The Roles of Behavioral and Social Science Research in the Fight Against HIV/AIDS: A Functional Framework

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Abstract: Landmark advances have been made in HIV/AIDS prevention and treatment. These include proof-of-concept and public health implementation of preexposure prophylaxis and "treatment as prevention" to reduce HIV transmission as well as definitive evidence of the clinical gain from early antiretroviral treatment initiation. Significant progress has been made in understanding and addressing the social contexts and behavioral factors that impact HIV prevention, care, and treatment interventions. These include facilitating uptake of testing and counseling, developing technology-based interventions that increase viral suppression, reducing HIV/AIDS-related stigma, and addressing other sociobehavioral and structural barriers to care and treatment. This evolving landscape provides an important juncture to assess current and future directions for HIV/AIDS behavioral and social science research (BSSR). We propose a functional framework for HIV/AIDS-related BSSR, highlighting 4 primary BSSR domains: (1) understanding vulnerable populations and contexts of risk ("Basic BSSR"); (2) improving behavioral and social factor approaches to risk reduction, prevention, and care ("Elemental BSSR"); (3) strengthening the design and outcomes of biomedically focused research in HIV/AIDS treatment and prevention ("Supportive BSSR"); and (4) contributing building blocks to integrated HIV/AIDS prevention and treatment approaches ("Integrative BSSR"). These domains and their resulting confluence at the highest level underscore how fundamental and essential BSSR is to current and future efforts to prevent, treat, and cure HIV/AIDS.

Key Words: behavioral science, social science, HIV/AIDS research

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The HIV/AIDS epidemic remains one of the most urgent global public health crises. AIDS causes over 1 million deaths each year, and there are over 2 million new HIV infections annually.[1] The United States has advanced a comprehensive national strategy to gain ground against HIV/AIDS,[2] and reducing HIV/AIDS is featured in the US Department of Health and Human Services' Healthy People 2020 goals.[3] These strategic plans and actions are joined by global organizations, nations, and communities around the world who are collectively responding to the crisis of HIV/AIDS.

Important advances have been made that could turn the tide in HIV/AIDS. Recent ground-breaking trials indicate that HIV preexposure prophylaxis (PrEP) and "treatment as prevention" (TasP) reduce HIV transmission.[4,5] Early initiation of antiretroviral treatment (ART) offers significant clinical benefits to people living with HIV (PLWH).[6] These advances have changed treatment, and public health guidelines and have fostered greater emphasis on identifying PLWH and engaging them in treatment and care, along with improving PrEP access and use among individuals at substantial risk for infection. Contributions from behavioral and social science research (BSSR) have occurred in parallel. Trial results indicate that mobilizing communities and reducing stigma can increase HIV testing and reduce HIV incidence,[7] and that the delivery of technology-based interventions can increase viral suppression.[8,9] On many fronts, this is a transformative time for HIV/AIDS research and practice.

This progress and the changing HIV/AIDS research and practice landscape represent an important juncture at which to assess evolving directions and opportunities for HIV-related BSSR. This article offers a functional framework regarding the primary areas of contribution (domains) that BSSR is positioned to make with respect to HIV/AIDS science and practice. This framework aims to assist scientists, program developers and implementers, clinicians, communities, policy makers, funders, and others to understand the full potential of BSSR, and it will be a tool to guide their respective roles and interrelated efforts to make gains against HIV and AIDS.

A FUNCTIONAL FRAMEWORK FOR HIV-RELATED BEHAVIORAL AND SOCIAL SCIENCE RESEARCH

The behavioral and social sciences incorporate many disciplines in the study of human behavior and social systems. Behavioral sciences such as psychology and psychiatry study behavior and its determinants. Social sciences, such as anthropology, sociology, political science, and

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economics study social organizations and structures as they shape individual and group experience and behavior. In the context of health and health promotion, "the core areas of behavioral and social sciences research are those that have a major and explicit focus on the understanding of behavioral or social processes, or on the use of these processes to predict or influence health outcomes or health risk factors."[10] A dynamic and integrated framework is necessary to understand the complex interactive factors that affect health, which includes health determinants at multiple levels.

