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Living with uncertainty

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The persistence of highly endemic parasitic, bacterial and viral diseases makes individuals and populations vulnerable to emerging and re-emerging diseases. Evaluating the role of multiple component, often interacting, causes of disease may be impossible with research tools designed to isolate single causes. Similarly, it may not be possible to identify statistically significant treatment effects, even for interventions known to be effective, when multiple morbidities are present. Evidence continues to accumulate that nutritional deficiencies, bacterial, viral and parasitic coinfections accelerate HIV transmission. Inclusion of antiparasitics and other beneficial interventions in HIV-prevention protocols is impeded by reliance on inappropriate methodologies. Lack of full scientific certainty is not a reason for postponing safe, cost-effective measures to prevent irreversible damage.

Old burdens, new challenges

Understanding the origins and trajectories of emerging diseases requires an appreciation of the ecologies of human and microbial communities. The persistence of highly endemic parasitic, bacterial and viral diseases makes individuals and populations vulnerable to emerging and re-emerging diseases. Standard research tools are often inadequate for demonstrating those interactions because they are intended to isolate single factors. This opinion article addresses the epistemological and methodological obstacles to understanding disease interactions and developing integrated health policies, with particular reference to the failure of HIV-prevention policy in sub-Saharan Africa (SSA).

The problem of AIDS in multiburdened populations

The most severe, generalized epidemics of HIV/AIDS developed in SSA in populations already burdened with multiple parasitic, bacterial, viral and nutritional diseases. HIV-prevention policy in the region has failed because it neglects individual and population vulnerability generated by those multiple disease burdens. Prevention policy is based instead on the presumption that differences in sexual behavior explain 50-fold differences in HIV between parts of SSA and the rest of the world. That notion is not even plausible, and yet it remains an obstacle to epidemiological inquiry into the multiple component causes of the epidemic [1].

By the late 1980s, discourse on AIDS in Africa and HIV prevention came to be dominated not by epidemiologists but by social scientists who emphasized sexual behavior almost exclusively. Over the past 30 years, considerable evidence has accumulated regarding the ecology of AIDS epidemics and recent events might suggest a growing understanding of the need to integrate programming for HIV and endemic diseases. Faced with little success in HIV prevention and plateauing funding, Joint United Nations Program on HIV/AIDS (UNAIDS) Director Michel Sidibé speaks of 'taking AIDS out of its silo'. The US government recently launched a Global Health Initiative and restructured the Centers for Disease Control and Prevention with a Center for Global Health that includes HIV/AIDS and malaria, tuberculosis, and neglected tropical diseases under one director. Both the focus and the structure of such a center could encourage integrated approaches to disease control and prevention. Global awareness of AIDS has also brought unprecedented attention to neglected diseases in Africa and other poor regions, and there is increasing discussion of the dual epidemics of tuberculosis (TB) and HIV and the challenge of malaria with HIV. Nevertheless, although most government budgets can provide little support for endemic disease priorities and basic health services, donors restrict AIDS spending to a narrow range of activities, almost all associated with anatomical or behavioral aspects of sex. There has been little change in the behavioral focus of HIV prevention or the allocation of AIDS funding to integrated disease control programs [2–5].

Individual risk and epidemics

AIDS discourse about Africa and HIV-prevention policy are derailed by confusion over what Rose calls 'causes of cases and causes of incidence' [6]. Heterosexual HIV transmission is a rare event, with less than 0.001 risk of transmission between otherwise healthy adults [7]. Individual risk factors that are associated only with proximate cause do not fully explain why one individual becomes infected and another does not, nor do they explain why one population has higher incidence than another.

Sex, although an important proximate cause of HIV infection, has been a red herring, distracting attention from biological and environmental factors in SSA that increase individual vulnerability and shift the entire distribution of risk for whole populations. Early mathematical modeling of heterosexual HIV epidemics generally assumed a constant, universal per-contact transmission risk, or one-risk-fits-all, so that infection appeared to depend only on number of sexual contacts and prevalence (likelihood of contact with an infected person). The modelers essentially solved for the independent variable, number of sex acts, which necessarily would mirror incidence. Recent modeling varies transmission risk over time, incorporating what is known about viral load fluctuation over stages of

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Box 1. The distraction of sexual behavior

Since the late 1980s, efforts to identify peculiar sexual behaviors to explain the high prevalence of HIV have dominated social science research on AIDS in SSA. Preoccupation with sexual behavior is fueled by long-held Western notions that there is something exotic and extraordinary about African sexuality. Explicit characterization of African behavior as anomalous was common in earlier works on AIDS in Africa [54–58]. Recent works still suggest that Africans – in their sexual behavior and in interpersonal relations more generally – are not like people elsewhere [59].

In all populations, certain sexual behaviors are associated at the individual level with higher risk of HIV infection, including early sexual initiation, premarital sex, extramarital sex, having multiple partners, alcohol use with sex and unprotected sex. From the beginning, however, cross-national surveys have consistently shown that there is no correlation between rates of those risky sexual behaviors and prevalence of HIV [60–63]. Survey evidence demonstrates that risky behaviors are, if anything, less common in SSA than in Europe and North America, where national rates of HIV are far less than 1% [11,12,64–66].

