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Non-communicable disease in HIV infection in low- and middle-income countries: gastrointestinal, hepatic, and nutritional aspects

Paul Kelly, MD, FRCP[1,2], **Haroon Saloojee, MBBCh, MSc, FCPaeds(SA)**[3], **Jennifer Y Chen, MD**[4], and **Raymond T Chung, MD**[4]

[1]Blizard Institute, Barts & The London School of Medicine, Queen Mary University of London, London E1 2AD, UK

[2]Department of Medicine, University of Zambia School of Medicine, Nationalist Road, Lusaka, Zambia

[3]Department of Paediatrics and Child Health, University of the Witwatersrand, Johannesburg, South Africa

[4]Massachusetts General Hospital 55 Fruit Street, Boston MA 02115

Abstract

The purpose of this review is to outline the interaction between HIV and non-communicable diseases (NCDs) affecting the gastrointestinal (GI) tract, liver, and nutritional disorders in low- and middle-income countries (LMICs), and to identify research priorities. Non-communicable GI tract disorders are only moderately influenced by HIV, and peptic ulceration is actually less common. However, the impact of HIV on GI cancers needs further investigation. HIV interacts strongly with environmental enteropathy, exacerbating malabsorption of nutrients and drugs. HIV has two major effects on non-communicable liver disease: drug-induced liver injury and non-alcoholic fatty liver disease (NAFLD) (particularly in persons of African genetic descent). The effect of HIV on nutrition was one of the first markers of the epidemic in the 1980s, and HIV continues to have major nutritional consequences. Childhood malnutrition and HIV frequently co-exist in some regions, e.g., southern Africa, resulting in powerful negative interactions with poorer responses to standard nutritional rehabilitation. HIV and nutritional care need to be better integrated, but many questions on how best to do this remain unanswered. Across the spectrum of gastrointestinal, hepatic, and nutritional disorders in HIV infection, there is increasing evidence that the microbiome may play an important role in disease pathogenesis, but work in this area, especially in LMICs, is in its infancy.

Corresponding author: Professor Paul Kelly, Blizard Institute, Barts & The London School of Medicine, Queen Mary University of London, London E1 2AD, UK, (tel: +44 20 7882 2643) and TROPGAN, Department of Medicine, University of Zambia School of Medicine, Nationalist Road, Lusaka, Zambia (tel: +260 966 751875). m.p.kelly@qmul.ac.uk.

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This article is intended to analyze what we know about the burden of non-communicable diseases (NCDs) affecting the gastrointestinal (GI) tract, liver, and nutritional disorders in HIV infection in low- and middle-income countries (LMICs), to make inferences about potential future problems based on data from high-income countries (HICs), and to predict issues which the authors believe may emerge. We deal first with disorders of the hollow GI tract (the esophagus, peptic ulceration, enteropathy, and cancers), then with hepatic disorders, and thereafter with nutritional issues. We set out in tables a summary of available data and data gaps and suggest where future work is most urgently needed.

1 Gastrointestinal NCDs

1.1 Landscape

1.1.1 Esophagus—While the esophagus is heavily affected by infectious complications of HIV-related immunosuppression such as candidiasis and giant ulcers, non-infectious disorders such as achalasia, gastro-esophageal reflux, and Barrett's esophagus occur infrequently in HIV-infected people in LMICs (Kelly, personal observations). This may change as populations move through a demographic transition to urban and more affluent lifestyles, with increasing abdominal adiposity and higher rates of tobacco smoking.

1.1.2 Peptic ulceration—Peptic ulceration is less common in HIV-infected[1] than in uninfected adults, despite the high prevalence of *Helicobacter pylori* in LMICs. This seems to be a consequence of hypochlorhydria (a lack of stomach acid)[2,3], but the explanation for reduced acid secretion in HIV is unclear[3]. Hypochlorhydria appears to predispose to gastrointestinal infections[4] irrespective of HIV but may protect against non-communicable disorders such as gastro-esophageal reflux and peptic ulceration. As the hypochlorhydria appears to be reversed by antiretroviral therapy (ART)[3], peptic ulceration (and gastro-esophageal reflux) may increase in HIV-infected populations receiving ART.

