Steatotic liver disease and HIV: an agenda for 2030

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People living with HIV are particularly susceptible to developing metabolic disorders, including metabolic dysfunction-associated steatotic liver disease and other forms of SLD. However, people living with HIV have been historically excluded from clinical trials and large cohort studies of SLD. Therefore, our understanding of the risk factors and natural history of SLD in this population is poor. Moreover, relevant knowledge gaps on the epidemiology and barriers for adequate health care, such as stigma, hamper adequate responses to the ongoing HIV and SLD syndemic. This Viewpoint provides a comprehensive perspective on how to tackle SLD in people living with HIV by examining the role of social determinants of health in the development of liver disease and metabolic syndrome comorbidities among this population, emphasising the importance of prioritising SLD management, summarising the most urgent needs in the field, and offering recommendations for advancing research to fill key data gaps and protect liver health of people living with HIV.

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See Online for appendix

Introduction

The HIV epidemic has been a long-standing challenge for health systems globally since the early 1980s. HIV treatment options have increased and transitioned HIV from a life-limiting illness to a manageable chronic condition. However, tremendous efforts are still required to meet the 95–95–95 targets set by UNAIDS and to ultimately end HIV and AIDS as public health threats by 2030.[1] To meet these objectives and to better respond to the changing health needs of people living with HIV, global institutions, national health systems, and health-care providers have begun promoting the need to address comorbidities beyond opportunistic infections, as reflected for instance in the WHO global health sector strategies on HIV, viral hepatitis, and sexually transmitted infections for the 2022–30 period.[2]

People living with HIV have an increased susceptibility to metabolic disorders owing to antiretroviral therapy (ART) toxicities, HIV infection, and dietary and physical exercise habits. This susceptibility has substantial implications when patients are burdened by other prevalent health conditions within the spectrum of metabolic syndrome, such as type 2 diabetes and obesity. The hepatic manifestation of metabolic syndrome is metabolic dysfunction-associated steatotic liver disease (MASLD)—a form of steatotic liver disease (SLD) formerly known as non-alcoholic fatty liver disease.[3] Additionally, people living with HIV are also disparately affected by other forms of SLD, particularly those induced by viral hepatitis, drugs, and alcohol.[4]

In this Viewpoint, we discuss the reasons why SLD should be systematically managed in people living with HIV and provide a set of recommendations on how to move the field forward in the coming years, while closing some relevant data gaps that put the liver health of people living with HIV at risk.

A syndemic lens

MASLD represents a growing global public health problem largely characterised by a therapeutic unmet need. These challenges complicate the design of care pathways to screen, diagnose, refer, and manage MASLD in a sustainable and equitable way in various settings.

The estimated prevalence of MASLD is high, at around 38% of the adult population.[3] Although genetic and individual health factors play a role, there is a growing consensus that societal patterns substantially influence the development of non-communicable diseases, including MASLD, through multiple social determinants of health (SDoH). SDoH are part of a complex, interconnected social system that can propagate poor health behaviours and the underlying factors (eg, commercial determinants that contribute to food insecurity) that are associated with health risks (appendix p 2).

Concurrently, social and commercial determinants of health continue to challenge many individuals in effectively and sustainably reaching optimal health outcomes. HIV and the different components of metabolic syndrome meet the criteria of a syndemic, that being disease concentration, disease interaction, and shared large-scale social forces that give rise to them. Although type 2 diabetes, obesity, dyslipidaemia, and lack of exercise coalesce to give rise to the high and growing MASLD prevalence, in the case of people living with HIV these risk factors have a deeper synergistic effect at inducing liver disease (particularly MASLD). As a result, MASLD might progress to steatohepatitis, advanced liver fibrosis, and cirrhosis at a higher rate among people living with HIV than in the general population.

Another important similarity between these two diseases lies in their association with cardiovascular risk. Both MASLD and chronic HIV infection are risk factors for the development and progression of cardiovascular disease. The interaction of these two conditions clearly influences the cardiovascular risk profile of the affected patients.[5] In addition, both metabolic risk factors and hepatic steatosis or fibrosis in people living with HIV have a negative effect on health-related quality of life.[6] Identifying modifiable metabolic risk factors that affect both cardiovascular disease and health-related quality of life could substantially improve health

outcomes, including patient-reported outcomes, thus preventing progression to more severe liver disease and possibly reversing fibrosis.

