

Integrating Demographic and Epidemiological Approaches to Research on HIV/AIDS: The Proximate-Determinants Framework

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This article presents a conceptual framework for the study of the distribution and determinants of human immunodeficiency virus (HIV) infection in populations, by combining demographic and epidemiological approaches. The proximate-determinants framework has been applied extensively in the study of fertility and child survival in developing countries. Key to the framework is the identification of a set of variables, called “proximate determinants,” that can be influenced by changes in contextual variables or by interventions and that have a direct effect on biological mechanisms to influence health outcomes. In HIV research, the biological mechanisms are the components that determine the reproductive rate of infection. The proximate-determinants framework can be used in study design, in the analysis and interpretation of risk factors or intervention studies that include both biological and behavioral data, and in ecological studies.

Studies of the distribution and determinants of HIV infection in populations have included a wide range of factors that may affect the risk of transmission. Comparative studies, such as the Joint United Nations Programme on HIV/AIDS (UNAIDS) 4-city study to explain differences in the spread of HIV in urban Africa [1] and efforts to explain the conflicting outcomes of intervention trials in Uganda and Tanzania [2], have included sociobehavioral, epidemiological, and biomedical factors. In addition, the importance of the role of underlying socioeconomic and cultural determinants has been increasingly acknowledged, and contextual variables have been receiving more attention in epidemiological research on the distribution and determinants of HIV and other sexually transmitted infections (STIs) [3]. Increasingly, descriptive and analytical

models have used both group-level variables and individual characteristics [4]. The increasing number of population-based surveys that have collected both biological and interview-based information on a large number of variables will allow more-extensive analyses of the determinants of HIV infection, by use of multivariate analytical methods [5].

Collection, analysis, and interpretation of data need to be guided by a conceptual framework that explains the hierarchical and nonhierarchical associations between the different variables. Demography and epidemiology are the 2 disciplines most concerned with the population-based study of the distribution and determinants of disease and mortality. Demographers and epidemiologists have different approaches with regard to study methodology, interpretation of data, and analysis and subsequent design of health interventions [6, 7]. In sociology and, notably, in demography, conceptual frameworks have been developed for the study of social, environmental, and biological determinants of fertility and mortality. In this article, we present a conceptual framework for the study of the distribution and determinants of HIV infection, based on the proximate-determinants framework used in demographic studies of the determinants of fertility and child survival.

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PROXIMATE-DETERMINANTS FRAMEWORK

Demography has its roots in the social and behavioral sciences. It is concerned with the size, composition, and distribution of populations and the changes of these characteristics over time [8]. The primary objects of demographic inquiry are fertility, mortality, and migration, and the significance of quantitative analysis is overriding. Like epidemiologists, demographers have been more comfortable with data and methods than with concepts and theory. In demography, the emphasis is on understanding aggregate processes, but attention also has been given to the implications of these processes for individuals [9]. Much of demography is focused on understanding the socioeconomic and sociocultural forces underlying population processes. The branch of demography concerned with health and mortality has been referred to as “biodemography.” In the study of fertility and mortality, conceptual frameworks used in demography have paid more attention to biological processes that link society to health outcomes than have those used in most other social sciences [6, 10].

Epidemiology has its roots in the biomedical sciences and relates to the distribution and determinants of diseases, with the ultimate purpose being the control and prevention of health problems. Much like demography, epidemiology is essentially an applied discipline. It does not have an internally structured body of theory, and its principal theoretical components are its complex of methods [11] and research objectives [12]. Most epidemiological studies are explicitly or implicitly guided by biomedical theories.

The epidemiology of individual risk factors has been the dominant paradigm in past decades, with a focus on behaviors and exposures [13, 14]. In recent years, several epidemiological journals have published the lively debate on the predominance of risk-factor epidemiology and the role of epidemiology in public health (e.g., in the *International Journal of Epidemiology* [15, 16]). This debate is driven by several factors, including the need for new models appropriate for the study of infectious diseases, rather than chronic diseases, and rapid developments in molecular biology, which some epidemiologists feel may compartmentalize the discipline [17] or pull epidemiology further in the direction of clinical medicine [18]. At the same time, social epidemiology—that is, the branch of epidemiology that studies the social distribution and social determinants of states of health [19]—appears to be gaining some prominence.

