the system (which is now strongly influenced by stigmatisation), will rapidly adapt into a new state.
Culture	The shared values and believes which are intrinsically part of the system and which, as such, contribute to the system dynamics and information flows.	In the Tanzanian culture, religious leaders and traditional healers play a prominent role. PLHIV may believe they are punished by god when they first find out about their status, or believe they will get cured by praying. Religious leaders and traditional healers may therefore play an important role in the spread of correct information and the motivation to adhere to the medication.

Continuous transdisciplinary reflexivity

Though linearly described above, the process of data collection, mapping and analysis is actually an iterative process in which more data is collected based on newly gained insights and different mapping and analysis rounds are needed to explore different lines of thinking. Throughout all this, it is important that the researchers adopt a transdisciplinary approach, truly integrating the knowledge of different disciplines while transcending disciplinary boundaries. As our education system today is largely disciplinary, a quantitatively trained researcher will have to immerse him- or herself into the qualitative research paradigm and vice versa. Posner. et al. and McGregor describe this transition from mono- to transdisciplinarity as a conceptual shift in ones ideas about reality, logic and knowledge [157,158]. Throughout the systems mapping and analysis process the researchers needs to be constantly aware of their potential disciplinary bias and need to search for active ways to avoid this, such as seeking continuous feedback from other disciplines or stakeholders, organizing group validation sessions etc. Moreover, the researcher should be aware that the systems map will never be truly finished as situations and conditions are continuously changing. Rather, the map should be seen as a dynamic tool that serves the research purposes, while staying open for changes. In short, we advise researchers to 1) immerse themselves into the literature and research paradigm of other relevant disciplines before starting the research, 2) aim for multi-disciplinarity within the research team, 3) continuously reflect on the possibility of disciplinary bias, and find ways to minimise it and 4) accept the dynamic and unfinished nature of systems maps.

Conclusion

Systems approaches are increasingly used to study complex health problems. The development of a systems map of the factors influencing the topic under investigation is not only useful as a process of transcending disciplinary boundaries and creating a holistic overview of the situation, but also as a means of gaining deep systems related insights in the underlying dynamics that drive this issue. In this article we have laid out a practical guideline for developing and analysing a systems maps for complex public health issues. Such systems maps can be used to identify the root causes and intervention points in the system and to understand the dynamics that lead to the

adaptiveness of a system. They may also potentially serve as a basis for further quantitative modelling.

Chapter 6

HIV and SARS-CoV-2: the interplay of two wicked problems

Comment

Manuscript in preparation

Kiekens, A.; Bwire, G.M.; Decouttere, C.; Jordan, M.; Mangara, A.; Mosha, I.H.; Rinke de Wit, T.F.; Sangeda, R.Z.; Swalehe, O.; Vandaele, N.; Killewo, J.; Vandamme, AM.

Concern is justified observing the link between the AIDS and COVID-19 pandemics. COVID-19 outcomes are significantly worse in many people living with HIV (PLHIV) even when vaccinated because of their impaired immune system. Moreover, CD4 T-cells are affected by both HIV and SARS-CoV-2 [159–161]. SARS-CoV-2 variants can evolve in immunosuppressed patients due to prolonged viral replication in the context of inadequate immune response [162]. Accelerated intra-host evolution of SARS-CoV-2 was reported in a South African HIV patient with antiretroviral therapy (ART) failure [163,164]. With 25 million HIV patients in sub-Saharan Africa (SSA) of whom an estimated 8 million are not virologically suppressed, this potentially creates a reservoir for future variants. Such variants, arising in PLHIV anywhere in the world, can spread to other continents, as reported for both variants of concern (VoCs) (Beta, Omicron) and variants of interest (VoIs) (B.1.6.20) or (B.1.640.2) that arose in Africa [165–167].

Conversely, the COVID-19 pandemic impacts HIV treatment programmes, due to supply chain issues, overburdening of healthcare systems, limiting access to testing, treatment and prevention programmes and further increasing inequalities [168]. Modelled COVID-19 disruptions of HIV programmes in sub-Saharan Africa included decreased functionality of HIV prevention programmes, HIV testing and treatment, and care such as viral load testing, adherence counselling, drug regimen switches, and ART interruptions, which may lead to selection of drug-resistant HIV [169]. A 6-month interruption affecting 50% of the population, would lead to a median number of excess deaths of 296,000, during one year. Scientists advocate the AIDS and COVID-19 pandemics in Africa to be addressed simultaneously, by increasing African access to COVID-19 vaccines, prioritizing research on the interaction between HIV care and COVID-19, maintaining high quality HIV services and integrating health services for both viruses [165].

Both the COVID-19 and the AIDS pandemic, more specifically the issue of HIV drug resistance (HIVDR) have previously been described as *wicked problems*[4], best studied as complex adaptive systems (CASs) [124,130,170,171]. Wicked problems consist of diverse interconnected factors and require *complexity-informed*[5] and locally adapted

[4] Wicked problems are extremely complex societal problems, that are slightly different in different area's and for which no one-size-fits-all solution exists.

[5] Wicked problems require complexity-informed interventions. This means that interventions should be designed keeping in mind the different aspects of the system it could affect rather than only considering a single cause and effect.

solutions rather than one solution that fits all. We recently designed a qualitative model of all known factors influencing HIVDR in SSA and analysed its complexity [130]. Our detailed systems map featured three main feedback loops driving HIVDR, representing 1) the alternation between adherence and non-adherence, 2) the impact of an overburdened healthcare system, and 3) the importance of sustaining global efforts of tackling HIVDR even when new antiretroviral drugs with high genetic barriers become available. These HIV related feedback loops are interconnected with COVID-19 pandemic impact (in yellow, Figure 24). The loop starts from PLHIV with an unsuppressed viral load, which weakens the immune system and may in turn slow down immune clearance of SARS-CoV-2, allowing prolonged replication and mutation of the virus in the context of an inadequate immune response. Prolonged viral clearance facilitates the selection of immune escape SARS-CoV-2 variants. Variants may emerge that have a selective advantage and therefore may spread through populations due to increased transmissibility (with possibly increased virulence), thereby creating additional burden on the healthcare system, putting the overall healthcare system and the HIV care at risk. These stressors on the health care system lead to a higher risk of unsuppressed viral load in PLHIV, increasing the risk of HIVDR. Figure 24 shows the need to address both wicked problems simultaneously and do so in a complexity-informed manner as they are inevitably linked and influence each other.