People living with HIV have been systematically excluded from clinical trials and large prospective cohort studies on MASLD and its more advanced form, metabolic dysfunction-associated steatohepatitis (MASH), which implies risk of progression of liver fibrosis, liver-related decompensation, and hepatocellular carcinoma.[7] Yet, in addition to its syndemic nature with other epidemics, the characteristics of HIV infection confer a special susceptibility to metabolically induced liver damage. These factors prompt a question of whether people living with HIV can be considered a special population within the SLD spectrum from the standpoint of pathophysiology, natural history, epidemiology, and clinical presentation. Some of the most salient features that make people living with HIV a group at high risk for SLD include the systemic chronic inflammation derived from HIV infection beyond the increased incidence of metabolic abnormalities, the increased risk of liver steatosis associated with some ART drugs, and the high incidence of chronic viral hepatitis and excessive alcohol intake, which can also lead to SLD.[3] As in the case of specific highly vulnerable populations, tailored approaches were proposed[8] under the umbrella of micro-elimination for the screening and treatment of hepatitis C (including people with advanced liver disease, men who have sex with men, patients with haemophilia and other blood disorders, people who are incarcerated, and people who inject drugs); we believe that the concept of special population will promote awareness and investment in the necessary research and policy efforts to better characterise SLD in people living with HIV.

SDoH

SDoH refer to the conditions in which people are born, grow, live, work, and age, and the wider set of forces and systems shaping the conditions of daily life.[9] These determinants include factors such as socioeconomic status, education, occupational status, and health-care systems built on systemic racism. The unequal distribution of SDoH within and across societies has strong implications on how the risk factors, the burden of disease, and the ability to cope with factors threatening health and quality of life are distributed across populations and subgroups (figure).

Research has shown the effect SDoH have on the health outcomes of people and populations globally, including people living with HIV. However, exploration of the effects of SDoH on liver health in general, and MASLD specifically, is only just beginning. Preliminary research in this field suggests that for both HIV and MASLD, SDoH such as lower socioeconomic status and female gender are closely associated with poorer health outcomes. Individuals who are socioeconomically disadvantaged also tend to live in areas with poor physical environmental factors, such as air pollution and no access to green spaces, both of which have direct consequences on people's overall health and particularly metabolic and liver health.[10]

Apart from promoting disease and facilitating its progression, SDoH also exert a limiting influence on the implementation of preventive, diagnostic, and therapeutic interventions. Recognising the SDoH promoting liver disease, metabolic syndrome comorbidity and multimorbidity, and amplifying the challenges of people living with HIV regarding access to care is necessary to better tackle this growing syndemic.

The natural history of SLD in people living with HIV

People living with HIV are increasingly more susceptible to non-communicable diseases than the general population.[11] In response, the management of comorbidities, particularly cardiometabolic conditions, has become a mainstay of HIV care. Factors contributing to a higher morbidity in this population are likely multifaceted. Although drugs known to cause metabolic changes, such as lipodystrophy, are no longer in use, new ART drugs have been associated with some metabolic side-effects including changes in weight and lipid metabolism.[11] Since the turn of the century, there has been a growing interest in understanding the role of systemic immune activation and alterations in the composition of the gut microbiota in driving metabolic changes in people living with HIV.[11] Furthermore, people living with HIV have an increased prevalence of concurrent aetiologies associated with SLD (apart from those associated with metabolic dysfunction), including co-infections (eg, hepatitis C virus or hepatitis B virus), drug-induced liver injury, and excessive alcohol consumption, which increase the risk of disease progression.[12] Liver fibrosis, the main prognostic determinant in SLD, is known to progress faster in the presence of MASH and comorbidities, such as type 2 diabetes. Roughly 20–30% of patients with MASLD will develop MASH, and among these, 40% will have fibrosis progression.[3,7] Ultimately, 10–15% of all patients with MASH will develop cirrhosis. The estimated annual incidence of hepatocelluar carcinoma ranges from 0·5% to 2·6% among patients with MASLD-associated cirrhosis. These figures are still unknown for people living with HIV. Several HIV cohort studies and systematic reviews have explored the prevalence of steatosis, consistently reporting its higher occurrence in people living with HIV compared with the general population (appendix p 3).[13–22] The complex interplay between ART and the development and progression of SLD remains to be fully understood. Among other relevant factors, direct effects of HIV on fibrogenic pathways and some ART-related mitochondrial dysfunction lead to oxidative stress and downstream

profibrogenic effects linked to hepatic stellate cells activation. Some studies have shown an association between integrase strand inhibitors or tenofovir alafenamide and the development of SLD.[22] Although still a matter of debate, there is increasing concern regarding the association of integrase inhibitors and tenofovir alafenamide with weight gain and visceral fat accumulation, leading to increased risk of metabolic syndrome, cardiovascular disease, and SLD.[12]

