Identifying mechanisms behind HIV drug resistance in Sub-Saharan Africa: a systems approach

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Abstract

Introduction

HIV drug resistance (HIVDR) continues to threaten the effectiveness of worldwide antiretroviral therapy (ART). Emergence and transmission of HIVDR is driven by several interconnected factors. Though much has been done to uncover factors influencing HIVDR, overall interconnectedness between these factors remain unclear and African policy makers encounter difficulties setting priorities combating HIVDR. By employing a systems approach, involving multi-disciplinary HIVDR experts, we aimed to gain a deeper understanding of key determinants and their interactions driving HIVDR.

Methods

We designed a detailed system 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 institutions. The resulting detailed system map was conceptualized into three main HIVDR feedback loops and further strengthened with literature evidence.

Results

Factors influencing HIVDR in SSA 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 increased 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.

Conclusions

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.

Introduction

HIV drug resistance

Despite major efforts being made, 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 global 90-90-90 goals by 2020 and to end the HIV epidemic as a public health threat by 2030 [1]. However, levels of HIVDR are rising, compromising the effectiveness of ART and potentially compromising efforts to attain the last 90 goal [2]. In 2017, mathematical modeling predicted that if left unchecked, excess levels of pretreatment HIVDR to the 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) [3]. Recently several cases of multi-drug class resistant HIV have been reported [4, 5].

Several causes of both pre-treatment 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 psychological, structural factors related to ART delivery, or other factors) and a low genetic barrier of ART may lead to the emergence of HIVDR [6]. 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 [7]. Other crucial aspects to prevent HIVDR are for example sufficient ART availability and

a well-functioning ART supply system [8]. These and other factors described in literature relate to several fields of science and in some cases also to other complex problems.

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, pre-treatment HIVDR, especially in SSA, is still increasing [9].

A systems approach towards HIVDR

As the factors influencing the emergence of HIVDR are numerous, have roots related to different fields of science and are interconnected to other complex problems, we argue that HIVDR should be approached as a complex adaptive system, 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' [10]. 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 favorable way [10, 11]. CAS have been studied in several other contexts such as ecosystem management, healthcare management and obesity [12–14].. Moreover, the importance of using systems thinking in health care has been widely described in the literature [10, 11, 15–17]. 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 [11]. 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 [18]. Identifying leverage points is difficult and sometimes counterintuitive. Gaining insights in subsystems or feedback loops may therefore facilitate the identification of leverage points [19].

In this study we describe how we identified three interconnected feedback loops influencing HIVDR by developing a systems map that represents the complex adaptive system of HIVDR. We discuss the insights gained from these feedback loops and possible applications for quantitative modelling, intervention design and policy implications [20, 21]. By employing a systems approach and involving HIVDR experts from different disciplines, we aimed to gain a deeper understanding of the system of factors influencing HIVDR in order to facilitate the initiation of complexity-informed interventions.

Methods

Research team and reflexivity

The study was designed and conducted by AK, AV and BD who have a combined background in HIVDR, systems thinking, transdisciplinarity and qualitative research methodology. Throughout all stages of the project input was received from colleagues and external stakeholders, either involved in transdisciplinary research projects or in HIVDR research, in order to guard the quality and societal relevance of the research. Semi-structured interviews were conducted and analyzed by AK. Analysis and interpretation of the data were discussed with AV and BD on a regular basis.

Semi-structured interviews

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 with a minimum of five years of experience. The participants were selected 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. 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, 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 by AK. An interview guide was used and adapted according to insights developed through analysis (See additional File 1). All experts were asked about their experience with and perspectives on the causes of HIVDR. Subsequently, depending on the expertise of the participant, the questions aimed to clarify the deeper reasons behind some of those initially indicated causes. 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.

Data analysis

Analysis of the semi-structured interviews was inspired by the QUAGOL method and done simultaneously with the data collection [22]. 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 AK 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, mentioned either explicitly or implicitly by the interviewee, was extracted. 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 there on 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.

The model was designed in KUMU, an online mapping tool which enables the user to save data such as interview quotes and memos for each element and connection [23]. 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. 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 perceived by international experts

In total 15 international experts were interviewed. Table 1 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 complex adaptive system. Out of the 15 participants, 13 were researchers or had previous research experience in the field of HIVDR.

Table 1
Participant characteristics

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		

Table 1: *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.*

Data saturation for elements (factors influencing HIVDR) was reached after nine interviews and for connections (pathways of influence between two elements) after 12 interviews (Fig. 1).

A first model was drafted based on the data collected from the semi-structured interviews (Fig. 2). The elements were divided in five layers according to their relation to biology (elements and processes happening inside the body), individual (psychology, personal factors and behavior 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' (such as international policy, research and funding).