Fertility. Almost half a century ago, Davis and Blake [20] developed an analytical framework for the comparative study of the sociology of fertility. The key to the framework was a set of “intermediate variables through which any social factors influencing the level of fertility must operate” [20, p. 211]. Three groups of intermediate variables were identified: factors affecting exposure to intercourse, factors affecting exposure to conception, and factors affecting gestation and successful de-

livery. Each of these biological factors can be influenced by a set of behavioral intermediate variables that are directly linked to the biological factors.

This framework was further developed by Bongaarts [10, 21], who replaced the term “intermediate variables” with “proximate determinants.” He developed a simple statistical model in which any variation in the level of fertility, between populations or over time, can be decomposed into variations in the proximate determinants of marriage (exposure to sexual intercourse), postpartum infecundity (associated with lactation and abstinence), induced abortion, and contraceptive use. In this model, a level of fertility in the absence of deliberate fertility-control measures, called “natural fertility” or “total fecundity,” is hypothesized [10]. Recently, Stover [22] proposed to replace the term “total fecundity” with “potential fertility,” after the introduction of an index of natural sterility into the model. Potential fertility is ~21 births/woman (20-month intervals between births, during 35 years of reproductive life) and, at the level of populations and societies, is reduced by the operation of the proximate determinants.

The proximate-determinants framework for fertility has been used extensively for a variety of purposes, including studies of the determinants of fertility, evaluation of factors affecting fertility trends, and comparative analyses. Its main use has been with decomposition analysis, using a simple statistical model for the relationship between the proximate determinants and fertility [21, 22]. The application of the framework to the study of fertility has been successful because it deals with a relatively simple process consisting of events that take place in a fixed order—that is, intercourse, conception, gestation, and birth.

Child survival. Using the proximate-determinants framework for fertility as a basis, Mosley and Chen [6] developed a conceptual framework for research on child survival, to facilitate and promote interdisciplinary communication and to lay a theoretical groundwork for further investigation. The basic feature of the Mosley-Chen framework is the specification of a set of proximate determinants through which all socioeconomic determinants must operate in order to influence the risk of morbidity and mortality among children. Van Norren et al. [23, 24] further specified the proximate determinants and more clearly distinguished the biological factors from the mixed behavioral-biological proximate determinants. They argued that, analogous with the work in fertility research by Davis and Blake [20], the proximate determinants have to be both biological and behavioral and, therefore, act as a hinge between the social and biological systems. In the original Mosley-Chen framework, the proximate determinants were either biological or behavioral or both.

A quantification of the effects of the proximate determinants on child health and its demographic outcome (i.e., mortality) may be crucial to furthering our understanding of the deter-