There is a small number of prospective cohort studies investigating the determinants of progression to steatohepatitis and fibrosis in people living with HIV. Consequently, our understanding of the natural history and risk of progression of SLD in this population remains incomplete, and the effect of specific ART components is uncertain. Furthermore, the exclusion of people living with HIV from most clinical trials in this field not only hinders this group's access to treatment but also results in a crucial data gap. This absence of knowledge has substantial implications for the development of guidelines for prevention, diagnosis, and management of SLD and MASLD in people living with HIV (appendix p 5).

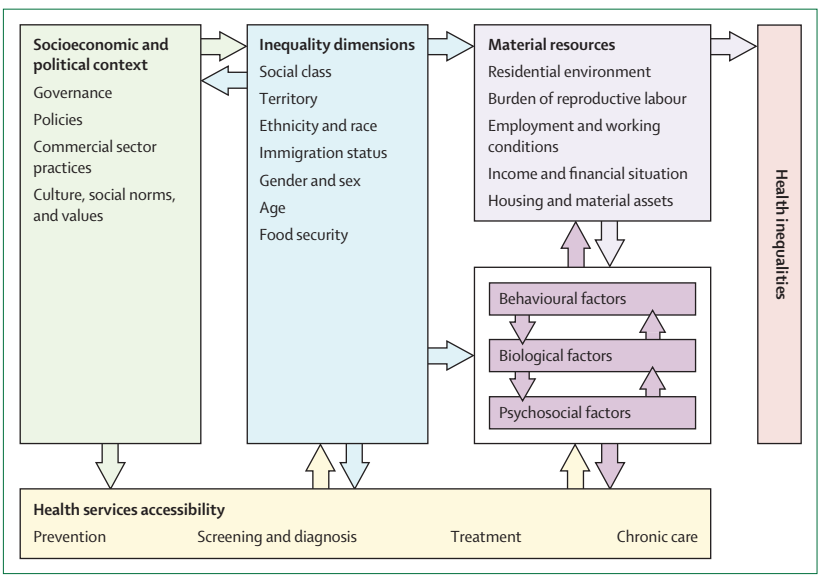

Figure: **Social determinants of health framework for both HIV and metabolic dysfunction-associated steatotic liver disease**
Figure created with BioRender.com.

An HIV–SLD agenda for 2030

Raising awareness

Members of multidisciplinary teams that care for people living with HIV at community and health system levels must know that liver disease in general and SLD in particular are prevalent and potentially severe. These stakeholders should understand the main predisposing factors for SLD among people living with HIV to provide recommendations regarding detection, prevention, and treatment (panel). It is key that the proposals we put forward in this Viewpoint are adapted to the resources available in each of the countries where they are implemented. Majority of population affected by HIV resides in low-income countries with restricted health-care resources, making implementation challenging. Considering the substantial HIV burden in Africa, which has the largest proportion of infected individuals, it is easy to recognise that these populations might require tailored recommendations and interventions to comprehensively address their needs. Concurrently, the increasing number of migrants from HIV-endemic countries to Organisation for Economic Co-operation and Development countries might be placing additional strains on already stretched health-care systems, and might require unique guidelines and strategies.[9,16] To navigate these challenges, addressing public health policies, strengthening health-care systems, and tackling the underlying causes of health-care access disparities among other measures might be necessary.

Improving the knowledge of HIV–SLD

Some unexplored or rarely studied aspects of SLD epidemiology, pathophysiology, and natural history need to be addressed in the immediate future, as they might have profound implications on the design and implementation of care pathways that contribute to the UNAIDS goals.[1] Despite the scarcity of longitudinal data on the natural progression of SLD and risk factors associated with its progression to fibrosis or steatohepatitis, the identification of some of these factors in cross-sectional studies, such as the presence of type 2 diabetes, large waist circumference, or female sex highlights the need to pay closer attention to individuals with these risk factors. Individuals with such risk factors might warrant intensified or specific management to early detection and prevention of disease progression. Compared with other regions, sub-Saharan Africa reports the lowest SLD prevalence, ranging from 5 to 15% in the general population and 10 to 70% in individuals with type 2 diabetes.[15] A 2022 study from Zambia on people with and without HIV, revealed a low prevalence of SLD (10%) in those with HIV despite a high prevalence of obesity (32%)[17] raising questions about underlying differences in genetic, metabolic, and nutritional factors across continents. However, this discrepancy between obesity and SLD prevalence could be due to limitations associated with BMI measurements. To ensure that this difference is not caused by a limitation in measurement tools, the use of more accurate methods for determining visceral adiposity should be encouraged. Measures including waist circumference or bioimpedance can help determine visceral adiposity, which is strongly associated with an increased risk of SLD. There is a need for simple diagnostic tools to facilitate screening and improve our knowledge of SLD in low-resource settings, where urbanisation and lifestyle changes contribute to the increasing burden of non-communicable diseases.