1.1.3 Intestinal disorders—Environmental Enteropathy (EE)[5,6] is ubiquitous in many populations[7,8]. EE is a disorder without clear-cut clinical manifestations, but it has subtle consequences, including malabsorption of micronutrients and drugs, bacterial translocation leading to systemic immune activation, and impaired responses to oral vaccines[9]. EE and HIV enteropathy (HIVE) may be superimposed, and morphologically and functionally they are indistinguishable[8]. The extent to which HIVE and intestinal immune dysfunction are reversible with ART is not clear[10], but even if fully reversible, many people with HIVE living in LMICs would still be left with EE once the HIV-related changes have been normalized. There is an urgent need to investigate aspects of malabsorption that occur in the overlap between EE and HIVE, and to test prevention or treatment modalities.

1.1.4 GI cancers—Upper GI cancers are common causes of cancer death throughout the world[11,12]. A recent retrospective review of registry and population data in the U.S. suggests

modest increases in the risk of cancers of the upper GI tract related to HIV - esophageal adenocarcinoma (standardized incidence rate (SIR) 1.91; 95% CI 1.31–2.70), esophageal squamous cell carcinoma (SIR 1.47; 95% CI 1.10 –1.92), and gastric adenocarcinoma (SIR 1.44; 95% CI 1.17–1.76)[13]. However, this potentially important problem has been the focus of very little research in LMICs[14]. Cancers of the digestive system are occurring more frequently among young adults in southern Africa, the age group with the highest HIV rate[15]. There was no association between gastric cancer and HIV in a case-control study in Zambia[16]. We found no publications relevant to LMICs about colorectal or pancreatic cancers and HIV. While there has been work on GI cancers in HIV and their treatment[23] in the industrialized world[17-22], there is a paucity of information in LMICs, particularly on the additional risks of oncological therapy in HIV-infected adults and children. There is a major transition taking place around the world in the epidemiology of esophageal cancer, with adenocarcinoma emerging now as the dominant type in HICs. This may also occur in LMICs over time, and if it does, HIV-infected persons will also be affected, as discussed in this issue's article on HIV-associated malignancies by Adebamowo et al.

1.2 Data challenges and research priorities (see Table 2)

The consequences of EE and HIVE for health in LMICs need to be better defined in terms of the effect on absorption of drugs and micronutrients. This will require investment in physiological, pharmacological, and metabolic studies which demand a range of expertise not commonly found in LMICs, so well-balanced North-South collaborations will be required. Diagnostic facilities for cancer need to be upgraded, with investments in endoscopy and radiology facilities. Investments in cancer registries, which will be needed to explore the epidemiological shifts currently in progress, are dealt with in an accompanying article[24]. As work on malabsorption and GI cancers is likely to be resource-intensive, a sentinel surveillance approach could be adopted, with centers of GI science supported to do work on representative samples of well-defined populations. Ultimately, this work would permit an estimate of the proportion of the cancer burden that might be preventable by ART or other preventive measures. For example, how much of the gastric cancer burden could be prevented by nutritional interventions, such as enhanced antioxidant supplements, or by treatment of *Helicobacter pylori*?

2 Hepatic NCDs

2.1 Landscape

With the introduction of ART and the decrease in overall AIDS-related mortality, liver-related complications have become a leading cause of hospitalization and death in HIV-infected individuals. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study conducted in HICs, liver disease was a leading cause of non-AIDS-related deaths (14.5%), of which 76% were associated with hepatitis B (HBV) or hepatitis C (HCV) infection and 3% with ART[25]. In a follow-up study, the incidence of liver-related deaths in HIV-infected persons without HCV or HBV was 0.10/1000 person-years[26]. A French study similarly found that a majority of liver disease in persons with HIV was attributed to chronic HBV and HCV infection as well as excessive alcohol use[27].

It remains unknown whether the burden of liver disease among HIV-infected patients in LMICs is similar in magnitude; moreover, the extent of non-communicable diseases (NCDs) of the liver, such as alcoholic liver disease, drug-induced liver injury, and non-alcoholic fatty liver disease (NAFLD) has not been defined. It is also unclear whether there is a more rapid progression of fibrosis among those with HIV infection and liver disease from non-infectious etiologies, as has been reported for HIV and HCV co-infection, and whether the use of ART modifies this potential relationship. In Uganda, in symptomatic patients with acute liver disease, 30% had nevirapine and/or isoniazid-induced liver injury, 15% were positive for hepatitis B surface antigen, 3% were positive for anti-hepatitis C antibody, 9% had presumed granulomatous hepatitis due to tuberculosis, and 5% were diagnosed with alcoholic liver disease[28]. Data from rural Uganda suggested a significant association between HIV infection and liver fibrosis (as measured by transient elastography, a non-invasive method for analyzing liver stiffness) after controlling for factors such as alcohol use, occupational exposure to schistosomiasis, and chronic hepatitis B infection[29]. Nevertheless, in this study, three-quarters of liver disease remained unexplained both in the overall and HIV-infected population.

