

HIV and Noncommunicable Disease Comorbidities in the Era of Antiretroviral Therapy: A Vital Agenda for Research in Low- and Middle-Income Country Settings

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Abstract: In this special 2014 issue of *JAIDS*, international investigator teams review a host of noncommunicable diseases (NCDs) that are often reported among people living and aging with HIV in sub-Saharan Africa. With the longer lifespans that antiretroviral therapy programs have made possible, NCDs are occurring due to a mix of chronic immune activation, medication side effects, coinfections, and the aging process itself. Cancer; cardiovascular and pulmonary diseases; metabolic, body, and bone disorders; gastrointestinal, hepatic, and nutritional aspects; mental, neurological, and substance use disorders; and renal and genitourinary diseases are discussed. Cost-effectiveness, key research methods, and issues of special importance in Asia, Latin America, and the Caribbean are also addressed. In this introduction, we present some of the challenges and opportunities for addressing HIV and NCD comorbidities in low- and middle-income countries, and preview the research agenda that emerges from the articles that follow.

Key Words: noncommunicable diseases, HIV, AIDS, developing country, low- and middle-income countries, sub-Saharan Africa, antiretroviral therapy, disease complications, comorbidities

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INTRODUCTION

The story of the response to HIV/AIDS is an inspiring example of how research, capacity strengthening, and international partnerships successfully transformed a fatal and poorly understood infectious disease into a chronic, treatable disease. International clinical trials provided data that identified combination antiretroviral therapy (ART) regimens that were not only effective in controlling and limiting mortality from HIV but also—by using combinations of drugs—limited the emergence of drug resistance. Given this evidence base, large-scale HIV treatment and prevention programs around

the world, supported by donors such as the US President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria, decreased HIV incidence and lowered mortality rates from HIV/AIDS on every continent studied.^{1,2} The strong fight against HIV/AIDS, with its focus on stopping transmission, implementing treatment protocols, improving drug delivery systems, and strengthening medical facilities, can in many ways serve as a model for the treatment of noncommunicable disease (NCD) in low- and middle-income countries (LMICs).^{3–11}

Today, with over 35 million people living (and aging) with HIV (PLHIV) and over 2 million becoming infected every year,¹² we are faced with a new challenge: addressing morbidity and mortality from NCDs—heart disease, stroke, diabetes and metabolic complications, renal disease, cancers, liver disease, and mental illness—that increase with age and may be related to HIV and its treatment.^{13–16} We are now in an era when PLHIV may experience a reduction in quality of life or die, not from HIV itself, but from a preventable NCD that may be a consequence of HIV-related immunosuppression, antiretroviral drug toxicities, or HIV-related inflammation and hypercoagulation.

The link between treatable HIV disease and increased morbidity and mortality from NCDs poses a familiar challenge: when a primary disorder is treated, but not cured, underlying pathogenic processes may continue and increase vulnerability to other comorbidities. We cite as an example the first case of successful human diabetes treatment with insulin to a patient who then died from pneumonia.¹⁷

Leonard Thompson was a 14-year-old Canadian with type 1 diabetes mellitus when he was treated with “pancreatic extract” in 1922. The teenager weighed less than 30 kg and had mental obtundation. Once Leonard received a purified extract, his symptoms improved and his blood sugar normalized. With daily insulin treatment, Leonard resumed his growth and had a good quality of life until he died of pneumonia at age 27.

In this historic case, the patient's first and primary NCD (diabetes) was managed, but he succumbed to an infection. In sub-Saharan Africa today, HIV care is more widely available than in previous decades, but it is not accompanied by parallel

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care services for NCDs, resulting in preventable, premature morbidity and death. Although an excess risk of NCDs in persons living with HIV/AIDS in LMICs still needs to be better quantified, increasing rates of NCDs among aging persons who have HIV, many of whom are receiving HIV treatment, raise the concern that, if unaddressed, morbidity and mortality from NCDs may set back or even reverse the impressive health gains achieved over the last decade in HIV-infected populations. As we work toward building sustainable models of disease prevention, treatment, and care in LMICs in the context of an increasing, global NCD epidemic, a better understanding of the interactions between long-term HIV, HIV treatment, and NCD comorbidities will enable us to maintain gains in HIV-infected populations while improving NCD control and treatment. More and better data regarding NCDs in aging PLHIV receiving different ART treatments will inform the development of cost-effective interventions and enhancements to existing HIV and health systems in LMICs so that they incorporate both HIV and NCD diagnosis and treatment. Designing and conducting studies will require a paradigm shift in places like sub-Saharan Africa, where, to date, the primary focus has been on HIV prevention and treatment. Just as the advent of widespread ART demanded a seismic shift in global human capacity and health systems for the emergency response to HIV, emerging NCD comorbidities among those with HIV in LMICs will demand no less.

