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Multimorbidity and cardiovascular disease: a perspective on low- and middle-income countries

Friedrich Thienemann^{1,2,3}, Ntobeko A. B. Ntusi², Edouard Battegay^{1,4}, Beatrice U. Mueller¹, Marcus Cheetham^{1,4}

¹Department of Internal Medicine, University Hospital Zurich, University of Zurich, Zurich, Switzerland; ²Department of Medicine, Faculty of Health Science, University of Cape Town, Cape Town, South Africa; ³Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Science, University of Cape Town, Cape Town, South Africa; ⁴University Research Priority Program “Dynamics of Healthy Aging”, University of Zurich, Zurich, Switzerland

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Correspondence to: Edouard Battegay, MD, FACP. Professor of Internal Medicine, Director, Department of Internal Medicine, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. Email: edouard.battegay@usz.ch.

Abstract: New and changing patterns of multimorbidity (MM), i.e., multiple concurrent acute or chronic diseases in a person, are emerging in low- and middle-income countries (LMICs). The interplay of underlying population-specific factors and lifestyle habits combined with the colliding epidemics of communicable and non-communicable diseases presents new disease combinations, complexities and risks that are not common in high-income countries (HICs). The complexities and risks include those arising from potentially harmful drug-drug and drug-disease interactions (DDIs), the management of which may be considered as MM in the true sense. A major concern in LMICs is the increasing burden of leading cardiovascular diseases, prevalence of associated risk factors and co-occurrence with other morbidities. New models of MM management and integrated care can respond to the needs of specific multimorbid populations, with some LMICs making substantial progress (e.g., integration of tuberculosis and HIV services in South Africa). But there is a dearth of relevant data on the changing patterns and underlying factors and determinants of MM, the associated complexities and risks of DDIs in MM management, and the barriers to integrated care in LMICs. This requires careful attention.

Keywords: Multimorbidity (MM); cardiovascular disease (CVD); poverty; low income countries; middle income countries; Africa

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Introduction

Multimorbidity (MM) refers to the presence of multiple concurrent acute or chronic diseases within a person (*Box 1*) (1,4). This simple disease count-based definition of MM dominates epidemiologic research, especially in high-income countries (HICs). Comparatively little is known about the burden of MM in low- and middle-income countries (LMICs) (5-7). This is in part because studies

have largely focused on single diseases (8). The variation across studies in the choice of study design, methods, and measures limits comparability of findings on the distribution and determinants of MM disease burden. Nevertheless, there is mounting recognition that there are different and changing demographic and epidemiological patterns of MM within and across different HICs and LMICs populations, that a complex interplay of population-specific demographic, economic, social, cultural and psychological

Box 1 Definitions of multimorbidity

“Multimorbidity is the co-occurrence of multiple chronic or acute diseases and medical conditions within one person” (1)

In contrast to an index disease taking central place in the disease combination, multimorbidity is the *“co-existence of two or more chronic conditions, where one is not necessarily more central than the others” (2)*

“Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or bio-psychosocial factor (associated or not) or somatic risk factor” (3)

factors, and lifestyle habits (e.g., lack of exercise, unhealthy diets, smoking or alcohol consumption) contribute to these differences, and that these patterns and contributory factors require careful attention if healthcare delivery is to respond adequately to the needs of specific multimorbid populations (9,10).

Multimorbid patients with cardiovascular disease (CVD), chronic kidney and lung disease, and concurrent other non-communicable diseases (NCDs) and infectious diseases (and their care providers) face major challenges. These challenges require careful attention, particularly in LMICs. The urban community in LMICs, especially in sub-Saharan Africa (SSA), has undergone an immense epidemiological transition towards cardiac risk factors. Besides the shift in the global burden of hypertension from HICs to LMICs over the past decades, the number of adults living with diabetes has increased from 108 million in 1980 to 422 million in 2014 (11,12). This has led to a dramatic increase in ischaemic heart disease, stroke, hypertensive heart failure, and atrial fibrillation. In addition, traditional CVDs are still prevalent in LMICs, such as rheumatic heart diseases, cardiomyopathy, undiagnosed hypertension, untreated congenital heart disease, and endomyocardial fibrosis. Chronic kidney disease does have numerous causes, but diabetes and hypertension are the two main risk factors. In the Global Burden of Disease Study 2017, chronic obstructive pulmonary disease (COPD) ranked as the seventh leading cause of early death (13). NCDs interact in a complex fashion with the top three global infectious diseases epidemics: human-immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis, and malaria. In 2017, 36.9 million people were living with HIV, with 95% of new HIV infections occurring in Eastern Europe, central Asia, the Middle East, and North Africa (14). Tuberculosis remains one of the top 10 causes of death globally. About 10 million new infections occurred in 2017, 9% of which were people living with HIV (72% of them in Africa) (15). In the same year, the World Health Organization (WHO) reported 219 million cases of malaria worldwide (16). In

