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Developing and Evaluating Comprehensive HIV Infection Control Strategies: Issues and Challenges

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Abstract

As described elsewhere in this supplement, development of effective methods for prevention of human immunodeficiency virus (HIV) infection has proven to be more challenging than development of effective treatment for the disease. New strategies to control the HIV epidemic are urgently needed; this urgency creates interest in investigation of the possibility of using antiretroviral treatment in combination with other modalities to control the epidemic. This article summarizes current knowledge concerning prevention modalities in the context of the drivers of the HIV epidemic in specific communities, describes challenges in investigating test-and-treat strategies, and proposes research directions for addressing these challenges to investigate the impact of prevention strategies on mitigation of epidemics.

PREVENTING THE SPREAD OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Transmission of HIV can be impeded by decreasing infectiousness or reducing susceptibility. A focus on the former characterizes the current Centers for Disease Control and Prevention and President's Emergency Plan for AIDS Relief interest in "prevention with positives," a smaller group than at-risk HIV-uninfected persons [1]; biologic interventions have targeted both. For example, male circumcision has demonstrated a 60% reduction in risk among men exposed to HIV through heterosexual sex [2–4]. Antiretroviral therapy (ART) can decrease the infectiousness of mothers and the susceptibility of neonates, thus preventing perinatal transmission [5,6]. It can also reduce the susceptibility of recently exposed individuals as postexposure prophylaxis [7]. Other biomedical approaches under investigation include preventive vaccines [8], microbicides [9], and preexposure prophylaxis [10]. Studies of the effects of a range of behavioral interventions, such as reduction in the number of sex partners and use of condoms and clean needles, have also shown reductions in HIV transmission [11–14].

Because HIV load is a strong predictor of HIV transmission between discordant sex partners [15] and ART decreases viral load, expanded ART use may help mitigate epidemics by

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decreasing infectiousness. (reviewed in [16]). Interventions based on ART are likely to be expensive, but not all approaches are likely to be effective in all communities [17,18]. Nevertheless, even if ART alone is insufficient to control the spread of HIV infection in most settings, it might contribute significantly to the control of certain epidemics if it is used in conjunction with other prevention modalities, just as combinations of individual antiretroviral drugs enhance the overall treatment effectiveness. Therefore, the conditions under which ART interventions are likely to be cost effective must be investigated.

Prevention benefits at the individual and community levels

Prevention interventions can directly benefit persons receiving them and indirectly benefit the broader population. For example, male circumcision provides protective benefit to circumcised men and, more broadly, to their sex networks [19–23]. If male circumcision becomes sufficiently widespread, benefits at the level of the community should become detectable, with the degree of benefit depending on the proportion of men receiving male circumcision in a defined period [24]. The amount of benefit and the cost-effectiveness of male circumcision under differing scenarios can be investigated through mathematical modeling [20]. Similar community-level benefits may be realized with ART, resulting from reduced risk of transmission to sex partners (direct effect), as well as benefit to sexual networks (indirect effect) if enough potential source partners are treated. The impact on the spread of HIV infection may ultimately depend on many factors besides risk of transmission per contact; thus, total effect on the population cannot be predicted from the effect of ART on transmission alone.

The HIV epidemic among men who have sex with men (MSM) in industrialized countries proves these points. Individual randomized clinical trials and meta-analyses of these trial results have shown that programs for prevention of HIV infection can work at the individual level, but a systematic review of the incidence of HIV infection among MSM in western Europe, the United States, and Australia estimated that the mean incidence rate of 2.5% per year remained stable during 1995–2008 [25]. If such an incidence rate was present among a population of MSM 18–40 years of age, ~40% of MSM who are uninfected at 18 years of age will become infected before 40 years of age [25]. Thus, interventions apparently effective at the individual level are not having effects that are currently detectable at the population level. Although interventions may protect some individuals, they do not address the multiplicity of drivers of the epidemic or their interactions, which may change over time.