The subsystems behind HIVDR

The detailed systems map was conceptualized into three interconnected subsystems (Fig. 3). When interpreting the subsystems described below it is important to keep in mind that they are constantly influenced by each other and by other complex problems such as poverty, gender inequality etc. Each of the concepts in Fig. 3 represents several elements of the detailed systems map in Fig. 2 (see Additional File 3).

1. Adherence motivation subsystem

The first subsystem reveals 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 behavior 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 [24]. 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 center, such as adherence counseling, 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 counseling, viral load tests and thus on its turn increasing the healthcare system workload. In short, this loop represents a sequence of events through which a high burden on the healthcare system may amplify 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 delay in acting on non-suppressed viral load in turn contributes to an increase in overall HIVDR burden at the personal and programme level. The World Health Organization (WHO) reports that, though the African region carries the highest disease burden, they have the highest population/provider ratios [25]. In line with our findings, a study in Cameroon identified high health system workload as a possible risk factor for emerging HIVDR [26].

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 [27, 28]. With the introduction in SSA of integrase inhibitor-based ART, 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 pre-treatment HIVDR to NRTIs and/or NNRTIs predicts virologic failure for regimens containing Dolutegravir [29, 30]. Altogether, this subsystem reveals how 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.

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 incontinuous supply of drug, delayed switch in ART after detection of a 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 if PLHIV have to take the ART with a meal each day. Other examples are political instability and disease outbreaks (such as COVID-19), 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 introduced a novel way of approaching HIVDR as a complex adaptive system by combining the perspectives of diverse disciplines. We designed a detailed system map and described how the factors influencing HIVDR can be divided in five layers according to their relation with the biology, individual, social context, healthcare system and overarching factors. 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 complex adaptive systems such as emergence, adaptation and feedback and allowed to visualize the three interconnected subsystems [31]. 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 behavioral 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, whether education and other support is provided etc. 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 and 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, including the insights from PLHIV themselves is likely to significantly alter the systems map and strengthen its validity and will be necessary before locally sustainable and appropriate interventions tailored to specific local contexts can be designed. Perspectives from PLHIV and from other local stakeholders such as local doctors or local politicians, religious leaders, and other people of local influence will also help us 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.

Applications

Our model helps identifying leverage points in the system in order to design targeted and complexity-informed interventions. Our study illustrates the added value of qualitative methodology to visualize the complexity and dynamics of a system. 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 parameters which might not have been identified by a monodisciplinary approach.

Conclusion

We conclude that HIVDR is influenced by a complex and interconnected system of factors which transcend disciplines and population levels. We successfully undertook the first steps in unravelling the CAS representing HIVDR. The model suggests that overreliance on ART with a low risk to HIVDR emergence may be a driver for future HIVDR against those same ART; that when exceeding a certain threshold, the burden on the healthcare system amplifies itself; and that adherence tends to vary which is very individual- and context-dependent and might be difficult to influence 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.

Abbreviations

ART
antiretroviral therapy; CAS:complex adaptive systems; HIVDR:HIV drug resistance; PLHIV:people living with HIV; SSA:Sub-Saharan Africa; WHO:World Health Organization.

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 [32]. This study did not involve patients and the interview 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 study's 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 (Additional File 6). We also refer to the Italian law of 5 June 2019 "garante per la protezione dei dati personali" (Additional File 7). 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 (See Additional File 8). 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 (See Additional File 9 and 10).

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

AV declares consultancy fee from Gilead.

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Authors' contributions

AK: Study design, conduction of interviews, data analysis and interpretation, systems mapping, writing the manuscript. BDK: study design, data analysis and interpretation, regular feedback, writing manuscript. GP: study design, regular feedback, data interpretation, editing manuscript. IM: data interpretation, editing manuscript. FM: regular feedback, editing manuscript. TRW:

regular feedback, editing manuscript. RZS: data interpretation, editing manuscript. AS: design of interview guide, regular feedback, editing manuscript. NV: regular feedback, editing manuscript. LV: study design, regular feedback, editing manuscript. JK: data interpretation, editing manuscript. MJ: study design, data interpretation, regular feedback, writing the manuscript. AMV: Study design, study supervision, data interpretation, regular feedback, writing the manuscript. All authors have read and approved the final manuscript.