Panel: **Key challenges in the detection, evaluation, and treatment of suspected steatotic liver disease (SLD) in people living with HIV**

- The introduction of antiretroviral therapy (ART) in the mid-1990s improved survival of people living with HIV, transforming HIV into a chronic disease and resulting in health-care providers facing problems related to ageing and cardiometabolic risk of individuals with this condition. Cardiometabolic risk was initially associated with ART, but in the last decade has been suspected to be associated to chronic systemic inflammation.
- Patients with chronic HIV infection appear to have a high prevalence of hepatic steatosis and fibrosis independently of the presence of metabolic risk factors or ART.
- Chronic systemic inflammatory disease associated to HIV chronic infection might influence the development and progression of SLD. In turn, SLD might worsen HIV prognosis, suggesting a synergistic relationship between the two conditions.
- Cumulative effects of ART in the development of SLD must be investigated.
- Most clinical trials in SLD typically do not include people living with HIV, which not only creates obstacles to accessing treatment but also results in absence of key data on the disease's natural history.
- The social determinants of health, including cultural and commercial determinants, might act as a catalyst for both diseases and warrant a specific approach to address inequalities and to stop their spread.
- The literature on SLD in people living with HIV is scarce, but awareness of the condition is increasing.
- Only few regulatory guidelines or society position papers address disease burden, screening, diagnosis, and treatment approaches in people living with HIV with suspected SLD.
- Further validation studies on serum biomarkers to detect liver fibrosis in SLD in people living with HIV are needed.
- In the light of the latest nomenclature for SLD, should we regard people living with HIV as a distinct subpopulation with a unique category within the SLD spectrum?
- Should health-care providers consider people living with HIV as a population at high risk of SLD and implement systematic screening? Would such an approach prove to be cost-effective?

Evaluating the accuracy of non-invasive tests in HIV–SLD

To design cost-effective and equitable pathways for the screening of steatosis and referral of people living with HIV at high risk for advanced liver fibrosis, tests that are routinely used in various settings to screen for these conditions should be widely validated and, when necessary, recalibrated in cohorts of people living with HIV (eg, with Fibrosis-4 scoring system, which includes aspartate aminotransferase, alanine aminotransferase, platelet count, and age).[23] Multidisciplinary teams and seamless referral pathways must be the mainstay of the HIV and liver disease specialists' crosstalk, which might lead to further complementary test development and to provide personalised metabolic care.

People living with HIV should be systematically screened for steatosis and advanced liver fibrosis in HIV clinics. Preliminary evidence on the accuracy of several serum-based scores for the detection of steatosis and fibrosis largely used in SLD referral pathways shows similar area under the receiver operating curve to results found in the general population,[23] but further investigations are warranted (panel). Elastography, either through vibration-controlled transient elastography, ultrasound (eg, share-wave techniques), or magnetic resonance is the most widely used non-invasive method to assess fibrosis. Quantification of steatosis can be reliably done through controlled attenuation parameter, while simultaneously assessing fibrosis, or by MRI-derived proton density fat fraction, whereas traditional abdominal ultrasound techniques have low sensitivity.[24,25]

Gathering data on treatment strategies for HIV–SLD

Evidence regarding the effect of weight loss interventions, including dietetic and physical exercise counselling, or drugs prescribed for type 2 diabetes or obesity showing promising results in phase 2 trials (eg, pioglitazone, glucose-transporter lipid protein receptor agonists, or SGLT2 inhibitors)[26] could provide valuable data about the routine clinical care of various medical specialties regarding SLD in people living with HIV.