In this section, we review several etiologies of liver disease in HIV-infected individuals, with an emphasis on issues relevant to LMICs.

2.1.1 Drug-related liver disease—Several types of liver injury associated with ART have been described in HICs among HIV-infected patients, including hypersensitivity, idiosyncratic hepatotoxicity, mitochondrial toxicity, and immune reconstitution syndrome (IRIS). In addition, the use of didanosine, a reverse transcriptase inhibitor, has been associated with nodular regenerative hyperplasia (NRH)[30,31]. The mechanism underlying this association is unclear but potentially related to thrombophilia, a form of hypercoagulability that results in noncirrhotic portal hypertension.

Retrospective studies in HICs have shown overall incidence rates of ART-related severe hepatotoxicity from 8.5% to 23%, and life-threatening events occur at a rate of 2.6 per 100 person-years[32-37]. Several risk factors have been identified, including baseline elevation in serum aminotransferases, thrombocytopenia, and renal insufficiency, but these variables may have been indicative of undiagnosed chronic liver disease [35].

In LMICs, there is a potential for increased rates of hepatotoxicity given that nevirapine-based regimens are more frequently used and the prevalence of tuberculosis is higher (thus increasing the risk for isoniazid toxicity and IRIS); however, some studies have suggested a low rate of hepatotoxicity attributed to ART. In a cohort study of 546 HIV-infected individuals in Kampala, Uganda, after 36 months of ART, only 1.5% of patients had grade 3 aspartate aminotransferase elevations[38], and regimens included lamivudine paired with either nevirapine and stavudine (74%) or efavirenz and zidovudine (26%). In Cameroon, the rate of grade 2 or higher hepatotoxicity experienced by patients receiving nevirapine-based therapy was 16%[39], and in Malawi, severe hepatotoxicity (defined as greater than 5 times the upper limit of normal) occurred in 9% of patients but did not result in discontinuation of therapy[40]. The authors concluded that liver enzyme monitoring may not require high priority

in sub-Saharan Africa[40], but additional studies are needed to better evaluate hepatotoxicity associated with ART.

In addition, studies in Uganda have reported a significant association between the use of herbal medications and liver disease in settings where ART was available. Up to 60% of HIV-infected patients in Uganda[41] have used ART and herbal therapy concurrently, and the use of any herb was associated with increased liver fibrosis as measured by transient elastography[42]. This association appeared to be independent of ART hepatotoxicity.

2.1.2 Alcohol-related liver disease—Excess alcohol consumption (defined as > 40 g/day among females and > 60 g/day among males) is associated with progressive liver disease among HIV-infected patients[43]. In a study of the causes of mortality in patients with HIV infection, excess alcohol consumption was twice as high in those who died from liver disease than in those who died from other causes (59% vs 24%)[44]. Excess alcohol consumption has been documented in many LMICs, including Nigeria, South Africa, and Uganda[45,46]. In a cross-sectional study in Uganda, for example, 47% of respondents reported alcohol use, a third of whom drank alcohol daily[47]. Among those with HIV infection, the relationship between alcohol use, high-risk sexual behavior, and adherence to ART has been studied[48], but the contribution of alcohol use to liver disease in HIV infection has not been analyzed in LMICs.

2.1.3 NAFLD—Non-alcoholic fatty liver disease (NAFLD), defined as liver steatosis in the absence of excessive alcohol intake, HBV, or HCV infection, is the hepatic manifestation of the metabolic syndrome. It includes a spectrum of disorders, from mild fat deposition to non-alcoholic steatohepatitis (NASH) and cirrhosis, and is now a leading cause of end-stage liver disease.