From April 29 to May 1, 2013, the Fogarty International Center and the Office of AIDS Research at the US National Institutes of Health (NIH) assembled a multidisciplinary international group of experts at Fogarty's Center for Global Health Studies for a consultation on HIV and NCD comorbidities in LMICs. This group included representatives of 9 NIH Institutes and Centers (Fogarty International Center, National Cancer Institute, National Heart Lung and Blood Institute, National Institute of Allergy and Infectious Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Drug Abuse, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, and the Office of AIDS Research at the NIH Office of the Director) and other key agencies (the World Health Organization, the United States Agency for International Development, the US Centers for Disease Control and Prevention, The World Bank Group, and the Office of the Global AIDS Coordinator at the US Department of State), as well as researchers and policymakers with expertise in this field. The consultation provided a scientific forum to:

- Identify key research and research training priorities related to HIV and NCD comorbidities in LMICs and stimulate new research collaborations;
- Inform future investments of the NIH and other funding agencies; and
- Identify ways in which to harness existing research and care platforms to further the research and capacity building that best addresses HIV and NCD comorbidities.

After the consultation, US and LMIC scientists collaborated on articles that articulate the current scientific landscape

as well as the urgent research and capacity-building priorities associated with specific HIV and NCD comorbidities featured in this supplement: (1) cancers,¹⁸ (2) renal and genitourinary comorbidities,¹⁹ (3) metabolic, body, and bone disorders,²⁰ (4) cardiovascular and pulmonary diseases,²¹ (5) mental, neurological, and substance use disorders,²² and (6) gastrointestinal, hepatic and nutritional aspects,²³ as well as key related (7) methodological,²⁴ and (8) cost-effectiveness issues²⁵ on the subject. In addition, given that the focus of these articles is on sub-Saharan Africa, two commentaries were solicited to provide broad perspectives from both Latin American²⁶ and Asian²⁷ contexts. This introductory chapter presents some of the over-arching challenges and opportunities for addressing HIV and NCD comorbidities in LMICs, with the subsequent articles describing these issues and the epidemiology of these comorbidities in greater depth.

HIV AND NCDs IN LMICs: A RESEARCH AGENDA

Data from high-income countries and some LMICs have demonstrated that a variety of NCDs occur more commonly in HIV-infected populations. Although evidence from high-income countries is definitive as to the emerging importance of NCDs for PLHIV, there are far fewer data and research advances regarding such conditions in LMICs, where the great majority of PLHIV reside.²⁸ Research conducted in LMICs is critical to understanding how local environmental and genetic factors may play a role in the prevalence and level of expression of NCD comorbidities, the potential side effects of ART, and the interactions between ART and NCD therapies. Table 1 illustrates some complexities in HIV disease treatment faced in LMICs, where a greater prevalence of other coinfections may weaken immune systems and complicate treatment, and delayed screening, diagnosis, and treatment can be expected to alter NCD progression. As we build an HIV and NCD comorbidities research agenda and set priorities in the LMIC context, gaps and needs in local research capacity will need to be considered, including suboptimal surveillance and variable diagnostic capabilities. Strengthening in-country research capacity in targeted areas with respect to HIV-NCD burdens must be a high priority.

This series sets forth priorities for research and research training related to specific disease and conditions; below, we highlight overarching priorities that cut across multiple disease areas. In addressing these priorities, special attention should be paid to key populations and their comorbid conditions.^{29–37}

Public Health Surveillance and Clinical Epidemiology^{38–43}

- NCD incidence among PLHIV, including key population subgroups.
- Prevalence of different NCD risk factors and measures of their impact among PLHIV.
- Differences in NCD mortality rates and morbidity outcomes among persons with HIV, as compared with those without HIV.