Characterizing a local epidemic

To assess population benefit resulting from an intervention, it is useful to find metrics that characterize epidemics in these populations. One proposed metric arising from a focus on communities rather than individuals is community-level viral load, which is often mentioned in the context of test-and-treat strategies, to reflect the notion that mean viral load describes potential for HIV infection to spread within a community. A study detected an association between mean viral load and incidence of HIV infection in a cohort of injection drug users [26]. This association became nonsignificant after ART became more widely available in the population, reducing mean viral load to <20,000 HIV RNA copies/mL. Furthermore, incidence increased from its nadir in 2004, with no associated increase in mean viral load [26]. Although intuitive and useful in some contexts, the reduction of the characteristics of an epidemic to a single metric may not be adequate for investigating ART as a way to control the epidemic. In fact, the impact of the amount of circulating virus depends on its distribution among infected persons and on their sex networks, neither of which is reflected in a population mean. HIV infection does not spread evenly throughout a community; it spreads through sex networks with varying transmission rates that depend on factors that may vary greatly across communities. Therefore, although incidence may well correlate with

a population mean viral load, it would probably also correlate with other epidemic features, such as prevalence of recent HIV infection, frequency of risky behavior, and nature of social and sex networks (eg, concurrency and rates of partner change). To be useful for developing prevention policy, all of these factors must be reflected in the metrics used. Oversimplification may lead to implementation of interventions that are inadequate to impact local epidemics favorably and may not be cost-effective. We believe that research should now be directed to establish ways to characterize epidemics in different settings for purposes of providing information required for developing and implementing cost-effective prevention strategies with the goal of controlling local epidemics.

THE ROLE OF TEST-AND-TREAT STRATEGIES IN CONTROLLING THE HIV EPIDEMIC: FORMULATING RESEARCH QUESTIONS AND STRATEGIES

The global HIV/AIDS epidemic is composed of interacting subepidemics, each influenced by a myriad of factors (eg, biological, behavioral, and cultural) in each affected community. Behavioral drivers of the epidemic include sex acts (eg, number, type, and positioning), serosorting, concurrency, sexual mixing, needle sharing, lack of condom use, and substance use [27–31]. Biological drivers of the epidemic include a variety of host-and viral-specific factors, such as viral load in anatomical compartments [15], disease and treatment status [32], sexually transmitted infections and other coinfections [33], circumcision for men [23], host haplotype [34], state of immune activation, and viral subtype and phenotype [35]. Societal and/or structural drivers of the epidemic include such factors as stigma and discrimination, poverty, criminalization, imprisonment, sex inequality, migration, homelessness, and lack of education [36–40]. Policies facilitating or inhibiting sex education, needle exchange, and condom promotion can also have an impact on the epidemic [41,42].

Effective (and cost-effective) strategies to control the HIV epidemic are likely to be those that address as many of the individual drivers of local epidemics as possible. A wide range of questions must be addressed to investigate both the levels of efficacy associated with prevention efforts under various epidemic conditions and their cost. What is the individual effect of test-and-treat strategies on the incidence of HIV infection in the presence of other ongoing prevention efforts? What is the combined effect of test-and-treat and other modalities? What are the synergies and potential negative interactions among modalities? What are the characteristics of the communities that would permit cost-effective deployment of a package of interventions, and how can we assess these characteristics? How do we tailor the package to local epidemic conditions?

These questions illustrate that the efficacy of a strategy such as test-and-treat can not be discussed in general but only in the context of a particular epidemic in a community and in the presence of other available prevention modalities. Biomedical research studies often try to isolate the effect of a particular intervention by holding all conditions as equivalent as possible except for the intervention under study. Test-and-treat strategies can be studied in this way; for example, randomizing different communities to either adding a test-and-treat strategy to standard of care or standard of care alone (standard of care might include male circumcision, postexposure prophylaxis, or behavioral interventions). Challenges arise because communities may vary in their responses to an intervention, and how best to make analytical adjustment for features associated with this variability may not be readily apparent. Although it may be valuable for policy makers to know the individual contribution of test-and-treat strategies, it may be even more valuable to know whether a package of interventions is capable of actually achieving epidemic control. In fact, the individual effect of test-and-treat strategies may be misleading in the absence of knowledge regarding important synergies or negative interactions among various prevention modalities. For

example, if the effective reproductive rate in a community were 2.0 (ie, an infected persons transmits infection to a mean of 2.0 other individuals during his or her infectious period), a single intervention that reduced this rate to 1.2 individuals would still leave a self-sustaining epidemic, albeit one that would stabilize at a lower prevalence. Combination of 2 interventions, however, could make the epidemic ultimately unsustainable in this community, even though sporadic cases may still arise from contacts with infected individuals either in or outside the area where the interventions are being used.