The functional framework outlines four domains for current and future HIV/AIDS BSSR research: (1) understanding vulnerable populations and contexts of risk ("Basic BSSR"); (2) improving behavioral and social factor risk reduction, prevention, and care ("Elemental BSSR"); (3) strengthening the development and clinical testing of biomedically based HIV treatment and prevention products ("Supportive BSSR"); and (4) contributing to the implementation of multimodal and multilevel prevention and treatment strategies ("Integrative BSSR"). The successful development and delivery of effective evidence-based HIV prevention and treatment requires BSSR research in each of these four domains (Fig. 1).

BASIC BSSR

"Basic behavioral and social science research is critically important to NIH's mission and is a core value of its scientific plan."—NIH OBSSR[10]

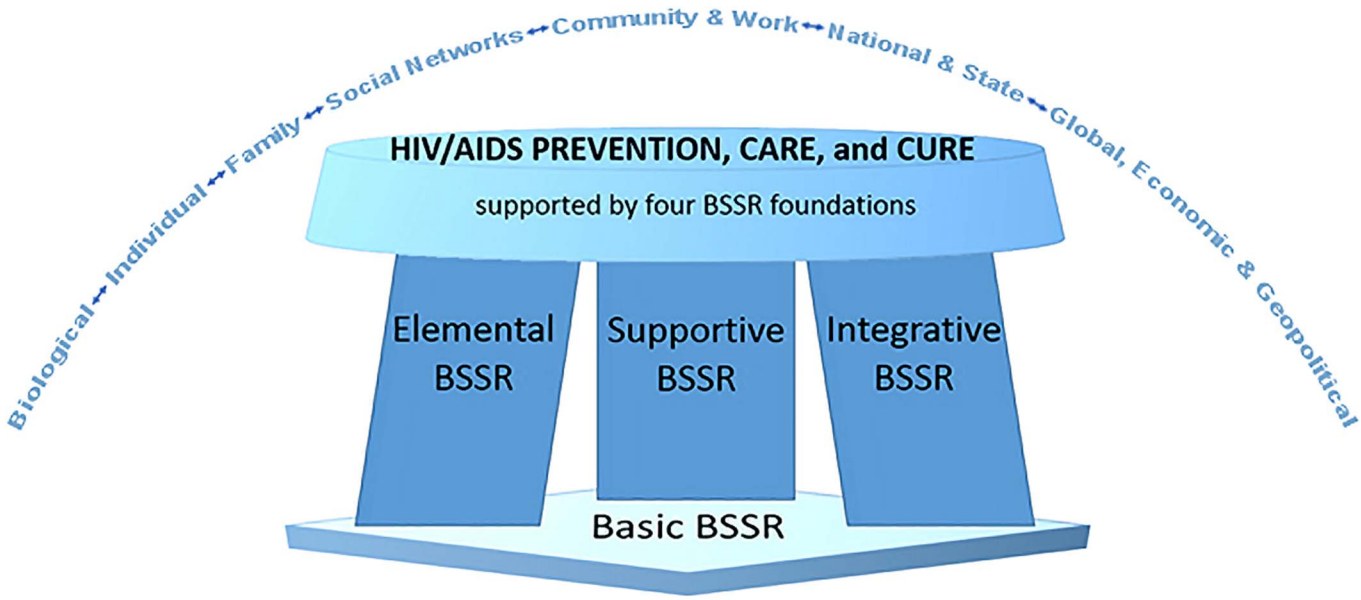
Basic BSSR provides a foundation for each of the other HIV/AIDS BSSR domains. Basic BSSR improves understanding of social and behavioral dynamics in key populations and their risks and resiliencies, identifies important intervention opportunities and targets, and informs strategies and contexts for the delivery of HIV preventive services and care.

The NIH Office of Behavioral and Social Science Research (OBSSR) sees Basic BSSR as research "designed to further our understanding of fundamental mechanisms and patterns of behavioral and social functioning relevant to the Nation's health and well-being, and as they interact with each other, with biology and the environment."[10] They explain:

> As is the case with basic biomedical research, basic behavioral and social sciences research does not address disease outcomes per se. Rather, it is designed to elucidate knowledge about underlying mechanisms and processes, knowledge that is fundamental to improving the understanding, explanation, observation, prediction, prevention, and management of illnesses, as well as the promotion of optimal health and well-being.[10]

Basic BSSR positions behavioral and social phenomena as outcomes that require study, understanding, and prediction. Basic BSSR includes the examination of patterns and determinants of behavior and social dynamics, and advancement of innovative measurement.