Emerging data suggest that the prevalence of hepatic steatosis among HIV-infected patients is increasing in HICs, but few studies have examined the prevalence of NAFLD in LMICs. In the aforementioned D:A:D study, the prevalence of metabolic syndrome increased from 19% to 42% from 2000 to 2007 among HIV-infected patients receiving ART[25]. In two large cross-sectional studies, 30-40% of HIV-infected patients receiving ART had steatosis diagnosed by ultrasound,[49,50] and a Spanish study reported NAFLD as the leading etiology of HIV-infected patients with liver damage of uncertain origin[51]. Moreover, there may be a higher prevalence of NASH among HIV-infected patients: in 30 HIV-infected patients receiving ART with unexplained abnormal liver function tests, 72% had steatosis, and of these 53% had NASH[52]. There are several hypotheses on the increased risk of NAFLD among those with HIV infection, including the development of insulin resistance in the setting of ART[53]; mitochondrial toxicity and oxidative stress from ART; and the potential suppression by HIV of peroxisome proliferator-activated receptors (PPAR), a nuclear receptor transcription factor that regulates insulin sensitivity, glucose and lipid metabolism, and fibrosis[54].

Moreover, there has been an increasing recognition of the role of the gut microbiota in the pathogenesis of NAFLD in HICs (also see section 4). More specifically, through alteration of the gut microbiota and increased intestinal permeability, there is increased exposure of

the liver to gut-derived bacterial products, such as lipopolysaccharides (LPS), which stimulate the innate immune response and lead to activation of signaling pathways involved in liver inflammation and fibrogenesis[55,56].

2.1.4 Hepatocellular carcinoma—Hepatocellular carcinoma (HCC) is expected to increase significantly among patients with HIV, mainly due to coinfection with HBV and HCV, and has increased as a cause of non-AIDS-related death: in the 2005 French Mortalité study, among liver-related deaths, HCC increased from 15% in 2000 to 25% in 2005[57]. In a US-Canadian multicenter study, at the time of HCC diagnosis, patients with HIV infection presented at a younger age, were more frequently symptomatic, and had more advanced disease compared with those without HIV infection[44]. In LMICs, exposure to aflatoxin B1 contributes significantly to the risk of HCC, but the relationship between aflatoxin B1 exposure and HCC in HIV infection has not been studied extensively.

In comparison with patients diagnosed with HCC in HICs, those diagnosed in LMICs are more likely to have advanced disease[58], which may be the consequence of limited screening capabilities and lack of treatment options. For instance, 19% of patients with HCC in southern Africa had pulmonary metastases compared with 7% of patients in the United Kingdom[59,60]. Treatment options for HCC are limited for both resectable and unresectable disease in LMICs given the lack of resources available to perform liver transplantation as well as more palliative therapies such as radiofrequency ablation and transarterial chemoembolization. There have been no studies performed on the use of sorafenib in LMICs.

2.2 Data challenges and research priorities (see Table 2)

There is a shortage of information on most liver diseases of concern to HIV-infected individuals in LMICs, and we need to know much more about their burden and spectrum. This will require cohort studies to analyse infectious and non-infectious events and risk factors in relation to liver damage. The dominant problem is the paucity of diagnostic facilities offering ultrasound for detection of advanced fibrosis and cirrhosis, blood biochemistry, and liver biopsy, which often cannot be safely carried out or interpreted because of a severe shortage of skilled pathologists. Thus, there exist unique research opportunities to define liver disease among HIV-infected individuals in LMICs, utilizing the infrastructure developed for the management of HIV. Furthermore, there is an important opportunity to develop and validate a staging system for liver disease in LMICs through non-invasive methods to study fibrosis. Several methods, including APRI (AST to platelet ratio index)[61], Fib-4 index (which combines biochemical values such as ALT, AST, and platelet count as well as age), and transient elastography, have been studied among HIV-infected individuals in HICs,[62,63] but the most useful approach to staging has not been determined in LMICs. This determination will permit a deeper understanding of the interaction of alcohol, drugs, herbal medications, obesity, and the microbiota (see below). Drug interactions with herbal treatments and other risk factors also will require more targeted research. Interventions to reduce the impact of alcohol and substance abuse[48] could have a dramatic impact on liver disease, and where possible, this effect should be incorporated into studies of interventions to reduce alcohol-related harm.