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Figures

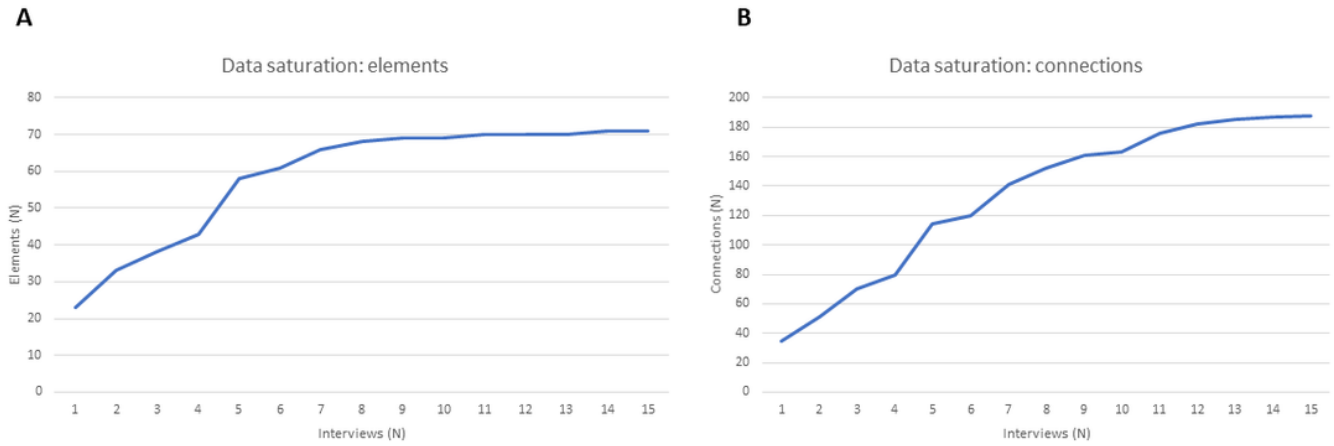

Figure 1

Data saturation curves. A) Number of elements in the system map after each consecutive interview. B) Number of connections in the system map after each consecutive interview.