Basic science is not unique to BSSR. Many domains of biomedical research (eg, neuroscience, virology, biology) maintain a strong tradition of basic science with recognition that basic science innovations inform advancements in applied research. The behavioral and social sciences are



Basic BSSR	Understanding vulnerable populations and risk settings
Elemental BSSR	Improving behavioral and social factor risk reduction
Supportive BSSR	Strengthening biomedical HIV product development and clinical trials
Integrative BSSR	Contributing to effective implementation of combination/multilevel strategies

FIGURE 1. A functional framework for HIV/AIDS BSSR.

similar to the biomedical sciences in this regard—the goal of basic BSSR is not academic but rather to guide downstream efforts to improve health. In HIV/AIDS research, basic BSSR furthers the understanding of vulnerable populations and risk environments, identifies opportunities and targets for intervention, and improves measurement in these domains.

Understanding Vulnerable Populations and Risk Environments

Basic BSSR can shed light on behavioral and cultural practices within key populations that may influence HIV transmission and prevention. For example, basic BSSR identified the practice of HIV seroadaptive behaviors such as serosorting and seropositioning among gay men and men who have sex with men (MSM).[11–13] The emergence of seroadaptive behaviors reflected efforts to reduce potential exposure to HIV in the absence of clear public health guidance regarding such strategies. As a result, it is now conventional to consider how persons at risk for HIV may be using a range of behavioral and prevention choices and strategies within their own social contexts. Another example of the contribution of Basic BSSR pertains to the practice of "dry sex." This is a cultural practice within certain regions of Sub-Saharan Africa which involves the application of detergents or other materials to the vagina with the aim of improving sexual sensation for men.[14–16] It is important to understand dry sex preferences and practices because they may contribute to HIV transmission and can challenge vaginal microbicide acceptability.

Basic BSSR also allows for discerning how behaviors and cultural practice are shaped and driven by social and structural factors. For example, early research among injection drug users suggested that prevention would be challenging because syringe sharing was a common cultural practice. Later it became clear that a core driver of this behavior was structural constraints on syringe access.[17,18] Basic BSSR has further helped to recognize how the criminalization of drug use and attendant law enforcement actions can impede use of sterile needles and syringes and engagement in syringe exchange programs.[19,20]

Basic BSSR additionally contributes to the understanding of community settings and environments where HIV prevention and treatment occurs. Examples that explore particular social settings and risk environments include research on South African shebeens, which are informal local establishments that serve alcohol and facilitate meeting sex partners.[21] Basic knowledge of such contexts and their social dynamics can inform the targeting and delivery of HIV risk-reduction interventions.[22] Organizational settings for delivery of HIV preventive services are another context where Basic BSSR can influence practice. Ethnographic research conducted in community-based organizations in New York City has identified the importance of creating "safe spaces" for Black MSM that provide shelter from discrimination and stigma, opportunities for peer support and skill-building, and platforms for HIV preventive service delivery.[23]

Identifying Opportunities and Targets for Intervention

Basic BSSR includes the study of mechanisms relevant to HIV prevention and care that could be intervention targets or tools. Mechanistic insights from behavioral economics offer an example.[24,25] A behavioral economic perspective postulates that people are not strictly rational and tend to favor heuristic decision-making strategies that follow a common set of biases. These biases include present-bias, a tendency to attend to short-term interests rather than long-term goals, as well as information salience, a tendency to focus on recent or memorable experiences over all available information. In the context of HIV/AIDS, research has indicated that decision-making biases such as these are common among adult men and women living with HIV and that individuals with strong present-bias are less likely than others to adhere well to oral ART.[25] Insights from behavioral economics could consequently help in targeting and testing novel interventions, such as capitalizing on present-bias by providing short-term incentives for daily behaviors (eg, ART adherence) that convey long-term health effects.