3 Nutrition

3.1 Landscape

3.1.1 HIV and malnutrition—The powerful interaction between HIV and undernutrition is a major problem in many LMICs, affecting children in particular. Many people with HIV present late with complex infectious co-morbidities and can be severely undernourished. At presentation, it is often difficult to distinguish between undernutrition due to primary food insecurity (which might be said to be a non-communicable co-morbidity) and that which is due to the inflammation caused by HIV and related opportunistic infection. In practice, this does not matter, as once malnutrition has become established, management of the undernutrition *per se* must be integrated into the management plan. Undernutrition has been consistently associated with increased risk of death in adults and children[64,65]. The term 'malnutrition,' however, also reflects abnormalities of nutritional status that are not necessarily reflected in wasting of body tissue, and it may also refer to depletion of vitamins and minerals.

Nutritional concerns in LMICs where ART is more widely available have now shifted to the lipodystrophy and metabolic alterations associated with the therapy[53]. However, even in the ART era, weight loss and severe acute malnutrition (SAM) remain common problems for HIV infected subgroups such as those diagnosed late in the course of the infection and those with failed or non-adherent antiretroviral regimens[66]. Conversely, malnutrition and reduced access to adequate or quality foods significantly increase non-adherence to ART[67].

In a Brazilian city, 43% of adults hospitalized with AIDS were undernourished (BMI< 18.5 kg/m^2)[68]. A systematic review found that 29% of children admitted to 17 sub-Saharan African centres with SAM were HIV-infected. Urban referral hospitals had higher HIV prevalence rates (>50%) and greater mortality (30%) among HIV-infected children with SAM[65]. The majority of children were not on ART and SAM was their first AIDS-defining illness. Re-admission rates for HIV-related SAM exceed 10%[69]. In addition, approximately 10-25% of severely malnourished children with HIV also have TB[70].

Determinants of the frequency, timing, and severity of SAM in children with HIV infection include their birth condition (e.g., preterm or low birth weight), food security (e.g., access to food, food diversity), family dynamics (e.g., primary caregiver, parents alive, income), clinical stage of HIV disease, the presence of co-infections (e.g., persistent diarrhea, pneumonia, TB), and access to services (e.g., cotrimoxazole prophylaxis, food supplementation). In adults, severe malnutrition has been associated with older age, poverty, and chronic diarrhea[68].

3.1.2 Therapy for malnutrition and knowledge gaps—The introduction of therapeutic diets including F-75, F-100, and ready-to-use therapeutic foods (RUTF) has improved the rehabilitation process and reduced hospital stays of children with SAM who are not infected with HIV. In many centres these supplements are also being used for adults. Evidence on the optimal feeding regimen to be used for HIV-infected children with SAM is lacking[69]. Suitable feeding and rehydration regimens are still needed for severe diarrhea commonly observed prior to and during rehabilitation of these children[69]. For prevention of

malnutrition and reduction in mortality, there is little evidence that macronutrient supplementation has benefit[71].

In LMICs, the ART gap remains large, with only 28% of the 2 million children needing ART receiving treatment[72]. Access to ART has significantly improved the survival of HIV-infected children. However, the optimal timing, regimen, and dosing of ART in children with SAM lack an evidence base and are guided primarily by expert opinion. Observational studies indicate that children with more severe wasting started on ART have a higher mortality rate[73-75]. There have been reports of children initiating ART and subsequently developing severe edematous malnutrition, which could be a form of IRIS. Existing strategies to prevent and manage lipodystrophy are considered too expensive to be feasible in LMICs. There is also concern that ART may lead to higher rates of decreased bone mineral density and pathologic fractures in children with SAM[53,76].

Despite the sustained growth response and catch-up growth in children with advanced HIV disease who are treated with ART, normal weights and heights were not achieved over 3 years of ART in African settings[77]. Although underweight and wasting rates fell during the first year of ART, the trend reversed from the second year onwards. Three years after starting ART, weight-for-height z scores ranged from -4.03 to -2.36 in children who started with a baseline z score of < -3 (defined as SAM).

The WHO has encouraged the use of RUTFs for community-based treatment of SAM among children. Initiation of RUTF and ART reduced wasting in HIV-positive children with uncomplicated SAM[78], and its provision for at least 4 months was associated with low proportions of undernutrition status[79]. Similarly, supplementary foods provided to adults for 3 months at ART initiation improved nutritional status and reduced mortality, but its effect lasted only during the intervention period[80]. The optimal role of RUTFs in the management of HIV-related SAM requires further investigation.