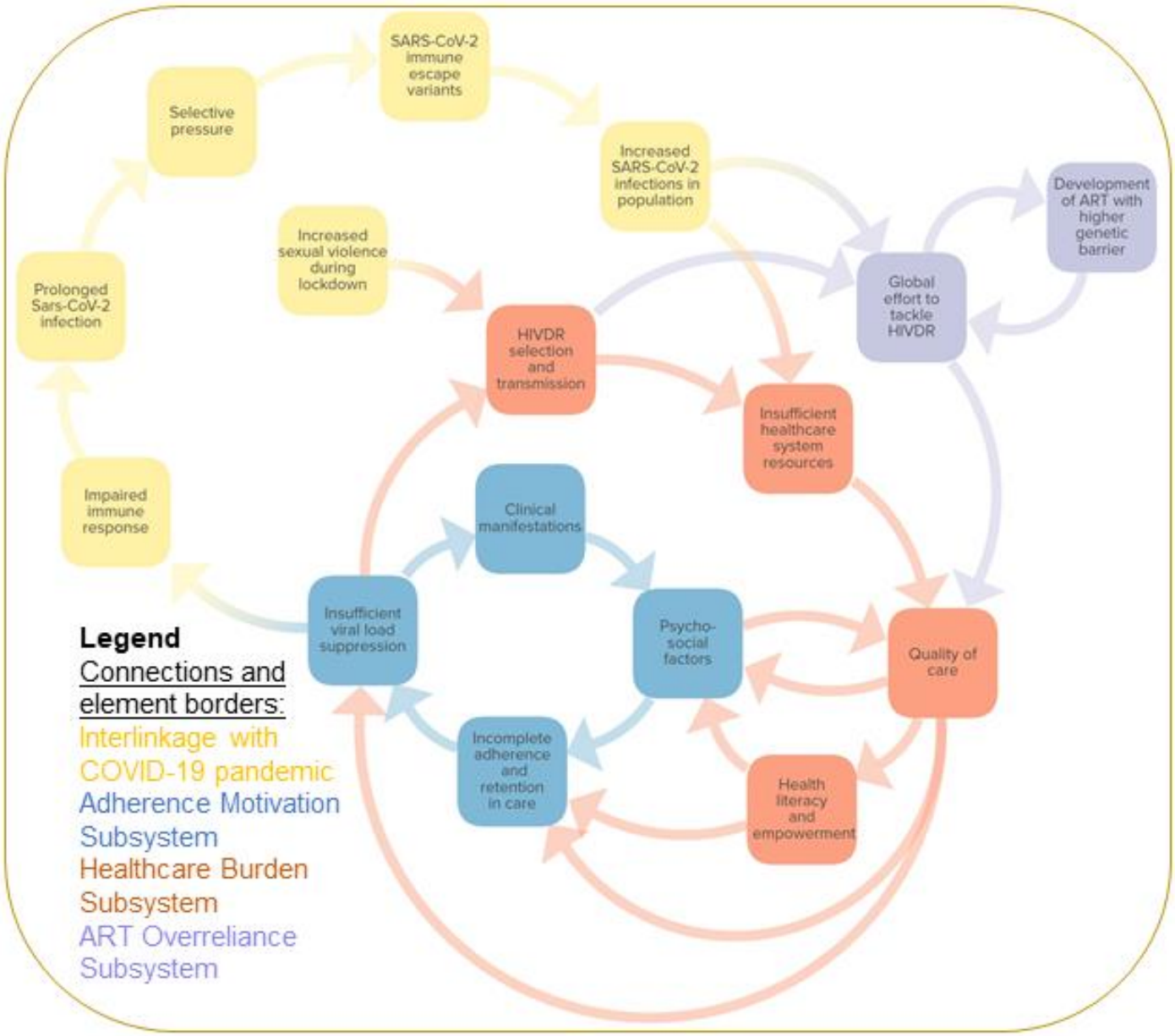

Figure 24: *Interlinkage of the HIV and COVID-19 complex adaptive system (CAS) at the international level, as supported by literature. The blue, pink and purple loops are feedback loops identified in the HIVDR CAS* [130]*. The yellow elements are related to the COVID-19 pandemic and illustrate the interlinkage between both complex problems. Other links between COVID-19 and the HIVDR CAS are to be expected, such as the likely increase in transmission of HIV(DR) due to increased sexual violence during lockdown* [172]*. The 60% increase in teenage pregnancies in South Africa during the pandemic points in the same direction* [173]*.*

At a local level we can visualize the impact of the COVID-19 pandemic and measures on HIV care and the lives of PLHIV. We did so based on a systems map of factors

influencing HIVDR in the Ukonga and Gongolamboto areas of Dar es Salaam, Tanzania [124]. In the period between March and June 2020 several COVID-19 related restrictions were implemented in Tanzania. These included banning social gatherings, avoiding non-essential travel, obligatory facemasks at health facilities, and the provision of 6-month ART for all PLHIV, instead of the usual programmatic recommendation of one- and three-month supplies for patients without and with recent viral suppression, respectively [174,175]. In Figure 25, we indicate the effects of both the measures and the pandemic in itself on the CAS of HIVDR which could be used to make complexity-informed decisions when rapid public health action is required. Systems maps help to make a first estimation of the impact of the COVID-19 pandemic and response measures on the HIVDR system. For example, due to restrictions in social activities, the feedback loop surrounding difficulties of carrying medication everywhere would have become obsolete for a certain period of time. On another note, many Tanzanians left the cities to go to the countryside at the start of the pandemic, due to the believe that SARS-CoV-2 circulated only in the cities. This migration, in combination with health care centres overburdened by patients suffering from COVID-19, combined with the implementation of other pandemic mitigation measures, would have made retention in care and continuous adherence to prescribed ART a challenge for PLHIV.

Our visualisations confirm the urgency to integrate care for PLHIV and the current and future pandemic response measures, in order to mitigate a prolongation of the current COVID-19 pandemic and a rise in drug-resistant HIV.