Basic BSSR can also illuminate social and structural drivers of HIV prevention and treatment behaviors that could help identify intervention targets. An example can be found in research on food insecurity. Food insecurity has been defined as "a situation that exists when people lack secure access to sufficient amounts of safe and nutritious food for normal growth and development and an active and healthy life."[26] Food insecurity was significantly associated with HIV sexual risk behavior among women in Botswana and Swaziland, where food insecure women were much more likely than others to report condomless sex and selling sex for money or resources.[27] Food insecurity also has strong effects on ART adherence, viral suppression, and mortality among individuals living with HIV infection.[28,29] The mechanisms that link food insecurity to poor HIV treatment outcomes may include mental health pathways (eg, stress and depression resulting from food insecurity); behavioral pathways (eg, challenges to ART adherence and clinic appointment retention); and nutritional pathways (eg, nutrient deficiencies).[30] Improved knowledge of food insecurity and the pathways through which it affects HIV/AIDS treatment outcomes can inform intervention choices to address this factor, such as efforts to provide food and nutritional supplementation, or to empower individuals through income generation or agricultural training.

Improved Measurement Tools

Basic BSSR also includes research designed to improve measurement of behavioral and social phenomena, with an eye toward enhanced assessment and prediction. For example, research has sought to improve understanding of self-report questions of medication adherence.[31] Cognitive testing and validation studies of ART adherence measures indicate that 30-day recall intervals tend to reduce ceiling effects (ie, reports of perfect adherence) relative to shorter intervals, and the phrase "the last 30 days" is preferable to "the last month" because the latter can be misunderstood as reflecting the

calendar month.[32] Relatedly, individuals completing self-report scales typically make estimates of their adherence behavior rather than conscientiously remembering and counting doses taken or missed.[33] Therefore, self-report measures with rating scales as response options (eg, "In the last 30 days, how good a job did you do at taking HIV medicines in the way you were supposed to? Never, Rarely, Sometimes, Usually, Almost Always, Always") yield greater variability and reduced ceiling effects than measures asking about a specific number of missed doses.[32,34,35] An ART adherence measure derived from this basic BSSR has been validated through prediction of electronically monitored adherence and viral load.[36,37] This work to optimize self-reports of ART adherence joins other efforts to advance the science and practice of adherence assessment, such as studies to advance novel technologic and mobile health assessment tools.[38]

ELEMENTAL BSSR

"Studies have shown that HIV risk behaviors can be reduced in any targeted population through interventions that provide risk reduction counseling, stress cognitive approaches to problem solving and behavior change, and help individuals to build the skills they need to reduce HIV risk. Voluntary counseling and testing has also been clearly shown to reduce risk behaviors, especially among HIV-infected persons and in extramarital partnerships."—NIAID[39]

Elemental BSSR represents research to understand and address behavioral practices and social conditions that directly impact HIV/AIDS prevention, treatment, care, and cure outcomes. Elemental BSSR works to develop behavioral and social HIV prevention, treatment, and care interventions. If proven effective, these Elemental BSSR approaches can independently contribute to HIV-related outcomes, and they are additionally available for use in combination with other tools and approaches, whether they may be biomedical, social, and/or behavioral. Often, Elemental BSSR provides BSS-driven "building blocks" (tools/approaches) for use in both Supportive and Integrative BSSR and practice (as explained in later sections of this article). Examples of Elemental BSSR include evidence-based behavioral risk-reduction strategies such as voluntary HIV testing and counseling, male and female condom use, and the use of clean needles for drug injections, and seroadaptive practices. Many social factors also have strong influences on HIV transmission and efforts to address HIV-related outcomes. HIV stigma represents one of the foremost examples of social factors that can compromise efforts to prevent, treat, and eventually cure HIV/AIDS. Stigma related to other co-occurring conditions such as socioeconomic status, sexual orientation, and drug use also helps perpetuate the HIV/AIDS epidemic.

Attention to Elemental BSSR is important for at least two primary reasons. First, biomedically based prevention approaches such as PrEP are not indicated for all HIV negative individuals who are at-risk.[40] With clinical guidelines directing PrEP use to individuals at substantial risk for HIV infection, the Centers for Disease Control and Prevention estimates that approximately 24.7% of sexually active MSM, 18.5% of injection drug users, and 0.4% of heterosexually active adults are in need of PrEP.[41] The large proportions of these groups for whom PrEP is not indicated will require continued engagement in behavioral and social factor risk reduction. Behavioral risk reduction can also benefit many people worldwide who presently lack access to PrEP, despite the many efforts underway to scale up access, as well as those with access and indications for PrEP who may not choose it as a preferred HIV prevention method.