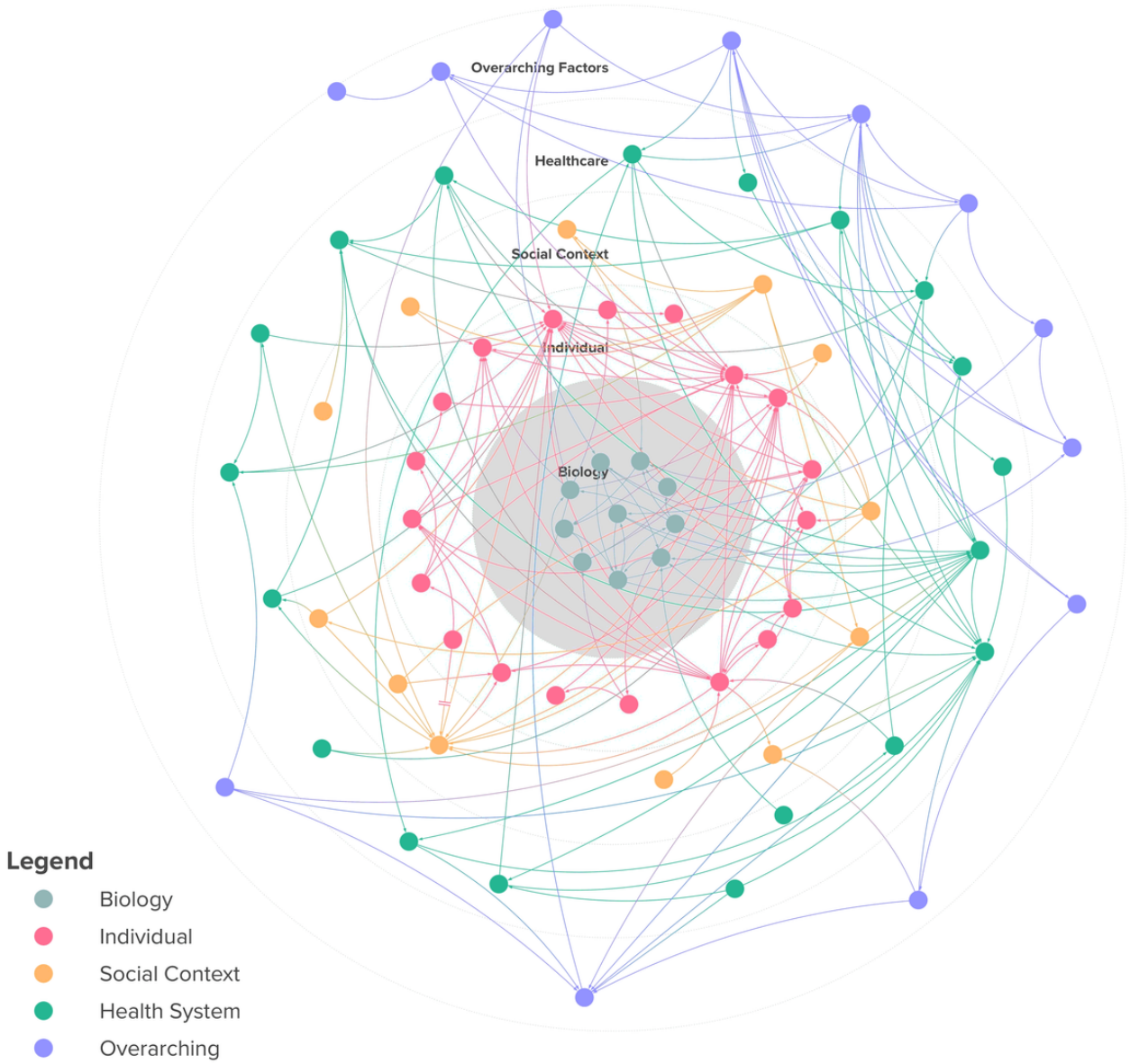

Figure 2

Systems map representing the complexity of factors influencing HIVDR. Each element represents a factor influencing HIVDR and each line represents a connection between two factors. Factors are organized in five levels according to their connection with biology, the individual, the social context, the healthcare system and 'overarching'. A detailed and interactive version of this map is included in Additional File 2.

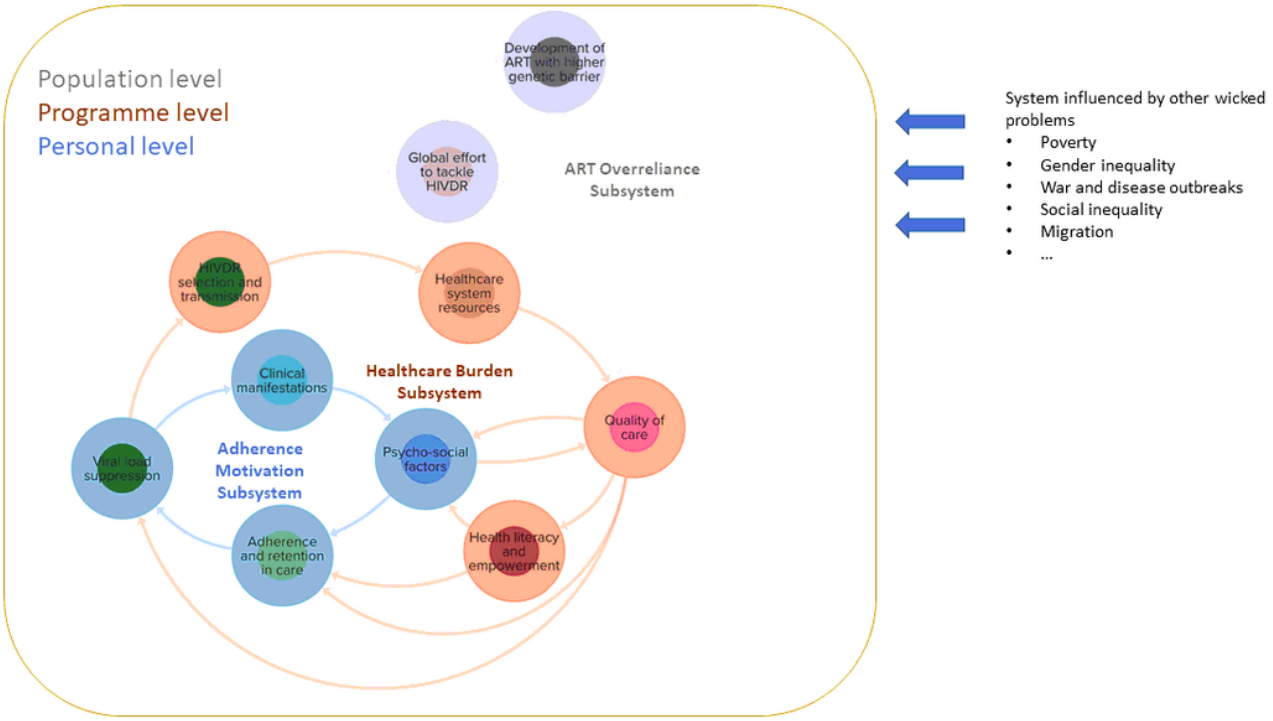

Figure 3

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 factor of this map consists of several interconnected elements. A detailed overview of these separate elements, can be found in Additional File 3. The color of the core of each factor in this figure corresponds with the color of the related elements in Additional File 3.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- KiekensAdditionalFile1.docx
- KiekensAdditionalFile2.xlsx
- KiekensAdditionalFile3.pdf
- KiekensAdditionalFile4.xlsx