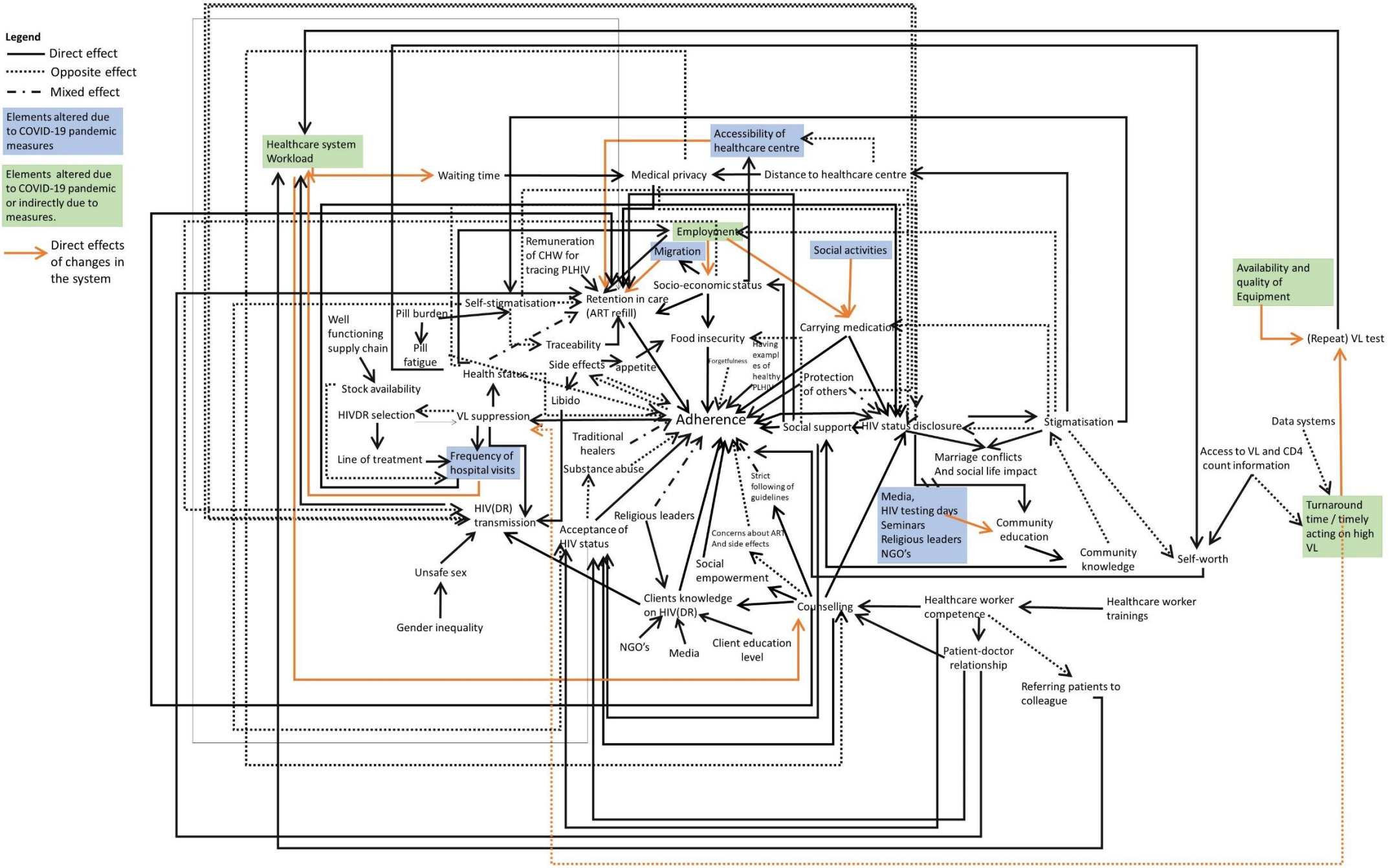
Legend
Direct effect
Opposite effect
Mixed effect
Elements altered due to COVID-19 pandemic measures
Elements altered due to COVID-19 pandemic or indirectly due to measures.
Direct effects of changes in the system
Healthcare system Workload
Waiting time
Accessibility of healthcare centre
Medical privacy
Distance to healthcare centre
Employment
Remuneration of CHW for tracing PLHIV
Migration
Social activities
Availability and quality of Equipment
(Repeat) VL test
Socio-economic status
Retention in care (ART refill)
Self-stigmatisation
Pill burden
Well functioning supply chain
Pill fatigue
Traceability
Food insecurity
Carrying medication
Having examples of healthy PLHIV
Forgetfulness
Side effects
appetite
Health status
Protection of others
Stock availability
Libido
HIVDR selection
VL suppression
Adherence
Social support
HIV status disclosure
Stigmatisation
Data systems
Traditional healers
Marriage conflicts And social life impact
Access to VL and CD4 count information
Line of treatment
Frequency of hospital visits
Substance abuse
Strict following of guidelines
Media, HIV testing days Seminars Religious leaders NGO's
Community education
Turnaround time / timely acting on high VL
HIV(DR) transmission
Religious leaders
Concerns about ART And side effects
Community knowledge
Self-worth
Acceptance of HIV status
Unsafe sex
Social empowerment
Clients knowledge on HIV(DR)
Counselling
Healthcare worker competence
Healthcare worker trainings
Gender inequality
NGO's
Media
Client education level
Patient-doctor relationship
Referring patients to colleague

Figure 25: *Effects of the COVID-19 pandemic and related measures on the HIVDR CAS in the study site. Between March and June 2020 social gatherings were cancelled, the number of pill pick-ups was reduced, public transportation seats were limited to allow physical distancing, and patients were obliged to wear facemasks at the healthcare centre, impairing access for people who were not able to afford masks. Moreover, some people were afraid of going to healthcare centres and instead bought their ART at pharmacies or chose to interrupt their treatment. Places in the system affected by government measures are indicated in blue. While the healthcare system's HIV-related workload temporarily decreased, there was an increase in COVID-19 related workload, and due to worldwide stock-outs of reagents, laboratory capacity was reduced and delays in turnaround time of VL tests were noted. The pandemic also decreased employment opportunities. These indirect effects of the pandemic and/or measures are indicated in green. Effects on other elements are indicated with an orange arrow.*

Chapter 7

General discussion

7.1 Transdisciplinary context

As described at the beginning of this manuscript, this research has grown within, and together with a developing institute for transdisciplinary research. This meant that the transdisciplinary way of working and the possibilities to do so within our setting still had to be explored. While eventually the core of this thesis became to be the exploration of the complexity of HIV drug resistance, the work has been done with the aim of growing into a larger transdisciplinary research endeavour. I have therefore tried to incorporate transdisciplinary elements, next to the involvement of experts, local actors and people living with HIV (PLHIV) described in Chapter 3 and 4, in order to secure a constant flow of feedback from diverse disciplinary angles and relevant stakeholders throughout the whole project (Table 11).

Table 11. *Contributions to transdisciplinarity at different levels of the research process.*

Level	Description	Contribution to transdisciplinarity
1. Work environment	This study was conducted part time in a research environment (KU Leuven) and part time in an NGO implementing public health projects in SSA (Doctors with Africa CUAMM).	• This provided the opportunity to regularly reflect on the research both from an academic perspective and a practical, field-oriented point of view.
2. Knowledge expansion	Attending conferences and following courses and seminars on a wide array of topics such as public health, statistics, economy, health technology, social science methodology, systems design and implementation research.	• Developing an understanding of the paradigm difference between quantitative and qualitative sciences. • Familiarizing with terminology and key aspects of different disciplines.
3. One-on-one stakeholder consultations	Regular one-on-one stakeholder meetings have been organized throughout the whole project. Stakeholders included representatives of the	• Developing a broad understanding of the needs and interests of different stakeholders. • Creating a continuous flow of feedback and

		pharma industry, locally active NGO's, HIVDR testing laboratories and researchers from diverse disciplines.	ensuring relevance of the project.
4.	Stakeholder group consultations	While most researchers aim to present their work to peers from time to time, we consciously aimed at reaching mixed stakeholder and scientist groups on several occasions.	• Incorporating insights from different fields of science and different stakeholders.
5.	Peer mentoring group	Monthly meetings between KU Leuven PhD researchers working on HIV in SSA. Members were from the faculties of social science, economics and biomedical science. Every month one member's project was discussed with the group.	• Gaining a deep understanding of how other disciplines approach the same complex problem, what their underlying assumptions are and how they view and appreciate each other's approach.
6.	Student involvement	Coaching a multi-disciplinary student team working on HIVDR in parallel with the first year of this project.	• Allowing for fresh and interdisciplinary perspectives on the topic.

While none of the above is groundbreakingly new in terms of methodology, all of the elements taken together help to guard the relevance of the research and to gain an overview, as complete as possible, of the different viewpoints on the complex problem. This is needed for follow-up projects which will use this work as a basis to design complexity-informed interventions on HIV drug resistance (HIVDR) with stakeholders and which will continue the research process together with them. A first indication of success of this continuous integration of perspectives and involvement of stakeholders and actors became apparent during a dissemination workshop of our systems mapping work done in the Ukonga and Gongolamboto district of Dar es Salaam. The workshop with ten PLHIV had a dual aim, presenting and discussing the results of our study on the one hand and together with them shaping a transdisciplinary follow-up project for

which we were submitting a project proposal on the other hand. The participants indicated that they recognised themselves in the study results and that they felt heard. After the workshop they remained together for a conversation and at own initiative decided to form a combined microfinance and peer support group, which was one of our proposed leverage points. They appointed a leader and called one of our involved field coordinators to ask for his guidance on how to organize and conduct the group (unpublished results). This is a first indication that our efforts to start integrating transdisciplinary components during our complexity analysis are forming a locally supported basis for further transdisciplinary projects on HIVDR, carried by PLHIV and other actors themselves in our study site.