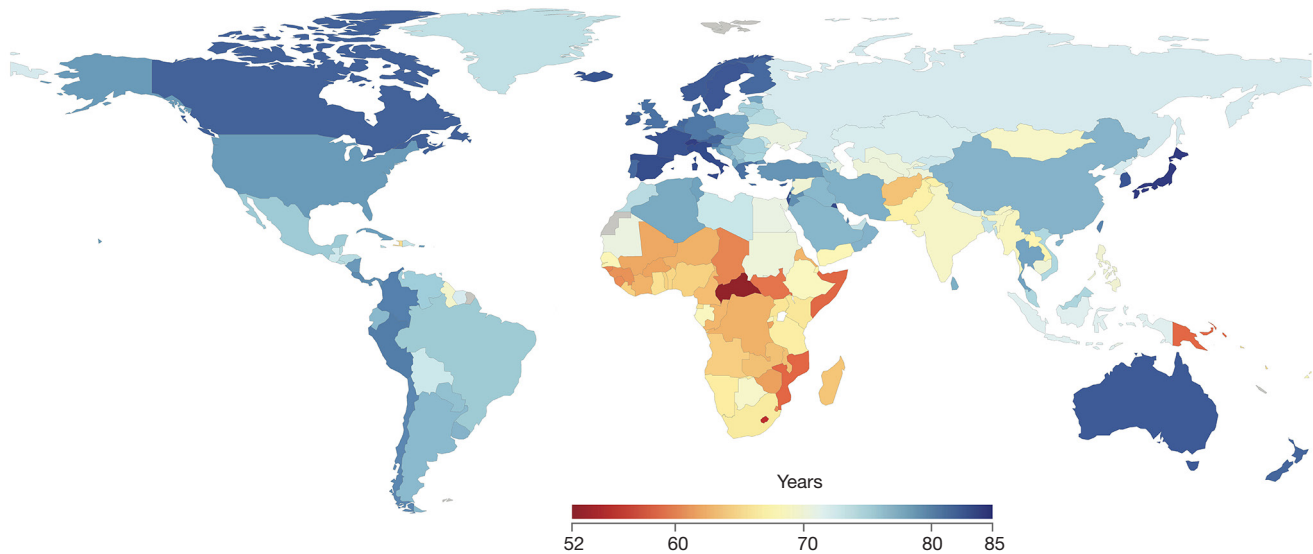
addition, chronic parasitic infections such as schistosomiasis and filariasis may interact with NCDs and lead to substantial chronic disease morbidity, e.g., schistosomiasis-associated pulmonary arterial hypertension (17).

Demographic transition and MM

The demographic transition to older populations is a driver of MM prevalence (18). Globally, fertility and mortality rates have dropped substantially, except in SSA where in many regions the onset and pace of change are substantially delayed (19). Life expectancy rates in HICs show some stagnation and even decline, while the increasing rate of population aging in LMICs is strong and expected to continue for years to come (20,21). Differences in pace may be set in the context of other differences between HICs and LMICs. For instance, average life expectancy at birth (in 2016) reached 83.3 years in Switzerland and 78.6 years in the United States, but only 63.6 years in South Africa, 52.9 years in Lesotho, and 53.1 years in Sierra Leone (*Figure 1*) (22,23). Importantly, recent data indicates that the severity of MM (based on disease count) increases with age in both HICs and LMICs (10,24), but the rates of prevalence in older populations are fundamentally different. MM affects 66.1% of those aged 65 and over in HICs and 7.8% of those aged 60 and over in LMICs (10,25,26).