The second reason for the continued need for behavioral risk reduction is that gaps in the HIV care continuum limit the impact of TasP. There is substantial evidence that viral suppression through ART confers strong preventive benefits, based on landmark clinical trials such as HPTN 052[4] and real-world observational studies of HIV serodiscordant couples such as the Partners PrEP demonstration project[42] and the PARTNER study.[43] The potential for TasP to reduce new infections, however, will be constrained until the HIV care continuum can be optimized and durable viral suppression is more broadly maintained. It is estimated that only 30% of US PLWH maintain viral suppression because of a combination of undiagnosed HIV infections, delayed linkage to care, poor retention in care, and suboptimal ART adherence.[44] Individuals who are either HIV undiagnosed or diagnosed and poorly retained in HIV care drive more than 90% of new infections in the United States.[45] While efforts to strengthen the HIV care continuum advance, behavioral and social risk reduction can pick up where TasP leaves off.

The use of condoms features prominently in current and future efforts to end HIV/AIDS. A modeling study designed to identify a "Fast Track" approach to ending the HIV/AIDS epidemic by 2030 indicates that more than one-third of new infections will need to be averted through intensified condom use and promotion, with the remainder derived through use of ART, PrEP, male circumcision, and other methods.[46] Another modeling study designed to inform the allocation of HIV prevention resources in Nairobi Kenya found that approximately half of achievable reductions in HIV infections could be realized through comparatively low-cost efforts to promote condom use among male sex workers and MSM.[47] Attention to larger social factors will also be required. The Fast Track modeling study underscored that "the service package for key populations is not limited to provision of condoms, safe needles or information and education but also includes population services for discrimination reduction, promotion of access to testing, treatment, and retention."[46]

Behavioral and social level interventions are effective. Research syntheses of behavioral interventions have demonstrated that individual and group-based counseling can reduce sexual risk behavior, defined as increased condom use and decreased condomless anal intercourse with a serostatus negative or unknown partner.[48,49] A meta-

analysis focused on PLWH found that behavioral interventions significantly reduce condomless sex and acquisition of sexually transmitted diseases.[50] The Centers for Disease Control and Prevention maintains an extensive inventory of proven BSSR HIV risk-reduction interventions, as well as ART adherence support interventions and HIV care engagement interventions.

The impact of Elemental BSSR—as well as its challenges—can be seen in examples where behavioral risk reduction has changed HIV incidence. Changes in HIV incidence from behavioral risk reduction among US gay men and MSM early in the course of the HIV/AIDS epidemic represents one of the most rapid and dramatic changes in health behavior ever documented in public health.[51] Behavioral risk-reduction approaches have also produced impact in international contexts, such as in Uganda, where nationwide social mobilization around a constellation of behavioral prevention strategies ("ABC"—Abstain, Be faithful, and/or Use Condoms) may have contributed to declines in HIV incidence during the first decade of the new millennium.[52] The challenge with these BSSR approaches is that their impact has not always been sustained. Among US MSM and in Uganda, HIV infections have risen since these earlier reductions. These may not be failures of behavioral prevention, per se, but rather, failures to appropriately support behavioral prevention with substantial and continued investment.[48,53]

Further research on behavioral and social risk reduction can take a number of forms. Efforts to promote HIV testing behavior and reduce undiagnosed HIV infections represent a key priority for Elemental BSSR. New innovations in rapid HIV tests for personal use in home or community settings represent one front. Research to reduce the risks of injection drug use and promote safe injection practices is also particularly important, because injection drug use is driving a dramatic increase in HIV infections in Russia and other Eastern European settings, as well as a recent US HIV outbreak in rural southeastern Indiana. Research addressing the HIV prevention needs of key populations disproportionately affected by HIV, such as young MSM under age 18, may benefit from BSSR approaches. The widespread adoption of new technologies such as wireless smartphones and the advent of mobile apps, social media, and text messaging offers unprecedented new opportunities for monitoring of HIV health behaviors and delivery of personally tailored interventions on as-needed basis. Research is also needed regarding how best to sustain the impact of behavioral and social risk reduction, at both the individual and population levels.