7.2 Main findings of this project

Rising levels of HIVDR, especially in low-and middle-income countries, remain a major threat to the effectiveness of antiretroviral therapy (ART). Although the factors influencing HIVDR are relatively well-studied, they are very diverse and interconnected. In Chapter 3 and 4, we successfully mapped the known factors influencing HIVDR at an international and local level respectively. Studying HIVDR as a complex adaptive system (CAS) has allowed us to identify three main feedback loops at international level: 1) an adherence motivation feedback loop which indicates the emergent alternation between adherence and non-adherence, depending on a whole range of different interacting factors, 2) a reinforcing feedback loop indicating how a high health system workload eventually increases itself as the lack of resources will cause an increase in HIVDR and 3) a balancing feedback loop which shows that overreliance on new ART with a higher genetic barrier without maintaining high standards of care, will eventually lead to HIVDR development over time. At the local level we designed a detailed systems map of the factors locally influencing HIVDR based on the experiences of PLHIV and local actors. Based on these insights we suggested three leverage points for addressing HIVDR in the study site: 1) strengthening a reinforcing feedback loop aimed at adherence motivation, 2) community education with the aim to weaken the feedback loops driven by stigmatization and 3) the combination of different elements of care for PLHIV through for example combined microfinance and peer support groups. We consciously kept this chapter focused on HIVDR rather than on the methodology as this was the result of a collaboration with Muhimbili University for Health and Allied Sciences, whose main

interest was in understanding the local complexity of HIVDR and identifying potential leverage points. When we compared the systems map informed by international experts and the one informed by local actors and PLHIV, we found that the included elements and connections were largely similar although the main focus was different. Healthcare system related factors were central in the international expert map, whereas factors impacting the personal situation of PLHIV, such as food insecurity, were at the core of the local systems map. This shows the importance of understanding the local nuances of a CAS and not relying on international models only to design locally tailored interventions. As systems mapping approaches have only scarcely been described in the public health literature, we operationalized a systems mapping approach for visualizing and analysing complex public health problems as CASs, starting from semi-structured interviews (Chapter 5). The methodology presented in this chapter was developed and refined throughout the study and therefore shows some inconsistencies with the empirical chapters as we progressively gained new insights. Moreover, the methodological chapter aimed to describe the methodology in such way that it can be adapted according to specific study topics and contexts. For example, while in Chapter 5 we point out the advantage of making a separate systems map of each transcript we did not do so ourselves in Chapter 3 when there was only one researcher analysing the data and only the first interviews were separately mapped. We did find this to be valuable in Chapter 4 when two researchers were analysing the data and each separate map could be discussed with the team. In Chapter 6 we illustrated an application of the systems maps by visualizing the interactions between the AIDS and COVID-19 pandemics and showing the importance of addressing both pandemics simultaneously.

7.3 How do we know leverage points are “true” or “false”?

In 2020, an approach similar to ours was published by Glenn et al., who describe how to develop a systems map for the case of neglected tropical diseases [142]. Like us, Glenn and colleagues conducted semi-structured interviews with stakeholders from different backgrounds, coded those interviews into a codebook with elements and connections, and used that input to build their model. However, while they describe the modelling process in detail, the authors are not transparent about the methodology used for the interpretation of the system and the identification of leverage points. Indeed, the authors write that their identification of leverage points depended largely

on their subjective interpretation of the model, which poses a problem for the reproducibility of the research. Our guideline described in Chapter 5 provides additional methodological ideas on how to analyse a CAS more consistently and proposes an operationalized use of systems thinking concepts, Nevertheless, a certain degree of subjective interpretation of the researcher will always be present in qualitative research.

So how can we really be sure that interventions in these leverage points will have a lasting, system-wide impact? While we define leverage points as points in the system where a small shift will have a big impact, there is no fixed set of criteria, which a place in the system has to fulfil in order to be called a leverage point [87]. Leverage points are identified by integrating different perspectives on the system and by studying the feedback loops, adaptation, emergence and other properties of the system. Preferably this is done together with the stakeholders, who throughout the process will develop a common understanding of the complex problem and the dynamics involved and will ideally come to feel ownership of the work and join forces to design and implement an intervention on the leverage point [146]. The fact that our participants have, at their own initiative, started organizing themselves into a combined microfinance and peer support group as described in section 7.1, indicates that this could be indeed a deep leverage point. However, as for all leverage points, we will only truly know after having implemented interventions on them and studied their effects on the system. In terms of epistemological stance this positions our view on leverage points in the middle of the realist-relativist spectrum (where realists assume one fixed reality and relativists accept different views of reality) in the American pragmatism paradigm, which argues that the truth of an idea can only be assessed in function of its practical real world outcomes [176].

7.4 Systems maps applications for HIVDR research

There are several potential applications of this research. First, while systems thinking methodology has been used to study several other wicked problems, to our knowledge this is the first time it has been applied to HIVDR. Our systems maps may therefore be used by researchers or stakeholders who would like to develop a deeper understanding of the CAS or who would like to visualize the potential effects of a planned intervention. Similarly, they may be used to understand the effect of unplanned changes in the system caused by for example the COVID-19 pandemic, as described

in Chapter 6. Second, the systems maps were developed for a general adult population of PLHIV at international and local level. Additional data may be collected to adapt the map to better reflect the specific situation of for example a certain key population, or gender group. Third, equally important as the developed models themselves, is that methodology used opens the door towards understanding HIVDR as a CAS and as such, paves the way for further systems-oriented research and complexity-informed intervention design in other study sites.

7.5 Qualitative versus quantitative modelling

Throughout this project, questions concerning the value of qualitative modelling without a quantification aspect have come up several times. Can you rely on a qualitative model if it has not been validated using large datasets? Can you make decisions based on qualitative models alone? And how can you be sure your model is "true"? Interestingly, Forrester (1971/1985) argues that all decisions are based on models and all models are wrong, therefore they cannot be validated into one true model [177]. In reality, models are always changing because the real world and circumstances are continuously changing. More important than developing the perfect model is to learn how to see the problem through different lenses and how to appreciate differences in views and understanding of the problem. Forrester therefore argues that better models can be reached, more will be learned and there is a higher chance of system improvement when one focusses on the process of modelling rather than on the outcome itself. On the importance of including qualitative and unmeasurable values in a system, Forrester writes the following: *"To omit such variables is equivalent to saying they have zero effect – probably the only value that is known to be wrong"* [178]. Yet, Sterman (2002) states that "*Ignoring numerical data or failing to use statistical tools when appropriate is sloppy and lazy"* [179]. A more nuanced take on this could be to acknowledge the value and the necessity of qualitative models to precede quantitative ones. If the reflection accompanying the construction of a qualitative model is skipped, quantitative models may not acknowledge all factors that are important. Starting from a qualitative exploration helps the researchers to deepen their understanding of the social phenomenon under investigation and allows for the opportunity to identify all important variables instead of only the quantifiable ones [125]. Consideration of these unquantifiable variables will later be of utmost importance for the interpretation of the quantitative analysis. Moreover, as described above in this section and in Chapter 5,

the modelling process in itself is of value as it may stimulate both researchers and stakeholders to see the complex problem through different lenses and to understand each other's viewpoints. Qualitative and quantitative modelling therefore go hand in hand, and with our attempt to operationalize the well-established social science methodology and systems thinking theory within the field of medicine, we aimed to introduce this complexity-related thinking in an otherwise largely linear field. Qualitative modelling can thus help to generate hypotheses, part of which can then be verified using quantitative methods.