Micronutrient deficiencies are common in HIV-positive individuals. There is considerable evidence of suboptimal micronutrient status[81]. Bulk minerals such as potassium, calcium, magnesium, and phosphate are not strictly micronutrients, but they also can be deficient, and there is some evidence that these have an impact on mortality[82]. Intervention studies are very heterogeneous in terms of the nature of the intervention (single or multiple nutrients, dose) and outcomes. However, a recent meta-analysis[83] suggests that vitamin A reduces mortality in HIV-infected children and selenium has beneficial effects on CD4 counts; in addition a clinical trial in Zambia showed a beneficial effect of multiple micronutrients on mortality in adults[84]. The mortality benefit was more robust in another, more comprehensive review, which showed that multiple micronutrients significantly reduced mortality in patients without TB (RR 0.75; 95%CI 0.58-0.95)[85]. In addition to selenium, zinc supplementation may also have benefits for CD4 counts in adults[86].

3.2 Data challenges and research and training opportunities (see Table 2)

In contrast to non-communicable GI and liver diseases, where there is a great need for simple descriptive studies, much work has already been done on HIV and malnutrition, and there is firm evidence that HIV contributes to mortality in childhood malnutrition. The need

now is for randomized controlled trials and metabolic studies; as well, the physical infrastructure for conducting these needs to be supported alongside employment and training opportunities for research physicians, scientists, and nurses.

In addition to this, there is a need for an expansion of basic science on nutrition, especially the interplay of HIV and inflammation, co-infections and ART, and their interaction during initiation of ART. There is a surprising dearth of information on nutritional requirements in this critical early phase of ART when mortality is high. The role of RUTFs, particularly in the absence of ART or for children under 6 months old, needs to be defined. Priority questions for randomized controlled trials include both the optimal timing and drug composition of ART in malnourished children and how those drugs interact with others such as TB drugs. Pharmacokinetic studies may be required.

In 2007, 50 clinical and child-health researchers and practitioners from several southern African countries met in Blantyre, Malawi, and established the Blantyre Working Group. Together they cared for more than 100 000 severely malnourished children annually[87]. Such consortia, if formally structured, could deliver important observational data, mechanistic analyses of pathophysiology, and clinical trial data. However, they would require substantial funding. What is necessary to move the SAM in HIV agenda forward is a critical mass of collaborating clinical scientists working within recognized scientific institutions. Reconstituting and supporting the Blantyre Working Group or similar networks may be the natural start.

4 The microbiome

The microbiome has emerged as an important determinant of the biology, development, and host defence of the gastrointestinal tract; the health of the liver (see above); and of nutrition. For all three major areas (gastrointestinal, hepatic, nutrition) there are research questions relating to the microbiome[88] that need to be answered, such as:

- What impact does HIV (untreated and treated) have on the microbiome? What is the effect on EE, GI cancers, NAFLD, and obesity? There is a need for observational and mechanistic studies in LMICs.
- Do antibiotics or probiotic strategies[89] contribute to improved health for HIV-infected people in the long term? Answering these questions will require phase 1, 2, and 3 trials of probiotic and antibiotic treatment strategies in ameliorating enteropathy, reducing cancer risk, preventing NAFLD, and improving nutritional status in adults and children.

Conclusion

The effects of the demographic transition to urban and more affluent lifestyles on NCDs of the GI tract are not yet clear. Among those who are HIV-positive, it seems likely that this change will have a significant effect on disorders of the esophagus and liver, especially alcoholic liver disease and NAFLD. There may also be an impact on the epidemiology of GI cancers, but this is likely to be more subtle. It is important to define the consequences of EE and HIVE for absorption of nutrients and drugs, as this may have far-reaching implications

for treatment programs for a wide range of disorders. Understanding and responding to the interaction of HIV and malnutrition is a crucial challenge which is likely to require a high degree of cooperation between pediatricians, physicians, virologists, public health physicians, and nutrition policymakers. There is no longer any doubt that HIV has a major effect on the efficacy of treatment for SAM, so a new set of well-designed randomized controlled trials is needed among affected children. Our experience suggests that an integrated approach to management of malnutrition and HIV, in communities where both are common, is essential.