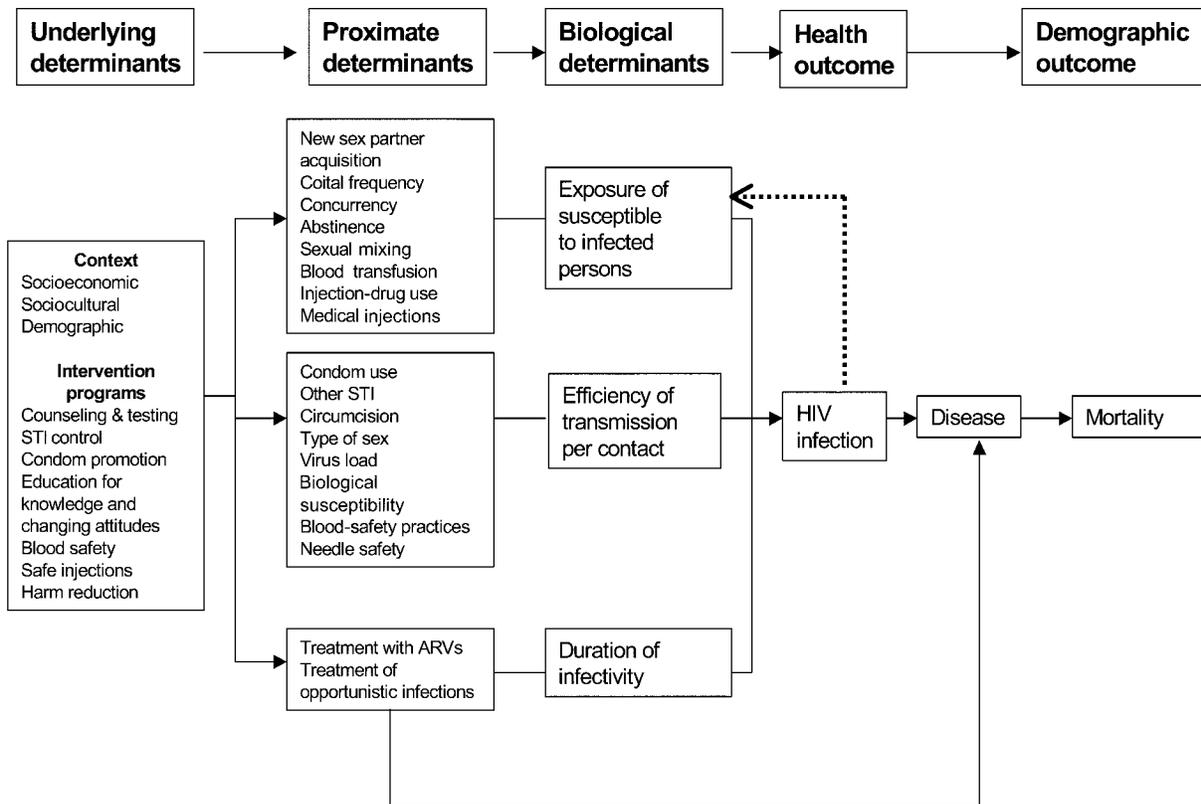


Figure 1. Proximate-determinants conceptual framework for factors affecting the risk of sexual transmission of HIV. ARVs, antiretrovirals; STI, sexually transmitted infection.

minants of child survival and to the design of more-effective health programs. Mosley and Becker [25] developed an analytical model, based on the Mosley-Chen framework [6], to show how multiple disease conditions interact through mechanisms of competing risks and acquired frailty, resulting in high levels of childhood mortality. Becker and Black [26] expanded this model to include efficacy and coverage of interventions and developed a statistical model to measure the relative importance and size of the effects of changes in the proximate determinants that may affect child health and mortality. As was done with the determinants in the framework for fertility research, Becker and Black determined a “natural” level of disease incidence and case fatality that was based on potential disease incidence and case fatality in the absence of factors such as clean water, sanitation, breast-feeding, or good delivery practices. Interventions were classified into those that reduced disease incidence, frailty, or case fatality. Multiple disease conditions were assumed to interact through the mechanisms of competing risks and acquired frailty, resulting in high child mortality. Simulations showed how certain interventions, such as measles vaccination or reduction of vitamin A deficiency, potentially have a large effect on child survival. Because of the much greater complexity of the factors affecting child survival, compared with those affecting fertility, the use of the proximate-determinants framework in research on child survival has been limited to guidance in questionnaire design and interpretation of results (e.g., the global Demographic and Health Surveys program; ORC Macro, Calverton, MD).

HIV/AIDS. Figure 1 shows the levels of the proximate-determinants framework for the determinants of HIV infection, which links the social and environmental system on the left with the biological system on the right. The sociocultural and economic determinants and program characteristics influence the proximate determinants, which, by definition, have both behavioral and biological components. The proximate determinants have direct links to the biological determinants, which affect the rate of new infection (which, in the case of HIV infection, continues to persist), determine the prevalence of infection, and lead to disease and premature death. The emphasis of the framework is best viewed as an explanatory sequence at the population level, with the underlying social, economic, and environmental factors leading to exposure, transmission, infection, disease, and death. The framework is much closer to the framework for fertility than to the framework for child survival.

The underlying social, economic, and environmental determinants must operate through proximate determinants in order to affect the biological outcome. The distinction between underlying and proximate determinants is important for the con-

mate-determinants framework in research on child survival has been limited to guidance in questionnaire design and interpretation of results (e.g., the global Demographic and Health Surveys program; ORC Macro, Calverton, MD).

ceptualization of pathways through which underlying determinants, including interventions, may affect infection. For the determinants of incidence (or prevalence) of HIV and other STIs, statistical analyses that indiscriminately include underlying and proximate determinants in the same model and that do not take advantage of the multilevel structure outlined in the framework will produce estimates likely to be difficult to interpret. A careful examination and, if possible, statistical evaluation of pathways will improve estimates of the associations between determinants and transmission of HIV infection.

The biological determinants for transmission of HIV are factors that affect the reproductive number of an infection, defined as the average number of secondary cases that arise from any new case of infection [27]. Models of transmission suggest that this reproductive number is determined by the product of 3 biological mechanisms: the rate of contact between susceptible and infected persons, the efficiency of transmission during exposure between susceptible and infected partners, and the duration of infectivity [28, 29]. Reducing any of the 3 biological factors will reduce the incidence of HIV infection, and reducing any of the factors to 0 will stop transmission of HIV completely.