7.6 Ecological systems theory

It should be noted that our layered systems map of factors influencing HIVDR in sub-Saharan Africa, informed by international experts (Chapter 3, Supplementary Figure 1), has some resemblance with Bronfenbrenner's Ecological Systems Theory [180]. The theory was originally developed to study how different aspects of a person's environment influences their being but has since then also been used to study several other topics [181–183]. It is often represented by an onion-layered model, in which the central individual is surrounded by the microsystem (groups they are directly in contact with), mesosystem (interactions between these groups), exosystem (indirectly influencing factors) and macrosystem (shared believes, values and laws) (Figure 26). Later, the chronosystem layer was added to represent the shifting environmental conditions over time.

While our layers are similar to the Bronfenbrenner model, our main purpose for them was to bring some structure in the systems map while at the same time also highlighting its complexity as interconnections of the elements are transcending the boundaries of those layers. Going further than Bronfenbrenner, the elements in our system are not only connected between neighbouring layers but throughout the whole system. Overarching factors for example (what would in the ecological systems theory be called the macrosystem), can directly influence the individual.

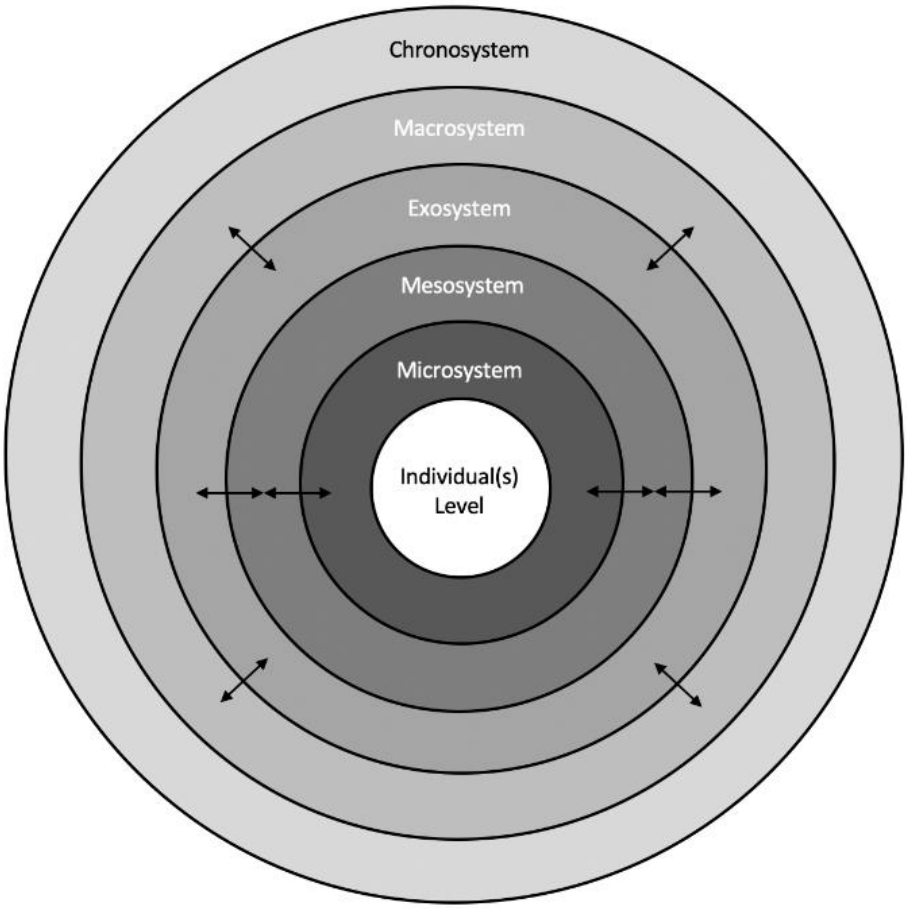

Figure 26: *Bronfenbrenner's Ecological Systems Theory. (Source: Jacquelinecp16, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons).*

What we weren't able to visualize however, is how the CAS is constantly changing and reorganizing itself after changes or disruptions in the system. Bronfenbrenner did include the element of time as the chronosystem. Nevertheless, a single visual representation such as Bronfenbrenner's model and our systems maps when studied separately, remains quite static in nature while in reality, the system is adaptive and dynamic. To this end, our visualizations are not meant to be single fixed models but should be used and adapted to indicate changes, highlight events that are important for certain subpopulations or visualize the interactions with other complex problems. This is illustrated in Chapter 6, where 1) the visualization of the interaction between the COVID19 pandemic and the HIVDR CAS indicates the need to address both pandemics simultaneously and 2) highlighting the impact of the pandemic and

measures at local level shows how certain pathways may become more or less prominent or how possibly new causal loops or pathways are formed.

7.7 Limitations

As is the case in all interpretative studies, we need to be aware of potential biases within the participant selection, data collection and interpretation of the data. A limitation of this study is that for part of the work, the interviews described in Chapter 3, only one researcher was available to analyse and interpret the data. Ideally, the data would have been analysed by at least two researchers so that differences in interpretation could be discussed, as was done for the interviews described in Chapter 4. We did mitigate this bias as well as possible by discussing a limited selection of the interviews in a group of three researchers, so that major interpretation differences would have been uncovered. For the local interviews, the main limitation was selection bias, as most of the interviewed PLHIV were enrolled in care and therefore easily reachable. When we noticed this bias, we managed to enrol another two PLHIV who were lost to follow up. While those two additional participants did not cause a significant shift in our data, future studies would benefit from additional efforts to contact PLHIV who have dropped out of care or have difficulties to adhere.

It is also important to point out that the systems maps developed in this study are based on the insights and experiences of experts, PLHIV and local actors. Although our findings are supported with literature evidence, the models do not represent one fixed truth, but provide us with interesting insights into the interconnectedness and dynamic properties of the CAS.

7.8 Future perspectives

This study lays the groundwork for studying HIVDR as a CAS and for future transdisciplinary projects, covering the whole system of interrelated factors and incorporating the insights of different stakeholders and scientific disciplines. The developed methodology allows us to gain deep insights into the problem, as well as design complexity-informed interventions. In addition to potential applications of the qualitative models which are discussed in section 7.4, I envision two main lines of future research following this work.

First, the systems maps and insights in the complexity of HIVDR can be used as the basis for future transdisciplinary collaborations. Concretely, the systems maps can serve as a communication tool, for instance by visualizing the intersection of different fields of expertise of experts who are jointly studying the complexity of HIVDR or by highlighting the potential effect of certain planned interventions to policy makers or funders. The map developed for the study site can be used as a guiding tool during a transdisciplinary process of co-creation of interventions, together with local PLHIV, stakeholders and actors. Also in this case it can be used as a communication tool, adapted to better understand the system for certain sub-populations or in order to understand the potential system-wide effects of interventions. Several frameworks for implementing such transdisciplinary research processes exist [184]. One example is the ten reflective steps framework of Pohl. Et al. which guides the researcher through the linking of the scientific research question with the societal one, the identification and involvement of societal actors and the continuous reflection on the research project [185]. In addition, several toolboxes with transdisciplinary methodology are available, which can be used for facilitating workshops with heterogeneous groups of participants. The td-Net toolbox for co-producing knowledge is one widely-used example [186].