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Search strategy and selection criteria

1. GI: searched Pubmed using ‘HIV’ and ‘Africa’ and (‘enteropathy’ or ‘gastric cancer’ or ‘esophageal cancer’ or ‘colorectal cancer’ or ‘achalasia’ or ‘inflammatory bowel disease’ or ‘celiac sprue’ or ‘coeliac disease’ or ‘Crohn's’ or ‘ulcerative colitis’)
2. Liver: searched Pubmed using ‘HIV infection’ and (‘alcoholic liver disease’ or ‘NAFLD’ or ‘ART hepatotoxicity’ or ‘autoimmune hepatitis’ or ‘hepatocellular carcinoma’) or ‘African American’ with (‘alcoholic liver disease’ or ‘NAFLD’ or ‘ART hepatotoxicity’ or ‘autoimmune hepatitis’ or ‘hepatocellular carcinoma’).
3. Nutrition: searched Pubmed using ‘HIV’ and ‘malnutrition’
4. Papers were selected on the basis of contribution to understanding of particular issues determined by the authors to correspond with emerging areas of importance. The literature cited is not exhaustive.

Table 1

Summary of extent of data available on gastrointestinal, hepatic, and nutritional NCDs in LMICs and HICs

Problem	Data available from LMICs	Data only available from HICs	Virtually no data available – emerging problem may be looming
Esophageal disorders			Changing epidemiology of carcinoma unlikely to leave HIV-infected individuals unaffected
Peptic ulceration			A few observations only
Environmental and HIV enteropathy	Considerable amount of data published, but implications for nutritional and drug therapy not yet clear		
Gastrointestinal cancers		Some data suggest HIV may have an effect on esophageal cancer	
Drug-induced liver injury	Some data available but much more needed		
Alcohol-related liver disease		Some data available, but data from LMICs needed	
Non-alcoholic fatty liver disease (NAFLD)		Emerging data suggest this is a problem; not yet addressed in LMICs	
Hepatocellular carcinoma (HCC)		Emerging data suggest this is a problem; not yet addressed in LMICs	
Severe acute malnutrition (SAM)	Extensive literature, but effect of HIV has been controversial; no RCT data yet published for HIV-SAM		
Micronutrient deficiencies	Some data available, but mechanisms not elucidated		
Microbiome			Emerging appreciation that this may be important, but no data yet

Table 2

Summary of the most urgent research and training priorities and recommendations

Gaps	Research/Training Focus	Recommendations
Basic science		
Effect of HIV on GI cancers and their immediate risk factors	Centres with the ability to diagnose and investigate GI cancers in relation to infectious and non-infectious risk factors. Training required to develop additional diagnostic expertise in these centres	Expansion of cancer monitoring to include GI cancers in centres with endoscopy and radiology facilities. Case-control studies of virologic and nutritional risk factors
Risk factors for liver disease	Cohort studies of HIV infected persons with analysis of intercurrent infections, alcohol and drug use, and nutritional factors. Training required in diagnostic services	Cohort studies
Impact of EE/HIVE and malnutrition on pharmacokinetics of drugs and nutrients	New infrastructure required in many LMICs. Training outside South Africa will be a challenge and partnerships will be required	Pharmacological and pharmacogenetic studies of drugs and nutrients in enteropathies (EE and HIVE) and in malnourished children and adults
Nutrient requirements in HIV-SAM	New infrastructure required for metabolic studies	Highly specialised small units able to carry out metabolic studies in HIV-SAM
Epidemiology and clinical research		
Epidemiology of GI cancers	Existing clinical records initially, supplemented by enhanced research as above	Exploitation of large ART provider datasets initially, with rapid progression to formal case-control studies in well-equipped centres with pathology expertise made available
Causes of death due to liver disease in HIV	Clinical research with strong basic science contribution (see above)	Cohort studies
Occurrence and risk factors for NAFLD	Existing clinical records initially, supplemented by enhanced research as above	Exploitation of large ART provider datasets initially, with rapid progression to formal case-control studies in well-equipped centres with pathology expertise made available
Optimal management of ART, treatment of co-infection, and malnutrition, especially in children	Clinical trials, using multicentre collaborations (e.g. the Blantyre Working Group). Clinical trials expertise in trials in SAM is available but needs strengthening	Establishment of networks of RCTs to address HIV-SAM as an urgent priority