Population aging is also a major driver of the global increase in CVD morbidity and mortality, with over 18 million CVD-related deaths globally in 2017 (27). In some countries in SSA, increasing life expectancy and the ageing population are linked to improvements in access and delivery of healthcare and control of infectious diseases, especially HIV/AIDS (28). As older populations are more vulnerable, the burden of leading CVDs, the prevalence of their risk factors, and their co-occurrence with other morbidities is likely to increase in LMICs (8,29). Risk factors include increasing body mass index (particularly affecting women in South Africa), systolic blood pressure (in East Africa), alcohol (particularly in southern regions of

Life expectancy, 2017*



*Data shown in the figure represent life expectancy at birth for both sexes.

Figure 1 Life expectancy at birth for both sexes. Findings from the Global Burden of Disease Study 2017 (13).

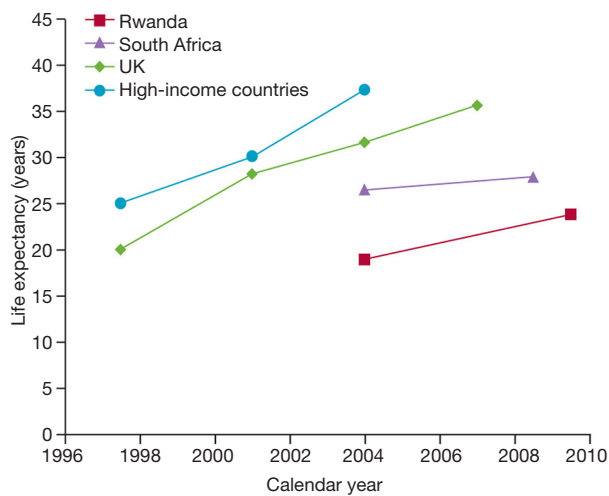


Figure 2 Trends in life expectancy for individuals initiating antiretroviral therapy at age 35 years from Rwanda, South Africa, United Kingdom (UK), and high-income countries in North America and Europe. Published by Egger & Johnson in *The Lancet Global Health* in 2015 (38).

SSA), tobacco use, and physical inactivity (30).

However, a focus on aging can divert attention away from MM burden in younger age groups (31). MM affects all age groups in HICs (32), as shown in Australia where 2.1%

of multimorbid persons are less than 60 years of age (33). But data are limited in LMICs. For example, in SSA younger adults are increasingly predisposed to NCDs, especially CVDs, this risk being linked to urbanization and lifestyle changes (34-36). In South Africa, 20% of women aged 15 years or older are severely obese (body mass index ≥ 35). Most of these are among coloured and black African populations (26% and 20%, respectively), affecting 17% of women of 25-34 years. Tobacco is consumed daily by as much as 6% of women and 30% of men, and alcohol abuse affects 5% of women and 28% of men (37).

South Africa has the biggest HIV epidemic in the world, with 7.2 million people living with HIV in 2017 (14). South Africa has introduced extensive measures to tackle this epidemic by rolling out the largest antiretroviral therapy (ART) program globally. In 2017, 86% of people living with HIV were aware of their status and 61% were receiving ART. Globally, this is the most successful campaign in tackling the HIV epidemic, starkly improving life expectancy rates in South Africa. Outside of South Africa, life expectancy rates have improved dramatically for those starting ART (*Figure 2*).

The aging HIV patient has an increased risk of chronic diseases compared with non-infected adults. More prevalent co-morbidities in people living with HIV include

Box 2 Typical multimorbidity combinations, or clusters, in high-income countries

Cardiovascular: coronary heart disease, cardiac insufficiency, stroke, hypertension, diabetes, dyslipidaemia, kidney problems

Psychiatric multimorbidity with alcohol and substances abuse, depression, personality disorder: alcohol-induced liver disease or hepatitis C, often in combination

Falls, frailty, Parkinson's disease, depression, cognitive deficits, social isolation

Chronic obstructive pulmonary disease, depression

Pain, depression, anxiety

Frailty, dementia, depression

The severity of the individual diseases can differ greatly between individuals. This may relate to social factors (e.g., social support and caregiver involvement in health management) that influence disease development

CVDs, kidney and liver diseases, cancer, and cognitive impairment (39). In addition, HIV-associated tuberculosis poses an additional risk for people living with HIV to develop post-tuberculosis chronic lung disease, such as fibro-cavitation and bronchiectasis, leading to a COPD-type disease often referred to as tuberculosis obstructive pulmonary disease (TOPD), and, if hypoxia is present, pulmonary hypertension, cor pulmonale, and right heart failure (17).