Second, there is also an opportunity for quantification of the model, an endeavour which has already been started in a follow-up project. In this follow-up project, our locally tailored systems map, representing the CAS of HIVDR in the Ukonga and Gongolamboto areas of Dar es Salaam, is used by local researchers to identify key performance indicators (KPI) for measuring the effects of interventions in the system. Such measured interventions can for example be already ongoing interventions in light of the SDGs. Stakeholder involvement in the design of these KPI's will be key because measuring the identified KPI's needs to be feasible within the local context and supported by local stakeholders, while the KPI's need to be representative for the leverage point towards which the interventions will be targeted. Examples of KPI's could be surveillance HIVDR levels, unemployment levels in the area, pharmacy refill adherence, or number of stock-outs per year. Next to the KPI's indicating the impact of interventions in certain areas of the system, the follow-up project is also in the process of setting up a yearly HIVDR surveillance and viral load measurement

programme, which, in a number of years, may provide concrete insights in the evolution of HIVDR in the study site.

7.9 Conclusions

In this thesis we describe how we successfully visualized the CAS surrounding HIVDR at international and at local level. This allowed us to study the complex dynamic properties and feedback loops of HIVDR for the first time. The next step is to set up a transdisciplinary collaboration with local actors and PLHIV in order to co-create interventions. A quantification of the model has also been started by identifying KPI's which are locally measurable and representative for system-wide effects of interventions targeted at leverage points. We identified three main feedback loops behind HIVDR at international level and several driving feedback loops at local level. We suggested three potential leverage points to be further explored through qualitative and quantitative analysis. We also developed a guideline for qualitative mapping and analysis of a CAS based on semi-structured interview data, which operationalizes the so far rather theoretical literature on systems thinking within the public health field. In conclusion, this research paves the way for future systems-oriented and transdisciplinary research on HIVDR and other complex public health problems and may help stakeholders and decisionmakers to better understand the complex properties of HIVDR in order to design complexity-informed interventions.

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Personal contribution

I performed the work in this thesis (including funding acquisition, conceptualization of the study, data analysis, figures and writing of the articles and thesis manuscript) with the exception of:

Chapter 3: transcribing the interviews, which was done by Marinka Transcriberen.nl & Interim Support. Frederica Fragapane supported the graphical design of Figure 9 and Supplementary Figure 1.

Chapter 4: Conducting the interviews which was done by Dr Idda Mosha (Muhimbilli University for Health and Allied Sciences, Tanzania), transcribing the interviews and translating them from Kiswahilli to English, which was done by Ms Winifrida Onesmo and Ms Mwasiti Sadala. Moreover, part of the data analysis was done together with master student Lara Zlatić.

Chapter 5: Frederica Fragapane supported the graphical design of Figures 21 and 23 A.

Moreover, throughout all phases of the study, the co-authors of the publications of this thesis and the colleagues mentioned in the scientific acknowledgements, provided advice and insights, helped to secure funding, conceptualize the study and methodology, brainstormed on data interpretation and reviewed manuscripts.

Conflict of interest statement

Part of this research was funded by VLIR-UOS, grant number TZ2019SIN263. The study sponsors had no role in the study design, the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the papers and thesis for publication.

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Scientific abstract

HIV drug resistance (HIVDR) remains a threat to the efficiency of antiretroviral therapy (ART), especially in low-and-middle income countries. To avoid HIVDR it is important that people living with HIV (PLHIV) adhere to their ART, which currently has to be taken on a daily basis. In sub-Saharan Africa, the still high levels of stigmatisation surrounding HIV, the need to take the ART with a meal to assure proper absorption and avoid side effects, and occasional drug stock outs are only a few of the reasons why adhering to therapy can be challenging. Moreover, it is essential that PLHIV are prescribed effective ART regimens and are timely switched to a different line of therapy when a high viral load persists. These and other influencing factors make HIVDR an extremely complex, or wicked, problem. Wicked problems require a systems approach, considering the whole network of interconnected factors and stepping away from a linear, reductionist way of thinking. We therefore, by our knowledge for the first time, studied HIVDR as a complex adaptive system (CAS). Such CASs consist of individual elements which are interconnected, behave in sometimes unpredictable ways and can interact as feedback loops.

To construct a first general overview of the HIVDR CAS in sub-Saharan Africa, we developed a systems map with all known factors influencing HIVDR based on interviews with HIVDR experts from diverse disciplines and institutions (Chapter 3). We identified three main interconnected feedback loops or subsystems. First, the ‘adherence-motivation subsystem’ concerns the interplay between all individual factors which may influence PLHIV to alternate between adherence and non-adherence. Second, at the local population level, the ‘healthcare burden subsystem’ reveals a reinforcing loop where an increase in healthcare burden leads to an increase in HIVDR, further increasing the healthcare burden and so on. Third, the ‘ART overreliance subsystem’ is a balancing feedback loop showing the potential risk of developing HIVDR against (new) ART when high standards of quality of care are not maintained.

We then continued to develop another systems map, this time representing the HIVDR CAS for a local study site, the Ukonga and Gongolamboto areas of Dar es Salaam, Tanzania, informed by interviews with local actors and PLHIV (Chapter 4). We

identified several interconnected feedback loops, and suggested three potential leverage points for sustainable interventions with a system-wide impact. The first leverage point is a reinforcing feedback loop which can be strengthened by stimulating the motivation to adhere to therapy, for example by positive, celebratory messages from healthcare workers when a suppressed viral load is reached. The second leverage point, is to weaken the feedback loops driven by stigmatization, possibly through community education provided by religious or traditional leaders. The third and deepest leverage point is at the design level of the system and concerns the organization of microfinance groups for PLHIV, simultaneously targeting the needs for economic support, HIV(DR) education and psycho-social support.

In Chapter 5, we bundled our experience with the HIVDR CAS and developed an operational methodological guide for mapping and analysing complex public health problems. The guideline particularly focuses on situations in which data is collected from semi-structured interviews, as this, in contrast to theoretical literature and group model building approaches, was only limitedly described in the public health literature. Next to providing concrete insights in how to collect data, map the system, analyse it and explore system dynamics, the guideline also stresses the importance of continuous transdisciplinary reflexivity throughout the process.

In Chapter 6 we illustrated one of the applications of our systems maps by visualizing the interconnectedness of the AIDS and the COVID-19 pandemics. This showed the importance of addressing both pandemics simultaneously.

Taken together, this thesis provides the groundwork for the further transdisciplinary exploration of HIVDR and other complex public health problems as CASs. This will help researchers, stakeholders and policy makers to design complexity-informed interventions with a system-wide impact, and to understand external impacts on the system such as the effects of the COVID-19 pandemic. Additionally, quantitative modelling based on our systems map will provide opportunities to establish key performant indicators that can monitor the effects of interventions or events on different parts of the system.