The proximate-determinants schema described in figure 1 is deliberately simple and is meant to outline a process, by moving conceptually from underlying determinants on the left to mortality on the right. The schema does not attempt to show either the complex interactions that may occur between the underlying, proximate, and biological determinants or the feedback mechanisms that link outcomes on the right with the determinants on the left. However, one critical feedback mechanism, prevalence of HIV infection, is included in the schema because of its importance in estimating the probability of exposure of susceptible persons to infected persons. This particular feedback mechanism is peculiar to infectious-disease epidemiology and, thus, is not a feature of the conceptual frameworks discussed earlier for fertility and child survival.

The infectious virulence of the pathogen, the amount and concentration of pathogens in body fluids (e.g., semen, genital fluids, and blood), and the biological susceptibility of the person exposed to infection have been identified as biological mechanisms determining the efficiency of transmission [3, 28]. Physical barriers or practices that limit the effective “dose” of exposure to HIV (e.g., condoms limiting exposure to infected genital fluids, gloves limiting exposure to infected blood, and bleach limiting exposure to infected needles) are included as proximate determinants of the efficiency of transmission, rather than as factors affecting exposure. Increasingly, research will distinguish between factors affecting host infectiousness, factors influencing biological susceptibility, and factors influencing both [30]. For example, ulcerative STIs may increase both host infectiousness and the biological susceptibility of the person exposed to HIV. The duration of infectivity is based on the

natural history of infection and may be divided into an acute initial phase during which virus loads are high, a subsequent phase during which virus loads decrease, and a final phase during which virus loads will increase again. All 3 biological determinants are influenced by the proximate determinants.

The primary focus of the framework is on the most common mode of transmission of HIV (i.e., sexual transmission). In general, indicators measuring sexual behavior are self-reported and subject to multiple reporting biases. Individual interviews provide only limited information on factors affecting the efficiency of transmission, particularly if interviews of sex partners are not linked and if the HIV status of respondents is unknown (table 1). Data for self-reported condom use are relatively easy to obtain by means of surveys on sexual behavior, but the effect of condom use on transmission efficiency is difficult to gauge without information on whether condoms are used during acts in which sexual contact is between infected and susceptible persons. Self-reporting of STIs is only marginally predictive of actual STI history, and asymptomatic infections further distort observed associations between self-reported cases of STI and transmission of HIV. Information on the prevalence of disease, obtained by use of biomarkers, is essential for measuring the true importance of coinfections. Of importance to note is that the incidence of STIs is affected by the same proximate determinants that affect the incidence of HIV infection; therefore, the prevalence of STIs may feed back into the proximate determinants. Treatment of STIs can affect this cycle and thus affect the incidence of HIV infection, as was found in Tanzania [2].

Insights into transmission of HIV via blood transfusion and injections also may be explored by use of the framework. Exposure to the risk of HIV infection is affected by the frequency of blood transfusions, unsafe injections in formal and informal health care settings, and the practice of needle sharing among injection drug users. The efficiency of transmission at exposure can be reduced greatly by the testing of donor blood for HIV and the selection of low-risk donors and by the bleaching of needles and syringes and can be reduced to 0 by the elimination of sharing of needles and syringes. Perinatal transmission is not included in this proximate-determinants model, to maintain simplicity, but a parallel proximate-determinants model for perinatal transmission could be developed. Perinatal exposure is determined by the infection status of the mother. The efficiency of perinatal transmission is determined by factors that include the virus load of the mother, the type of delivery, genetic susceptibility, birthing practices, and the use of anti-retroviral drugs.

The duration of infectivity is affected by the efficacy and coverage of treatment [3]. Although curative treatments generally shorten the duration of infectivity and may lengthen the life span, both the treatment of opportunistic infections and

Table 1. Information collected for proximate determinants of transmission of HIV, by surveys of households and at-risk populations.