GDP per capita and MM

MM prevalence shows a positive relationship with gross domestic product (GDP) per capita (10). For example, Switzerland has a GDP per capita of 80,189 USD in 2017 and belongs to the 30 HICs with a mean 66.1% MM prevalence in the elderly population (over 65 years) (26). South Africa, a middle-income country, has a GDP per capita of 3,589 USD and a MM prevalence of 30.1% in the elderly population (in 2013) (10). In South Africa, the risk of chronic disease and MM increases with increasing income (40). The relationship between MM and GDP is, however, subject to large population-specific differences in socio-economic status within countries (41). The risk of MM is higher in the highest income subpopulation of the low-income country Bangladesh (6), whereas lower income associates with higher MM rates in Scotland (41). All available studies show higher MM risk in subpopulations with higher deprivation levels (40).

NCDs are increasing in LMIC subpopulations with increasing socio-economic status (42). In SSA, improving socio-economic status enhances the risk of CVD as risk factors become more prevalent. Epidemiological transitions and changes in diets and unhealthy processed foods are affecting rural and poor urban communities in SSA (43-45). These

dietary changes are income-related and associated with main CVD risks, diabetes, obesity, and hypertension. The impact of change in income is not just affecting adults. Higher-income communities in Africa reveal enhanced obesity and other CVD risk factors, even in school children (46-48).

Health transition and MM

LMICs are subject to a rapid emergence of new patterns and trends in MM disease in the form of a health transition to NCDs (49). Combined with the high rates of HIV, tuberculosis and malaria (the top three infectious chronic diseases), this transition has led to the so-called colliding epidemics of communicable and NCDs in LMICs (also referred to as the double burden of disease), especially in SSA (50). Within SSA there are regional differences in the pace of the health transition and the underlying distributions of age, sex and socioeconomic factors (51). However, the double burden of communicable and NCDs has led to new multimorbid disease constellations of co-occurring communicable and NCDs that are not prevalent in HICs (*Box 2*).

At the beginning of this decade, multiple reports from Africa described the colliding epidemics. In response to this, the WHO developed a practical policy proposal for primary health care. The aim of this policy was to harness the potential for primary care clinics in SSA to prevent and treat NCDs within the primary care tuberculosis/HIV programs (52). Reports from India have highlighted an additional burden—the triple burden of disease—affecting the population and general health care system: Reproductive health-related diseases such as haemorrhage, sepsis abortion complications, and pre-eclampsia/eclampsia were leading to increased maternal mortality (53). In addition, late maternal deaths due to CVDs have been

Box 3 Drug-drug and drug-disease interactions

Interactions within a patient have three basic elements (60):

Drug-drug interactions (pharmacokinetic interactions): interactions between drugs are broadly covered scientifically, with extensive databases

Drug-disease interactions (pharmacodynamic interactions): the medication for one disease is harmful for another disease of the patient (e.g., anticoagulation and bleeding)

Disease-disease interactions: the patient's diagnostic and treatment process changes due to the simultaneous presence of two or more diseases

declared as a neglected responsibility and are due to cardiac diseases in maternity such as peripartum cardiomyopathy (54,55). The Department of Health in South Africa has also referred to a quadruple burden of disease, defining four colliding epidemics. This four-way collision comprises, firstly, communicable diseases (HIV and tuberculosis), second, NCDs, third, maternal, new-born and child health-related morbidity and mortality, and, finally, interpersonal violence and injuries (56).