In response to the flood of empirical evidence, proponents of a behavioral explanation argue that high HIV rates are due to higher prevalence of concurrent (overlapping) partnerships in SSA than in Europe and North America and that such concurrency accelerates the spread of HIV. Although both assertions have been shown to be incorrect, this concurrency hypothesis was quickly accepted as the conventional wisdom and incorporated into HIV-prevention programming, particularly in southern Africa, and is still promoted by UNAIDS [51]. The principal supporting articles for the hypothesis abound with numerical reporting errors, conflation of multiple partnerships with concurrent partnerships, failure to provide available comparative data for other regions, and frequent citation of non-representative samples and non-comparable data [64]. Recent nationally representative surveys in SSA, using the methodology approved by UNAIDS to measure concurrency, find its prevalence as low as or lower than in the US or Europe [66].

The concurrency hypothesis relies on an agent-based stochastic simulation model that proponents claim shows that concurrent sexual relations spread HIV more rapidly than sequential relations. The model, however, achieves those results only by using extremely unrealistic assumptions, including a per-act transmission rate almost 100× the consensus rate [7] and daily sex with every partner – up to four partners. Without those assumptions and exaggerated rates of concurrency, the model can produce only trivial difference in HIV infection. Subsequent models with realistic transmission rates, frequency of sex and rates of concurrency produce simulated epidemics that move to extinction either gradually [11] or quickly [12]. Clearly, HIV epidemics in SSA have grown rapidly and reached high prevalence. The emphasis on heterosexual behavior has eclipsed not only the role of endemic cofactors that increase heterosexual and vertical transmission but also accidental blood exposures (medical, cosmetic or drug-related) and homosexuality, which also contribute to prevalence in SSA.

infection. Transmission of HIV is dose-dependent, with very low probability when viral load is low [8,9]. For otherwise healthy persons, viral load is generally high in the early weeks of infection and drops to very low levels until the onset of AIDS [7]. Antiretroviral treatment (ART) is now a primary tool of HIV prevention because ART lowers viral load [10].

Models that incorporate variations in viral load by infection stage show that sexual behavior alone cannot explain HIV epidemics [11,12]. Viral load is affected by more than just stage of infection. Other biological characteristics of persons transmitting and persons acquiring infection affect risk. Across the population those vulnerabilities increase prevalence because the entire distribution of infection risk shifts due to widespread endemic factors [6,13]. Consequently, behavior-change programs, which do not address the significant relative risks that determine levels of HIV in multiply-burdened populations, have not had much effect on HIV prevalence in SSA (Box 1).

Biological cofactors of HIV transmission

The behavioral paradigm is a radical departure from standard epidemiological inquiry that considers multiple component causes. Numerous environmental factors affect health in SSA, including food security, access to healthcare, condition of housing, protection from vector-borne diseases, water supply and sanitation. Although HIV is not a commensal, it is not an especially virulent pathogen transmitted sexually, indicating that the rapid spread of HIV in Africa is an 'accident of susceptibility'. Defects in host immunity, mechanical or biochemical, [14] that are prevalent in SSA have a plausible causal association with HIV transmission or acquisition. Moreover, modeling, observational studies and randomized controlled trials (RCTs) have provided evidence of the interaction of HIV with those diseases and conditions.

Nutritional deficiencies

Iron-deficiency anemia, protein–energy malnutrition and vitamin-A deficiency are especially potent in impairing immune response. The effect of nutritional deficiencies on viral load, viral shedding, and vertical and sexual transmission of HIV are demonstrated in numerous studies [15–20], and the mechanisms by which nutritional deficiencies increase disease vulnerability are well understood. It has been difficult, however, to demonstrate the impact of particular deficiencies for enhancing transmission or acquisition of HIV, most probably because in populations with multiple morbidities, there is considerable trial 'noise'. Trials of vitamin A supplementation for HIV-infected pregnant women reveal the difficulty of attempting to isolate one factor in a complex terrain. Observational studies indicated that women who were deficient in vitamin A were more likely to transmit HIV to their infants [20], but most trials of vitamin A supplementation failed to demonstrate a statistically significant difference in newborn infection [21], although one trial supported the hypothesis [19]. Erroneously, some concluded that it is pointless to provide supplements to pregnant, vitamin A-deficient, HIV-infected women, in spite of known benefits of supplementation for women's health. Trial design permits only the conclusion that the intervention is or is not the silver bullet. The trial cannot generally evaluate partial solutions or contributing causes.

Malaria

Malaria interacts with HIV in many ways that are well summarized in the literature [22–24]. Malaria increases viral load, and HIV increases malarial parasitemia, placental malaria, infant malaria and anemia in both HIV– and HIV+ infants with HIV+ mothers, and causes more severe malaria, more anemia, loss of immunity, more preterm births and more intrauterine growth retardation

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