Biological determinant, proximate determinant	Interview question(s)
Exposure of susceptible persons to infected persons	
Rate of acquisition of new sex partners per unit of time	No. of new and total partners in last month or last year (by type of partner); no. of commercial sex partners in last year
Frequency of sex acts within each partnership	No. of acts with each partner in last week or month
Frequency of concurrent partnerships	No. of partners in last month (or other short recall period) or start and end dates of partnerships
Patterns of mixing between different segments or strata of the sexually active population	Characteristics of recent partners (age, residence, education, etc.)
Abstinence	Age at sexual debut; sexual activity in last year or month; postpartum sexual abstinence
Blood transfusion	No. of transfusions received
Health care–related injections	No. of injections received in last year
Injection-drug use	Frequency of injection-drug use and sharing of needles
Efficiency of transmission	
Use of barrier methods (male or female condom, microbicides)	Condom use at last sex with each partner
Type of sex practices, such as anal intercourse	In general, questions not in surveys of general population but only in risk-group surveys (some asked about “dry sex”)
Other STIs (genital ulcers, HSV-2 infection, trichomonas, etc.) and treatment of STIs	Genital ulcers or genital discharge in last year, with treatment utilization; whether received treatment
Physiological characteristics of the host, such as circumcision status	Self-reported circumcision status
ART	Currently no questions
Injection drug use practices	Use of bleach or other methods when sharing needles
Duration of infectivity	
ART or treatment of opportunistic infection	Currently no questions

NOTE. ART, antiretroviral therapy; HSV-2, herpes simplex virus type 2; STI, sexually transmitted infection.

the use of antiretroviral drugs do not cure HIV infection; therefore, the duration of infectivity is increased. On the other hand, use of antiretroviral drugs may affect transmission efficiency by reducing virus load.

APPLYING THE CONCEPTUAL FRAMEWORK

In research on the determinants of STIs and HIV infection and in intervention studies, different levels of association within the framework need to be considered. These include the associations between the underlying determinants and disease incidence, the associations between the underlying and the proximate determinants, the associations between the proximate determinants and the biological mechanisms, and the associations between the biological mechanisms and disease incidence.

Risk-factor studies. Many studies have reported significant associations between the risk of HIV infection and underlying factors, including demographic (e.g., sex, age, marital status, mobility, and residence), socioeconomic (e.g., income, education, and occupation), and sociocultural (e.g., religion and ethnicity) characteristics of individuals [1, 3]. Similarly, there is ample evidence that several proximate determinants, such as number and type of sexual contacts, lack of condom use, or the presence of concurrent STIs, are important risk factors. Most studies focus on the individual level. Ideally, the pathways for the effect of underlying determinants on transmission of HIV can be examined by running separate statistical models

without and with the proximate determinants. Unfortunately, problems associated with the measurement of the proximate determinants preclude this kind of analysis. These problems include reporting biases, the need for fairly extensive data on mixing patterns, and information on HIV status [29].

Measurement problems equally affect studies that aim to assess the socioeconomic, demographic, and sociocultural determinants of proximate determinants, such as sexual behavior. Methods that determine patterns of underlying or contextual variables that can serve as markers of the proximate determinants are needed. In some cases, the use of data from studies that focus on places where people meet new sex partners may be possible. The mapping and epidemiological study of such places can provide important information on the proximate determinants [31]. Area characteristics or group variables also may help provide such data. Derived group-level variables that summarize the characteristics of individuals in the group (e.g., proportion of women working in the sex trade, median income in the population, and sex ratio in the area) and integral group variables (e.g., presence of bars in the area and social cohesiveness) also have been shown to be important underlying determinants [4, 32]. A special factor in the derived group variables is the average of the dependent variable (e.g., prevalence of HIV infection) within the group. Particularly relevant in the study of infectious disease is that the prevalence of disease in the group affects the probability that a given individual will

acquire the infection and may modify the effects of individual-level variables on the risk of infection [33].

Ecological comparisons, such as that in the UNAIDS 4-city study [1], aim to enhance our understanding of the large differences in the spread of HIV infection within sub-Saharan Africa. In the 4-city study, a uniform cross-sectional study design was used for all sites, and the analysis focused on the exploration of population-level effects of risk-factor profiles, which often are difficult to identify from individual-level analyses. The focus was mostly on the proximate determinants and biological outcomes. The only group-level measures used were aggregated individual-level measures (such as proportion with herpes simplex virus type 2 infection in each city or median age at first sexual intercourse). In ecological analyses, the proximate-determinants framework helps the interpretation of findings. It also helps researchers focus on differences in the underlying determinants, as was shown in a comparison between rural populations in Zimbabwe and Tanzania, where the largest differences were observed for variables related to cohabitation of spouses and mobility but not for indicators of sexual behavior [34].