Rapid urbanization and climate change add another level of complexity to global health. More than half of the world's population live in urban areas of cities and 21 of the 30 fastest-growing cities are on the African continent (57). As mentioned above, urbanisation may lead to changes in diet and exercise, but also increases the risk of infectious diseases such as HIV, tuberculosis, Dengue, Zika, and many others. Causes are multifactorial from overcrowding and poor living conditions, violence and abusive behaviours, to health risks due to climate change that affects quantity and quality of food and water, increased air pollution, and alteration of pathogens and vector-borne diseases (58).

MM and interactions between diseases and drugs

The emergence of new combinations of co-occurring health issues arising from the double-to-quadruple burdens of disease also leads to increasing complexity and risk in MM management and healthcare (50,59). This relates to the potentially harmful effects of drug-drug and drug-disease interactions (DDIs, *Box 3*) (61). Limited evidence-based guidelines for MM (62), even for more prevalent forms of MM (60), enhances the reliance upon clinical guidelines that are intended for the treatment of single diseases (63). These guidelines do not adequately address the combined and cumulative risk of DDIs or adequately guide the clinician through the decision-making uncertainties and conflicts when trying to reconcile potentially harmful DDIs with a

suitable therapeutic strategy personalized to the patient's specific disease combination (64). Typical conflicts include concurrent bleeding (e.g., gastrointestinal, head injury) and anticoagulation (e.g., arterial fibrillation, pulmonary embolism), chronic kidney disease and metformin therapy for diabetes, steroid therapy (e.g., prednisone) and hypertension or diabetes.

Physicians and nurses often consider the challenges presented by DDIs as MM in the true sense (65). For example, in South Africa, DDIs may include HIV-infection with increased risk of CVD (66). The incidence of HIV-associated dilated cardiomyopathy prior to initiating ART was 15.9/1,000 per annum and the prevalence of HIV-associated pulmonary hypertension 1.6% to 5.0% (67). HIV-infection also amplifies the risk for ischaemic heart disease. HIV-associated dilated cardiomyopathy is even considered a criterion for WHO stage IV disease (also referred to as "AIDS") (68). Besides increased cardiovascular risk in HIV-infected individuals compared with the general population in HICs and LMICs, ART may further aggravate the risk of CVD (67,69,70). This may be due to direct adverse drug reactions or via associated dyslipidaemia and insulin resistance. *Table 1* summarizes the main classes of antiretroviral drugs, their effects on lipid and glucose metabolism, and the potential for contributing to the risk of CVD (67,71). In daily clinical routine, these complexities may diminish because the diseases aggregate in typical MM clusters (*Box 2*) (72,73). It should be noted that some DDIs effects may be protective, for example, sickle cell anaemia may provide protection against severe malaria (74,75). The most comprehensive guidelines to manage the complexity of MM in HIV-infection are the European AIDS Clinical Society Guidelines for treatment of HIV-infected adults (76).

Integrated care for MM in LMICs

In countries like South Africa, demographic change is

Table 1 Main classes of antiretroviral drugs and their impact on lipid and glucose metabolism and coronary artery disease

Drug class	Antiretroviral	Effects on lipids*	Effects on glucose*	Impact on coronary artery disease
Nucleos(t)ide reverse transcriptase inhibitors (NRTIs)	Abacavir	Dyslipidemia ⁺	No effect	Possible association with increased risk for MI (controversial results)
	Azidothymidine	Dyslipidemia ⁺⁺	Insulin resistance ⁺	No association with increased risk for MI
	Emtricitabine	Dyslipidemia ⁺	No effect	No association with increased risk for MI
	Lamivudine	Dyslipidemia ⁺	No effect	No association with increased risk for MI
	Stavudine	Dyslipidemia ⁺⁺	Insulin resistance ⁺	No association with increased risk for MI
	Tenofovir	Dyslipidemia ⁺	No effect	No association with increased risk for MI
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz	Dyslipidemia ⁺⁺	No effect	No association with increased risk for MI
	Etravirine	Neutral effect	No effect	No data available
	Nevirapine	Dyslipidemia ⁺	No effect	No association with increased risk for MI
	Rilpivirine	Neutral effect	No effect	No data available
Protease inhibitors (PIs)	Amprenavir + ritonavir	Dyslipidemia ⁺⁺⁺	Insulin resistance ⁺	Cumulative exposure independently increased risk for MI
	Atazanavir + ritonavir	Dyslipidemia ⁺	Insulin resistance ⁺	Possible association with coronary artery plaque
	Darunavir + ritonavir	Dyslipidemia ⁺	Insulin resistance ⁺	No data available
	Indinavir	Dyslipidemia ⁺⁺	Insulin resistance ⁺⁺⁺	Controversial results
	Lopinavir + ritonavir	Dyslipidemia ⁺⁺⁺	Insulin resistance ⁺⁺⁺	Cumulative exposure independently increased risk for MI
	Saquinavir	Dyslipidemia ⁺	Insulin resistance ⁺	No association with risk for MI
	Tipranavir + ritonavir	Dyslipidemia ⁺	Insulin resistance ⁺	No data available
Integrase inhibitors (INSTIs)	Dolutegravir	Neutral effect	No effect	No data available
	Elvitegravir	Neutral effect	No effect	
	Raltegravir	Neutral effect	No effect	
Entry inhibitors	Maraviroc	Neutral effect	No effect	No data available