Samenvatting

Hiv-geneesmiddelenresistentie (HIVDR) blijft een bedreiging voor de doeltreffendheid van antiretrovirale therapie (ART). Om HIVDR te voorkomen is het belangrijk dat mensen met hiv hun medicatie dagelijks innemen. Er zijn verschillende redenen waarom dat een uitdaging kan zijn in Sub-Sahara Afrika. Er hangt bijvoorbeeld nog steeds een groot stigma rond hiv, het is belangrijk om de medicatie te nemen bij het eten, om ervoor te zorgen dat de medicatie goed wordt geabsorbeerd en neveneffecten vermeden worden. Ook is de medicatie is soms niet beschikbaar omwille van bevoorradingsproblemen. Bovendien is het van essentieel belang dat aan mensen met hiv goed werkende combinaties van medicatie worden voorgeschreven en dat er tijdig op een andere therapielijn kan worden overgeschakeld wanneer een hoge virale lading aanhoudt. Deze en andere factoren maken HIVDR tot een uiterst complex, of "wicked" probleem. Bij problemen die “wicked” zijn is een systeembenadering nodig, waarbij er rekening wordt gehouden met het hele netwerk van onderling verbonden factoren en er wordt afgestapt van een lineaire, reductionistische manier van denken. Daarom hebben wij, naar ons weten voor het eerst, HIVDR bestudeerd als een complex adaptief systeem (CAS). Dergelijke CASs bestaan uit individuele elementen die onderling verbonden zijn, zich op soms onvoorspelbare wijze gedragen en als feedback loops op elkaar kunnen inwerken.

Om een eerste algemeen overzicht te geven van het HIVDR CAS in Sub-Sahara Afrika, hebben we een systeemkaart ontwikkeld met alle bekende factoren die van invloed zijn op HIVDR, gebaseerd op interviews met HIVDR-experts uit verschillende disciplines en instellingen (hoofdstuk 3). We identificeerden drie belangrijke met elkaar verbonden feedbacklussen of deelsystemen. Ten eerste, het 'therapietrouw en motivatie deelsysteem' beschouwt de wisselwerking tussen alle individuele factoren die mensen met hiv kunnen beïnvloeden om af te wisselen tussen het nemen en niet nemen van de medicatie. Ten tweede, op het niveau van de lokale bevolking, brengt het deelsysteem "belasting van de gezondheidszorg" een versterkende lus aan het licht waarbij een toename van de belasting van de gezondheidszorg leidt tot een toename van HIVDR, waardoor de belasting van de gezondheidszorg verder toeneemt, enzovoort. Ten derde is het deelsysteem "overmatige afhankelijkheid van ART" een balancerende lus die het potentiële risico van de ontwikkeling van HIVDR

ten opzichte van nieuwe ART laat zien wanneer de hoge kwaliteitsnormen van de zorg niet (kunnen) worden gehandhaafd.

Vervolgens hebben we een tweede systeemkaart ontwikkeld, deze keer van het HIVDR CAS voor een lokale studiesite, de Ukonga en Gongolamboto gebieden van Dar es Salaam, Tanzania, gebaseerd op interviews met lokale actoren en mensen met hiv (hoofdstuk 4). We identificeerden verschillende feedback loops en drie potentiële leverage points (punten met een hefboomeffect) voor duurzame interventies met een systeembrede impact. Het eerste leverage point is een versterkende lus die ondersteund kan worden door mensen met hiv te motiveren om therapie te blijven nemen, bijvoorbeeld door positieve, ondersteunende boodschappen van gezondheidswerkers wanneer een onderdrukte virale lading wordt bereikt. Het tweede leverage point is het afzwakken van feedback loops die gedreven worden door stigmatisering, mogelijks door voorlichting in de gemeenschap door religieuze of traditionele leiders. Het derde en diepste leverage point ligt op het ontwerpniveau van het systeem en betreft de organisatie van microfinancieringsgroepen voor mensen met hiv, gelijktijdig gericht op de behoeften aan economische ondersteuning, HIV(DR)-voorlichting en psychosociale ondersteuning.

In hoofdstuk 5 hebben we onze ervaring met het ontwerpen en analyseren van het HIVDR CAS gebundeld en een operationele methodologische leidraad ontwikkeld voor het in kaart brengen en analyseren van complexe volksgezondheidsproblemen. De leidraad richt zich in het bijzonder op situaties waarin gegevens worden verzameld uit semigestructureerde interviews, omdat dit slechts beperkt in de literatuur rond volksgezondheidsproblemen is beschreven, in tegenstelling tot de theoretische literatuur en de literatuur rond het bouwen van systeemmodellen in groep. De richtlijn verschaft concrete inzichten in hoe data verzameld dient te worden, hoe men best het systeem in kaart brengt en analyseert en hoe men de systeemdynamiek kan verkennen. Daarnaast benadrukt de richtlijn ook het belang van continue transdisciplinaire reflexiviteit gedurende het hele proces.

In hoofdstuk 6 illustreren we één van de toepassingen van onze systeemkaarten door de onderlinge verbondenheid van de AIDS en de COVID-19 pandemieën te visualiseren. Hierdoor toonden we aan dat een gelijktijdige aanpak van beide pandemieën van groot belang is.

Alles bij elkaar levert dit proefschrift de basis voor de verdere transdisciplinaire verkenning van HIVDR en andere complexe volksgezondheidsproblemen als CASs. Dit zal onderzoekers, belanghebbenden en beleidsmakers helpen om interventies met een systeembrede impact te ontwerpen die rekening houden met de complexiteit van het systeem, en om externe invloeden op het systeem, zoals de effecten van de COVID-19 pandemie, te begrijpen. Bovendien zal de kwantificering van onze systeemkaart mogelijkheden bieden om de effecten van interventies of gebeurtenissen op verschillende delen van het systeem te modelleren.

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Education

- Doctoral training in Biomedical Sciences / KU Leuven 2017 – April 2022
  "Exploring HIV drug resistance in sub-Saharan Africa as a complex adaptive system"
- Master in Biomedical Sciences / KU Leuven 2015 – 2017
  Master thesis: "Functional regulation of the LRRK2-14-3-3y complex by PAK6"
- Erasmus exchange / Università degli Studi di Padova, Italy 2016 – 2017
  Laboratory of biophysics and molecular and cellular physiology, department of biology
- Bachelor in Biomedical Sciences / University of Ghent 2012 – 2015
- High school degree Latin-Mathematics / OLVI-PIUSX, Zele 2006 – 2012

Experience

- 2021 - 2022: **Futures4Food project** – scientific researcher at the Rega Institute, Institute for the Future, KU Leuven
  - Team coordination, methodology development, project management
- 2020 - 2021: **Coronavirus Pandemic Preparedness project** – core team member at the Rega Institute, Institute for the Future, KU Leuven
  - Development of transdisciplinary methodology, workshop facilitation, strategic support
- 2019 - 2022: **WHO HIVResNet technical working group on Quality of HIV Care and Service Delivery** - member
- 2017 - 2018: **Institute for the Future**
  - Strategic and programme support, grant writing
- 2017-2018: **Young Researchers' Society for Sustainability** – core team member
  - Development of transdisciplinary methodology, workshop facilitation, programme support
- 2017-2018: **Honours Programme Transdisciplinary Insights**, - Coach of interdisciplinary student team working on "A way to understand and prevent HIV drug resistance in Africa" at KU Leuven
- 2018-2020: Mentorship of three students in their master thesis research