Involve people living with HIV in SLD-focused clinical trials

All MASH clinical trials should include sub-studies on people living with HIV. Particular focus should be placed on increasing the representation of women living with HIV who have been underrepresented in studies and found to be at a higher risk of MASH and advanced fibrosis.[27] Trials exclusively recruiting people living with HIV should be done beyond the few performed as of 2024 (eg, tesamorelin).[28] In the meantime, specific clinical trials for treating MASH in people living with HIV should be set up, by both academic institutions and the pharmaceutical industry, and ideally in collaboration. After more than two decades of negative clinical trials in MASH, the first drug (resmetirom) received approval by the US Food and Drug Administration in March, 2024. As a special population disproportionately affected by SLD, people living with HIV cannot be denied access to effective therapies any longer. Among several relevant data gaps derived from the generalised absence of evidence from clinical trials are the potential drug–drug interactions between novel drugs used for SLD and ART.

Tackling stigma and discrimination

Although the global MASLD research agenda has made strides in addressing HIV, discernible gaps remain,

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including HIV-related stigma and discrimination, and access to effective mental health care for people living with HIV. Furthermore, the experience of stigma, and discrimination can be amplified among people living with HIV who are also burdened by other comorbidities, such as MASLD or obesity. Special attention is warranted for women in this regard, as they are disproportionately affected by stigma, discrimination, and health inequities.[9,10,27] The stigma experienced by women with HIV is compounded when factors associated with metabolic syndrome, such as obesity, are involved. Ultimately, these negative experiences might hinder individual progress throughout steps of the HIV-care cascade.

Understand the cost-effectiveness of addressing HIV–SLD

Despite the high prevalence of SLD and its broad effects on public health, there is a concerning paucity of studies estimating the costs of this disease and the cost-effectiveness of screening people living with HIV.

Conclusion

HIV and SLD are tightly interrelated epidemics whose relationships are mediated by macro-level, meso-level, and micro-level factors, such as shared social determinants, metabolic risk, stigma and low awareness among both the general population and health-care providers—all of which too often lead to late diagnoses and synergistic effects on liver damage. These issues render people living with HIV as a special population within the SLD spectrum. Therefore, the international scientific community should join forces to tackle this mounting public health threat, from public policies to tailored health system interventions, including screening and referral pathways, treatment adherence support, and clinical trials to pathophysiology studies.

Contributors

JMP and JVL contributed to the conceptualisation of this manuscript. AKA, CR, AJ-M, and TMW searched the literature. JMP, AKA, CR, AJ-M, TMW, MBB, and JN wrote the manuscript. JMP and AJM prepared the tables. JMP, AJ-M, and ARM prepared the figures. ND, GG, AB, and GW reviewed and edited the manuscript. All authors approved the final draft.

Declaration of interests

JMP reports having received consulting fees from Boehringer Ingelheim, MSD and Novo Nordisk. He has received speaking fees from Gilead, Intercept, and Novo Nordisk, and travel expenses from Gilead, Rubió, Pfizer, Astellas, MSD, CUBICIN, and Novo Nordisk. He has received educational and research support from Madrigal, Gilead, Pfizer, Astellas, Accelerate, Novartis, AbbVie, ViiV, and MSD. CR reports honoraria for speaking activities from ViiV Healthcare. GG reports speaking fees from ViiV Healthcare. AB acknowledges having received consulting fees from Boehringer Ingelheim and speaking fees by GE Healthcare and Hologic. GW received research grants from Gilead Sciences and Roche Diagnostics. MBB has received grant support from National Institute of Health, US Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health, Pfizer, The Kinetix Group, Histoindex, and serves as a consultant for The Kinetix Group, Madrigal, Pfizer, Theratechnologies, Fibronostics, Novo Nordisk, and GSK. JN has received honoraria, speaking fees, and financial support for attending conferences from AbbVie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, and ViiV Healthcare, and consulting fees from ViiV Healthcare, Gilead Sciences, Janssen Cilag, and Merck Sharp & Dohme, outside the submitted work. JVL acknowledges grants from AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Madrigal, MSD, Novo Nordisk, Pfizer, and Roche Diagnostics; speaker fees from AbbVie, Echosens, Gilead Sciences, Janssen, Moderna, MSD, Novo Nordisk, and Pfizer; and consulting fees from Echosens, NovoVax, GSK, Novo Nordisk, and Pfizer, all outside the current work. JVL also acknowledges participation on the advisory board for the "Same-visit hepatitis C testing and treatment to accelerate cure among people who inject drugs (The QuickStart Study): a cluster randomised control trial–Australia" trial; had roles in the following committees: Member, European Association for the Study of the Liver, Public Health and Policy Committee; Healthy Livers, Health Livers (formed by AASLD, ALEH, APASL, European Association for the Study of the Liver) Global NASH Council; and was the Co-chair of HIV Outcomes. All other authors declare no competing interests.

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