Adapted from Thienemann *et al.* 2013 (67). *, Dyslipidemia defined as increased total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglycerides and decreased high-density lipoprotein cholesterol (HDL); +, weak effect; ++, moderate effect; +++, important effect. MI, myocardial infarction.

interacting with transitional change. The shift towards an increasing elderly population may add to the double burden of disease of communicable and NCDs (77,78). These changes require an adequate response for specific multimorbid populations. In 1978, the Declaration of Alma-Ata was the first international attempt by the WHO to adopt the primary health care model to promote health for all (79). However, many LMICs were unable to provide universal access to health care. By the end of the last century the advent of the three largest infectious epidemics HIV, tuberculosis and malaria were cause and consequence of this failure (80). The tremendous global response to

the HIV epidemic ensured that programmatic HIV and tuberculosis clinics were established to fight the epidemics. In the United Nations General Assembly 2016, the international community adopted a declaration to end the HIV epidemic by 2030 and to “take HIV out of isolation” making the Declaration of Alma-Ata more important than ever with the re-integration of HIV and tuberculosis into the primary health care model (81). According to the United Nations, integrated primary health care services shall include “HIV, tuberculosis, viral hepatitis, sexually transmitted infections, NCDs, including cervical cancer, drug dependence, food and nutrition support, maternal,

child and adolescent health, men's health, mental health and sexual and reproductive health, and to address gender-based and sexual violence" (81).

In recent years, the integration of tuberculosis and HIV services has been a major focus of research globally. Tuberculosis-HIV service integration can occur along a continuum, from encouraging referral between services to intensified screening for co-infection and full-service integration in one location provided by a single team. South Africa has made substantial progress in the integration of tuberculosis and HIV services. Many clinics in the country now offer a further level of integration that includes screening and management of sexually transmitted infections and NCDs (COPD, CVD, diabetes and cancer). Indeed, recent reports confirm data from tuberculosis and HIV services in South Africa, showing that patients who received dual tuberculosis and HIV treatment were significantly less likely to die or drop out when receiving care from one clinical team compared with non-integrated services (82). Despite this compelling evidence, barriers to integration remain: one of these is the fear that when vertical services are integrated with others or into the mainstream of health services, quality is compromised as services confront overall systems weaknesses (83). There is a strong need for integration efforts to focus on systems level strengthening for better outcomes in MM, especially with regards to supervision and support systems for primary health care (84). The concept of integration goes beyond the idea of bringing together two or more pre-existing vertical services to considerations of how to expand health service entitlements by introducing new services into the mainstream of healthcare. Integration of services does not necessarily have to occur through the channel of the primary health care system but may occur at every level of care or outside clinical centres.

Summary and conclusions

The confluence of demographic and health transitions and the emergence of new combinations of co-occurring diseases (in particular the double to quadruple burden of disease) in LMIC populations has altered the picture of complexity and risk that is commonly associated with MM management in HICs. This picture is better documented in HICs, providing therefore a vantage point from which to view the rapid emergence of different patterns and trends in MM disease in LMICs. The lack of scientific evidence and operationally applicable guidelines for managing DDIs

in HICs serves to highlight the challenges facing MM management LMICs.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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