New paradigm for research on control of HIV epidemics

Realistic epidemic models must be based on understanding of how networks operate rather than on unrealistic assumptions, such as mass action (ie, probability of infection is proportional to the product of the number of infected persons and the number of susceptible persons). To predict whether an intervention will be successful, we must know how it impacts local networks. Although randomized studies can provide valuable information, simple randomized comparisons of outcomes, such as incidence, will not suffice. Mathematical models that account for the underlying mechanisms by which interventions work will be essential for determining which prevention strategies will be cost-effective in given communities.

Most HIV research to date has been based on randomized clinical trials or observational studies in which the units of observation have been the individual participants. Achievement of the described goals will require a shift in focus from individual-level research to communities and networks that will allow for the dynamics of an epidemic to be characterized. Of course, few if any truly closed communities exist; whether the focus is on a neighborhood with large numbers of MSM in the United States or on a village in Africa, some individuals will undoubtedly become infected from outside the community or network of interest. An important goal of prevention research must be to assess how much infection from outside the community can be tolerated without generating a self-sustaining epidemic in the community. For example, in many communities in the United States and Europe, persons whose only risk factor is heterosexual sex continue to acquire infection, but the local epidemic is not generally sustained in these networks; the main reservoirs appear to be in MSM and injection drug users. By contrast, in other areas of the world, heterosexual activity alone appears to sustain epidemics. To study the effectiveness of test-and-treat strategies does not require finding closed communities but rather communities in which a significant proportion of new infections occur from within the network of interest.

Need for research in basic science and quantitative methods

Accomplishment of epidemic control will require considerable innovation in a variety of scientific disciplines, from basic virology and laboratory science to network and epidemic modeling, along with innovation in design and conduct of clinical research studies. Examples of needed research include (1) characterization of virological and immunological events after infection so that reliable assays to determine duration of infection can be developed; (2) modeling of risk networks on the basis of partial data, such as that arising from contact tracing, uncertain egocentric data about behavior, and respondent driven sampling; (3) development of agent-based epidemic models built on the network models; and (4) performance of randomized or single-site studies that focus on communities and networks of transmission. It is also necessary to determine the type of information required for characterization of an epidemic that is sufficiently accurate to serve as a basis for designing effective prevention strategies, as well as the impact of imprecision in this characterization on conclusions regarding such strategies. The required information must surely include the size of the population at risk, the prevalence and incidence of HIV infection, distribution of plasma viral load, features of the local sex network (eg, degree and

concurrency), prevalence of sexually transmitted infection and other coinfections, ART coverage, and the capacity of local health care systems to provide treatment for HIV infection and other conditions.

Local epidemics and networks

As mentioned above, understanding sex networks and individual-level risk factors is required to inform effective prevention research and resulting policies [43,44]. Because universal test-and-treat strategies may be not be affordable in some settings, network analysis may help to identify cost-effective targets [45]. For example, network analysis may allow for the identification of core individuals or venues that represent important connections in the transmission network [46], and targeting these cores may decrease the effective reproductive rate. Determination of the benefit of identifying these cores and engaging them in prevention efforts is likely to be important for appropriate deployment of resources.

Social network analysis has been used to map epidemiologic links among individuals or groups with regard to such factors as kinship, socioeconomic status, or HIV risk behaviors [43,47,48], and molecular studies have used viral sequence analysis to identify potential HIV transmission networks. Specifically, analysis of similarity of HIV sequences among individuals [49–52] allows for inferences regarding transmission links across a population of HIV-infected individuals and has been used to document the episodic nature and high rate of transmission during recent infection [53,54]. These methods have also been used to evaluate how public health measures, such as contact tracing, can target a transmission network [55]. This molecular epidemiology of HIV is possible because of the enormous amount of genetic diversity in HIV isolates [56–58] owing to error-prone replication [59], host immune pressures [60,61], transmission bottlenecks, and epidemic dynamics [62]. This genetic diversity in a population determines the variety of HIV phylogenies observed among individuals and populations [62]. The next step in the use of social network analysis in HIV infection prevention is to define shared factors in these transmission networks, such as shared venues, behavioral risk factors, or demographic characteristics; the melding of these social and molecular tools [62] has great potential to define the sex and transmission networks underlying a local HIV epidemic. To realize the power of network analysis and obtain community support for it, however, requires addressing ethical and legal quandaries.