Professional development

- Course: Participation and stakeholder management / Levuur 2021
- Courses: Project management and personal efficiency by Tom Jacobs / UGent 2021
- Course: Strategic management in the pharmaceutical industry / KU Leuven 2020-2021
- Part-time internship at NGO Medici con L'Africa CUAMM, Padua, Italy, supporting the development and execution of my PhD project / 2017-2020
- Course: "Partnering for change: Link Research to Societal Challenges" / University of Basel, March – May 2020
- Summer School "Quantitative methodology in health research"/ Antwerp, August 2019
- TDlab Winter school "Science meets practice" / ETH Zurich, Switzerland, January 2018

Peer reviewed publications

1. **Kiekens, A**., Dierckx de Casterlé, B., Pellizzer, G., Mosha, I., Mosha, F., Rinke de Wit, T., Sangeda, RZ., Surian, A., Vandaele, N., Vranken, L., Killewo, J., Jordan, M., Vandamme, AM. (2022), Exploring the mechanisms behind HIV drug resistance in sub-Saharan Africa: conceptual mapping of a complex adaptive system based on multi-disciplinary expert insights. *BMC Public Health*, 22:455. https://doi.org/10.1186/s12889-022-12738-4
2. **Kiekens, A.,** Dierckx de Casterlé, B., Vandamme, AM. (2022), Qualitative systems mapping for complex public health problems: a practical guide. *PLoS ONE 17(2): e0264463*. https://doi.org/10.1371/journal.pone.0264463
3. **Kiekens, A.;** Mosha, I.H.; Zlatić, L.; Bwire, G.M.; Mangara, A.; Dierckx de Casterlé, B.; Decouttere, C.; Vandaele, N.; Sangeda, R.Z.; Swalehe, O.; Cottone, P.; Surian, A.; Killewo, J.; Vandamme, A.-M. Factors Associated with HIV Drug Resistance in Dar es Salaam, Tanzania: Analysis of a Complex Adaptive System. *Pathogens* 2021, *10*, 1535. https://doi.org/10.3390/pathogens10121535
4. Michielsen, L.; **Kiekens, A.;** Vandamme, AM. (2020). The impact of community health workers on HIV therapy outcome in sub-Saharan Africa. *Transdisciplinary Insigh*ts, 4 (1), 1-24. Doi: https://doi.org/10.11116/TDI2020.4.1
5. **Kiekens, A**., Rongé, J., Van Eynde, S., Cleymans, S., Daems, D., De Ridder, B., Despeghel, J., Moonen, P., Ovaere, M., Smeets, N. (2019). How to move towards a common understanding of progress? A transdisciplinary exercise involving 10 young researchers. *Transdisciplinary Insights*, *3* (1), 187-197. Open Access
6. **Kiekens, A**., Dehens, J., de Hemptinne, M., Galouchka, M., Vanhoorebeeck, C., van Otzel, R.P., Wyszkowska, M., Baert, S., Bernard, E.J., Nova Blanco, J.R., Dierckx, T., Mosha, F., Sangeda, R.Z., Theys, K., Van den Eede, A., Jordan, M.R., Vandamme, A-M. (2019). HIV-related peer support in Dar es Salaam: a pilot questionnaire inquiry. *Transdisciplinary Insights*, *3* (1), 1-18. doi: 10.11116/TDI2019.3.1
7. Herrmann, J., Lushaba, J., Michielsen, L., Quirós, N., Saesen, R., Louw, C., Jordan, M., Vandamme, A., Van den Eede, A., **Kiekens, A**. (2018). HIV-positive men as a key population for fighting HIVDR in Africa. *Transdisciplinary Insights*, *2* (1), 78-91. doi: 10.11116/TDI2018.2.3 Open Access
8. Dehens, J., de Hemptinne, M., Galouchka, M., Sajud, A., van Otzel, R.P., Vanhoorebeeck, C., Wyszkowska, M., **Kiekens, A**., Nova, J.R., Vandamme, A. (2017). Transdisciplinary experience in a pilot year of a new Honours Program at the KU Leuven – University of Leuven: building a team, developing and improving a transdisciplinary project through addressing a challenge on HIV drug resistance in Africa. *Transdisciplinary Insights*, *1* (1), 33-39. doi: 10.11116/TDI2017.1.3 Open Access
9. Dehens, J., de Hemptinne, M., Galouchka, M., Sajud, A., van Otzel, R.P., Vanhoorebeeck, C., Wyszkowska, M., Mosha, S.F., Sangeda, R.Z., Bernard, E., Thompson, M., **Kiekens, A**., Baert, S., Nova Blanco, J.R., Jordan, M., Vandamme, A. (2017). Exploring the value and acceptability of peer support in the process of improving adherence to HIV antiretroviral drugs in Tanzania, Dar-es-Salaam. *Transdisciplinary Insights*, *1* (1), 9-32. doi: 10.11116/TDI2017.1.2 Open Access
10. Civiero, L., Cogo, S., **Kiekens, A**., Morganti, C., Tessari, I., Lobbestael, E., Baekelandt, V., Taymans, J-M., Chartier-Harlin, M-C., Franchin, C., Arrigoni, G., Lewis, P.A., Piccoli, G., Bubacco, L., Cookson, M.R., Pinton, P., Greggio, E. (2017). PAK6 phosphorylates 14-3-3γ to regulate steady state phosphorylation of LRRK2. *Frontiers in Molecular Neuroscience*, *10*, Art.No. 10.3389/fnmol.2017.00417. Open Access

Other publications and contributions

1. Vandamme, AM., Nguyen, T., Denis, M., **Kiekens, A.**, Nova Blanco, J., Pourkarim, M., Van Ranst, M., Naesens, L., Depypere, M., Ronse, M. et al. (2020). Belgium – Concerns about coronavirus contact-tracing apps. *Nature Communications,* 581, 384 *doi: https://doi.org/10.1038/d41586-020-01552-w*
2. Institute for the Future, Voices that Count. (2020). Ouderenzorg in tijden van Corona, tussentijds rapport. https://rega.kuleuven.be/if/wzc-report-tussentijds-rapport-ouderenzorg-in-tijden-van-corona
3. Vandamme, AM., Nguyen, T., Denis, M., Depypere, M., **Kiekens, A.,** Naesens, L., Nova Blanco J. R., Pourkarim, M. R., Ronse, M., Schuerman, L., Peeters, K., Van Daele, N., Van den Cruyce, N., Van Hoof, E., Van Ranst, M., Vercauteren, S., Vandermeulen, C., on behalf of the Coronavirus Pandemic Preparedness team. Factors that should shape the decision-making to deploy contact tracing apps for pandemic containment measures. (2020), *Institute for the Future*, https://rega.kuleuven.be/if/tracing-tools-for-pandemics
4. Poster presentation at the 17th European Meeting on HIV & Hepatitis Treatment Strategies & Antiviral Drug Resistance. 22-24 May 2019, Rome, Italy: "*Transdisciplinary systems map of causes leading to HIV Drug Resistance*"
5. Contribution to the Field Research collection of Medici con L'Africa CUAMM "*Transdisciplinary systems map of causes leading to HIV Drug Resistance"* (2018)
6. Poster presentation at the XXVII International Workshop on HIV Drug Resistance and Treatment Strategies. 22-23 October 2018, Johannesburg, South Africa: "*Transdisciplinary systems map of causes leading to HIV Drug Resistance"*