TABLE 1. Illustrative Examples of HIV Disease or HIV Therapy NCD Complications*

Illustrative Conditions	Principal Considerations in High-Income Countries	Additional Possible Clinical Concerns in LMICs	Comment
Peripheral neuropathy	Chronic immune activation in peripheral nervous system	Stavudine (d4T) toxicity	d4T is cheap and is still in use in many low-income countries
Mental disorders	Depression, alcohol and drug abuse, posttraumatic stress disorder	Symptoms of depression and other mental disorders can differ cross-culturally	Lack of diagnosis and treatment of depression in HIV care settings in low-income countries
Type 2 DM	Obesity, unhealthy diet, sedentary lifestyle, protease inhibitors	d4T toxicity	DM risk factors can be similar, but d4T is still used in low-income countries
Hepatitis	HCV, alcohol use	HBV, HDV, nevirapine toxicity, hepatic schistosomiasis	Interactions between HIV, hepatitis viral infections, and NCDs create unique coordinated care challenges in low-income countries
Kidney disease	Tenofovir toxicity, HIVAN, chronic kidney disease	HIVAN, urinary schistosomiasis	Persons of African genetic origin are more susceptible to HIVAN
Lung disease	HIV-associated pulmonary hypertension, chronic obstructive pulmonary disease, lung cancer, emphysema	TB, pneumonia, indoor air pollution	TB is far more prevalent in low-income nations, as is indoor air pollution
Gastrointestinal disease	NNRTI-associated pancreatitis, protease inhibitor-associated diarrhea or fatty liver	HIV-induced enteropathy, wasting syndrome, salmonellosis, cryptosporidiosis, candidiasis, CMV	Persons living with HIV in low-income settings may seek care later in their HIV disease course, increasing GI complications, and coordinated care challenges
AIDS-related cancers	Lymphomas	KS	KS is less common where more persons are on ART
Neurological disease	HIV-associated neurocognitive disorders, stroke	Cryptococcosis, toxoplasmosis, CMV	HIV-associated dementia is less common in immunocompetent and virologically suppressed individuals
Cardiovascular disease	Hyperlipidemia, lipoatrophy, atherosclerosis (may be associated with ART, eg, protease inhibitors)	Infectious myocarditis and pericarditis from opportunistic infections, heart failure, thrombophilia	CVD-related care may not be available in low-income rural areas apart from HIV centers

*Note that in low- and middle-income countries, as persons are diagnosed and treated both earlier and for longer time periods, the principal clinical considerations of high-income nations are likely to emerge with greater frequency. Middle-income nations already have a substantial mix of these concerns.

CMV, cytomegalovirus; CVD, cardiovascular disease; DM, diabetes mellitus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HDV, hepatitis D virus; HIVAN, HIV-associated nephropathy; KS, Kaposi sarcoma; NNRTI, nonnucleoside reverse transcriptase inhibitor; TB, tuberculosis.

Basic and Clinical Research⁴⁴⁻⁵²

- Role of inflammation, coagulation, and immune mechanisms in NCD expression for those infected with HIV.
- Development of NCD biomarkers suitable for use in low-income settings among those living with HIV.
- Differential response to NCD treatment in different subgroups and regions.
- Impact of ART regimens used in LMICs on NCD expression.
- Impact of NCD treatments on prognosis and outcomes.
- Interactions between HIV and NCD pathogenic processes.
- Identification of effective and cost-effective HIV-NCD drug regimens.

Implementation Science and Health Systems⁵³⁻⁶⁴

- Efficiency, cost-benefit, and feasibility of existing point-of-care screening tests, affordable diagnostics, and drug delivery tools for NCDs among PLHIV.

- Development of innovative and effective models of integrated NCD and HIV care, including task-sharing strategies.
- Application of existing telemedicine and mobile technologies to cope with shortages of expert staff.
- Effective strategies for transforming vertical HIV programs into horizontal chronic disease care systems.

Infrastructure, Training, Capacity, and Workforce Development⁶⁵⁻⁹¹

- Training scientists to work in multidisciplinary environments.
- New health workforce development to deliver joint HIV/NCD care.

CONCLUSIONS

Research advances related to HIV and NCD comorbidities can build on and help sustain the enormous progress that

has been made in combating the global HIV/AIDS epidemic, and further improve the lives and health of those living with HIV. As increasing numbers of those infected with HIV receive long-term treatment and are confronted by NCDs, evidence-based intervention strategies are critical to ensure that health gains in these populations made over the past decade are not threatened by the rising burden of NCDs. The research agenda for HIV and NCD comorbidities in LMICs is substantial and will require sustained investment and attention from a wide range of stakeholders. The expanded availability of ART and concurrent growth of in-country health infrastructure and human capacity provide unique opportunities to obtain real-time, high-quality data sets about the prevalence and characteristics of coexisting NCDs by building on current HIV data collection efforts. Similarly, drug delivery systems now devoted to ART and tuberculosis medicines could add essential and affordable drugs for NCD management and improve the long-term survival and quality of life of those living with HIV, while potentially enhancing adherence to ART. In a time of scarce resources, imaginative enhancement of HIV research and care platforms and expanded training for researchers and providers can strengthen health systems and improve the overall care of persons living with HIV/AIDS. This goal will require creative partnerships among a wide range of stakeholders, including funding agencies, research institutions, LMIC governments, and in-country researchers and program implementers.

In many parts of rural Africa, Latin America, and Asia, clinics are now attempting to provide services beyond acute care to treat long-term HIV, and health systems designed to manage HIV/AIDS are under the strain of managing patients with additional NCD comorbidities. Research will play a critical role in providing the evidence, strategies, and tools that can be deployed to address this new reality, while research training and capacity building programs will enable local scientists to conduct the research needed in their environments. Increased research capacity, the breakdown of disciplinary silos, and scientific vision and leadership will be critical as we address this new challenge to continue to improve the lives of people living with HIV across the globe.

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