Social and legal issues

An important issue that impacts the ability to use network analysis is the presence of legal codes that may undermine the goal of universal testing. In 2008, the Joint United Nations Programme on HIV/AIDS Reference Group on HIV and Human Rights, recognizing this tension, recommended that governments develop evidence-based programs to reduce HIV transmission while protecting the human rights of both HIV-infected and uninfected persons, rather than “focusing attention on ineffective and potentially counter-productive provisions criminalizing HIV exposure and/or transmission” [63, p 2]. Policies that apply criminal sanctions to unintentional HIV transmission will tend to worsen the stigma associated with infection and create disincentives for voluntary HIV testing and shared responsibility for disclosure of HIV and sexually transmitted infection status. As of 2008, 32 states in the United States had criminal statutes on HIV transmission [64]; these statutes could thwart test-and-treat strategies, especially those that incorporate phylogenetic analyses to evaluate epidemics.

Phylogenetic analyses are an important public health tool for identifying and responding to potential health threats. Such analyses can elucidate the longitudinal phylodynamic structure of a local epidemic [62] and help to identify potential targets for interventions, such as

increased testing, education campaigns, and ART. Identification of HIV transmission networks and linkages, however, is made more difficult by their legal implications [64–67], especially if phylogenetic analyses are used to confirm these linkages [49–52]. Although molecular epidemiology is valuable for surveillance of HIV transmission networks, obtaining the necessary community support for this will require policies that protect privacy rather than put those who seek testing in jeopardy. Community support for these procedures will depend on a recognition by public health and legal officials that molecular links do not provide a transmission link beyond a reasonable doubt, but they provide only a suggestion that individuals acquired HIV infection from the same network [68].

DESIGN OF STUDIES OF CONTROL STRATEGIES

Because investigating the control of HIV epidemics is so complex, it may be useful to pilot intervention studies such as test-and-treat strategies before progressing to full-scale studies. Such pilots could allow for the aforementioned modeling, both before and after the introduction of the intervention, and would provide useful information for designing an appropriate large-scale community randomized study. Because of the potential high cost of such studies, it is vital to ensure that they are appropriately powered and efficiently analyzed. Because epidemics will vary across communities, efficient analyses should make use of information on important predictors of incidence of HIV infection. How best to make use of such information requires an understanding of epidemic dynamics that would help identify the effect of these predictors. Furthermore, selection of an appropriate sample size requires determination of an appropriate effect size, and choice of effect size should not be ad hoc but, instead, guided by epidemic models that indicate what rates of decrease are consistent with ultimate epidemic control. For example, even a modest decrease in incidence in the first 2 years of a study might be compatible with eventual control in some settings, but determining the minimum reduction consistent with this goal requires a realistic epidemic model. It will also be important to design monitoring plans that would allow for mid-course corrections in prevention strategies if the predefined targets for efficacy are not met. Because many sites or communities may be required to obtain adequate power and it may not be possible to roll out an intervention simultaneously at all sites, it may be useful to consider a “stepped wedge” design [69], in which roll-out occurs in a sequential way. This design makes it possible to obtain varying durations of follow-up before and after the intervention, which may add power for assessing the interaction of the intervention with other ongoing prevention efforts.

CONCLUSIONS

Research on test-and-treat strategies, in combination with other prevention methods, will require major commitments from funding agencies, departments of public health, and local communities. The goal of such research should go beyond simply estimating the effect of test-and-treat strategies in given settings and also provide information on how to best implement a test-and-treat strategy and why it works or fails. Such understanding is necessary to assess the conditions under which such a strategy would be cost-effective and to develop the best approaches to roll-out optimal combinations of prevention strategies. Such an enterprise will also require an unprecedented degree of cooperation among clinical, laboratory, and quantitative scientists; this cooperation not only will have the potential to aid in controlling the spread of HIV infection, but also may lead more broadly to scientific advances necessary for optimal responses to other public health challenges.

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