The success of such interventions may be based in part on understanding social factors beyond the control of the individual. These social factors may have strong deterministic influences on potential infection and the ability to recognize, create, and access tools and pathways to successful HIV-related outcomes. Examples of constructive social and structural influences include education for young girls[55] and leadership from public health departments.[56] Deleterious social and structural influences include stigma and discrimination attached to HIV/AIDS and key populations, including homophobia and gender-based violence.[54,57,58] Stigma, as a particular BSSR issue, takes various forms (eg, self/internalized stigmas; external stigmas) that can interfere with the ability to prevent, treat, and one day cure HIV/AIDS. Research is needed not only to determine the harmful effects of forces such as homophobia, racism, and HIV stigma on HIV prevention—but also to more clearly document the precise mechanisms and mediators through which these social dynamics compromise HIV/AIDS prevention and treatment—so that appropriate interventions can be developed.

> "HIV-related stigma and discrimination are directly linked with delayed HIV testing, nondisclosure to partners and poor engagement with HIV services, including treatment retention."—UNAIDS[54]

Elemental BSSR is not only essential across the HIV/AIDS prevention, care, treatment and cure spectrum but also across all levels of analysis and influence. This includes HIV/AIDS prevention and treatment with individuals; community level HIV/AIDS prevention and treatment; and structural, policy, and environmental HIV/AIDS prevention and treatment interventions. Elemental BSSR can further contribute to understanding, adopting, and adjusting to changes in treating HIV infection and AIDS; psychological health in and across all aspects of HIV/AIDS; as well as operationalizing the transition from research to service and community/population scale-up.

SUPPORTIVE BSSR

> "The behavioral and social sciences play a key role in HIV prevention research, because every strategy that can be utilized for preventing the acquisition or transmission of HIV has one or more associated behavioral components that can influence its efficacy. These components may affect the adoption and acceptance of a specific prevention approach or may be critical in determining the use, acceptability, and potential efficacy of these strategies."—NIAID[39]

Supportive BSSR refers to behavioral and social science efforts to support and strengthen the development and clinical testing of biomedical approaches to HIV/AIDS prevention, treatment, and cure. Biomedical research has created important advances in HIV/AIDS, including the advent of combination ART, oral PrEP, and TasP. Preclinical and clinical research studies are presently advancing the next generation of biomedical products, including long-acting injectable PrEP and ART, vaginal rings to deliver microbicides and contraception, broadly neutralizing monoclonal antibodies for HIV prevention and treatment, and HIV vaccines. BSSR information and support need to be

considered and incorporated into the planning, implementation, data collection, analysis, and interpretation phases of any clinical trial testing a biomedical product. Integration of Supportive BSSR into all stages of biomedical product development will strengthen clinical trial conduct and help to optimize the ultimate uptake and use of HIV/AIDS biomedical prevention and therapeutic strategies.[59,60]

Integration of Supportive BSSR into the earliest stages of biomedical product development is key. BSSR can identify preferences regarding the look, feel, and usage schedule for products among key target groups to inform product development. Supportive BSSR can determine preferences for hypothetical products through qualitative methods such as interviews and focus groups as well as sophisticated quantitative methods such as conjoint analysis. Behavioral data about actual product use and acceptability during early stage clinical trials can additionally inform the selection of products or drug regimens for further clinical testing. For example, the choice of an 8-week schedule for intravenous administration of the broadly neutralizing antibody VRC01 during phase 2b trials was informed by two pieces of data collected during the phase 1 testing: pharmacokinetic data indicating sustained product concentrations on an 8-week schedule and behavioral data indicating better appointment completion on longer administration schedules compared with shorter ones.[61] Aspects of product acceptability, barriers to use, physical and perceived elements of the products, and many other BSS factors can be tackled in partnership with Supportive BSSR. The result is the development and selection of the most acceptable products for further testing.

In addition to informing biomedical product development, supportive BSSR can provide behavioral and social information regarding key populations and communities of research interest that are vital to planning successful clinical trial conduct. The HPTN 071 "PopART trial"[62] prepared for its large-scale test of a combination HIV prevention intervention through formative social science research.[63] An ethnographic survey was undertaken in the 21 Zambian and South African communities selected for the trial to describe the local environments, HIV landscape, and social and historical contexts of these study communities. This research revealed community-specific social and structural factors such as HIV stigma, short-term migratory population flows, and constraints on clinic-based health system capacity that could affect study implementation and findings, and these factors were considered when developing the large-scale trial.