Intervention research. Even though the conceptual framework is primarily designed for the study of the distribution and determinants of disease, it also can be used for intervention research, since interventions will have to influence ≥ 1 proximate determinant in order to affect transmission of HIV. The proximate determinants can be influenced by interventions, since the determinants are partly behavioral and, if changed, must have a biological effect. The framework increases the transparency of the pathways by which the components of a prevention program can be effective, by targeting the proximate determinants, and underscores the limited utility of program outcomes, such as increased knowledge of transmission, if an accompanying change in any of the proximate determinants does not occur. For example, an AIDS-prevention program (an underlying determinant) may aim to increase knowledge of the modes of transmission of HIV (another underlying determinant), delay sexual initiation (a proximate determinant of exposure to HIV), and increase condom use (a proximate determinant of the efficiency of transmission).

Grassly et al. [35] showed how the ultimate effect of an intervention in reducing risk of infection is determined by the socioeconomic setting and public health capacity. The epidemiological context determines whether such risk reduction translates into a measurable effect on the incidence rate of HIV infection. Four measures of the epidemiological context are proposed: the phase of the epidemic (characterized by the prevalence of HIV infection), the cofactor prevalence of STIs, mixing of the target population with other at-risk populations, and the sexual behavior of populations not targeted by the intervention. The epidemiological context is dynamic: 3 of these 4 measures are proximate determinants and can be changed by

interventions. The fourth measure (prevalence of HIV infection) appears as a feedback mechanism in the framework, affecting the probability of exposure, and will change as a result of changing incidence and mortality.

Similarly, Fishbein and Pequegnat [36] have argued that self-reporting of behavior can be valid and is an important measure for studying the efficacy and effectiveness of interventions that aim to change behavior. They argue that biological outcomes only are not sufficient, partly because data on incidence are difficult to collect and because measurement error can be a problem. Furthermore, successful programs targeting behavioral change, such as an increase in condom use, do not necessarily lead to changes in biological outcomes. The effect of a change in any 1 component of the reproductive rate of infection depends on the values of the other 2 parameters. For instance, if condom use increased as a consequence of a successful intervention, the effect of such an increase would depend on the extent to which condoms were used during sexual contact between infected and susceptible partners.

Statistical model. When proximate determinants change, can the effects on biological mechanisms and on the incidence of HIV infection be quantified? With an often very heterogeneous distribution of disease and risk behaviors within a population and an emphasis on the stage of an epidemic, the specific nature of current epidemics of STI and HIV infection seems to be less suited to the definition of natural incidence rates of STI and HIV infection, as was done for the respective outcomes in the models of fertility and child survival. The level and stage of an epidemic will affect the magnitude of the effect that a change in a proximate determinant has on the change in incidence of HIV infection. A statistical model would have to involve a complex feedback loop, with variable assumptions about the infectiousness of infected partners. In this case, the basic reproduction rate of infection is the best indicator of effect, as determined by the 3 groups of proximate determinants defined above. Mathematical models have been developed to study the dynamics of transmission of STIs and HIV in populations with different patterns of sexual behavior and levels of interventions, using assumptions about high and low levels for the components of the reproductive rate of infection (i.e., the biological mechanisms in the proximate-determinants model) [29]. No simple statistical formulas are available for the decomposition of changes in the incidence rate of HIV infection or STI into changes in the proximate determinants.

CONCLUSION

The proximate-determinants conceptual framework, developed for the comparative study of fertility and applied extensively in studies of fertility and child survival, is a useful conceptual framework for studies that include social and biological variables. The essential feature of the framework is the identification of a set

of proximate determinants, which are both biological and behavioral in nature and which affect 3 distinct biological determinants. In HIV and STI research, the biological determinants are the components of the basic reproductive rate of infection.

The framework can be used in study design, including the development of questionnaires and methods of measurement. In ecological analyses, the hierarchical nature of the framework helps in the assessment of complex relationships and differences between various types of underlying and proximate determinants. In individual-level analyses, it suggests pathway analysis as a tool for describing how underlying variables affect the risk of HIV infection. In addition, it encourages analyses that explicitly account for the effects of epidemiological context on the results of intervention studies.

Many research issues remain before we can better understand the distribution and determinants of HIV infection in the population in generalized epidemics. Little is known on how to best measure some of the underlying variables, at the individual or group level, and how to best take account of the effects of interactions between such variables. In this case, interactions are likely to be critical: for example, not only does the level of condom use matter but also which partners are using condoms with whom. Similar issues regarding measurement pertain to the proximate determinants. Their effects on the biological determinants are even more difficult to quantify, since the biological determinants can only be inferred, not measured directly.

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