Supportive BSSR further contributes data and methods to strengthen the design, implementation, and interpretation of biomedical clinical trials. Supportive BSSR offers systematic methods and strategies to guide clinical trial participant sampling and recruitment, such as respondent-driven sampling approaches.[64,65] Supportive BSSR further informs the development of research assessments regarding sexual behavior and other behavioral and psychosocial factors necessary for clinical trial screening and assessment procedures. These BSSR data can be crucial to the interpretation of clinical trial results. For example, analysis of behavioral data in the STEP vaccine trial determined that increased HIV infections among certain participant subgroups was not attributable to sexual risk behavior.[66] This underscored the need to examine biologic, rather than behavioral, mechanisms behind the increased risk.

Supportive BSSR has particularly important roles to play regarding product adherence in biomedical product clinical trials. At a fundamental level, the safety and efficacy of biomedical HIV prevention and therapeutic strategies cannot be determined without documented adherence to the investigational product. Shortfalls in product adherence have compromised proof-of-concept testing in a number of large HIV prevention clinical trials, including trials of acyclovir suppressive therapy against genital herpes as a method for HIV prevention[67] and oral and topical PrEP.[68,69] Supportive BSSR can provide strategies for assessing and improving product adherence in HIV clinical trials. Brief BSSR theory-based adherence counseling is an essential component of any clinical trial protocol. A number of counseling approaches have been developed for this purpose, including integrated Next Step Counseling.[70] Supportive BSSR can also strengthen adherence in clinical trials through a set of adherence monitoring and feedback approaches. In a substudy nested within the Partners PrEP trial, adherence was nearly perfect (~99%) under conditions where additional adherence counseling was provided to individuals evidencing <80% adherence during unannounced pill counts.[71]

Strong utilization of Supportive BSSR throughout the biomedically focused research process (from its very earliest planning stages to interpretation of outcomes) improves the development and clinical testing of biomedical products. It facilitates selection of the most acceptable products and identification of adherence support approaches to ensure proper proof-of-concept testing. Supportive BSSR helps plan for and better execute biomedically centered intervention and product oriented research.

INTEGRATIVE BSSR

Biomedical research or BSSR by themselves, as separate silo approaches, will not solve the global HIV/AIDS epidemic. Controlling and ultimately ending the epidemic will require selection and integration of a range of proven HIV tools and approaches in specific and varied ways, depending on the populations in need and their circumstances. An integrative approach will join behavioral, social, structural, and biomedical approaches together, for maximal impact. Integrative BSSR works to this end, namely to serve as BSS-oriented components working in conjunction with other BSS-oriented and biomedical components. Integrative BSSR is part of integrative science research, which combines and coordinates varied and diverse elements into a whole, whether that be an approach, an intervention, or a unified framework. As in combination prevention and combination ART, the integrated whole is greater than the sum of its parts.

Although ART and PrEP are commonly described as biomedical strategies, all available HIV prevention and treatment strategies are fundamentally biobehavioral in nature. For example, the achievement of sustained viral suppression through ART requires PLWH to successfully negotiate all

aspects of the HIV care continuum. This presents multiple challenges, and HIV-positive individuals are lost at each step.[72–74] Each gap in the HIV treatment cascade requires BSSR to develop effective responses and strengthen clinical outcomes. A mix of behavioral, social, and structural approaches is also needed to realize the potential of TasP.[75]

Behaviors are integral to biomedical prevention through PrEP as well. The US clinical guidelines for PrEP[40] indicate requisite behaviors that include engagement in primary medical care, attendance at quarterly medical appointments for clinical monitoring, HIV testing on a quarterly basis, filling and refilling PrEP prescriptions, adhering to a daily PrEP pill regimen, and continued use of condoms for risk reduction. Concepts for a "PrEP care continuum" further outline the steps required for individuals to benefit from PrEP, and the potential for gaps and disparities to occur across the continuum.[76] PrEP will not have its intended impact without Integrative BSSR to identify and intervene on relevant behavioral and social factors. Integrative BSSR to strengthen real-world implementation of proven HIV/AIDS interventions such as PrEP is essential to improve their uptake and reach.

Although efforts to understand and address individual-level factors may improve engagement with interventions and services, there is a concurrent need for implementation science and operations research to identify organizational and structural factors that either facilitate or impede the scale-up and effective provision of HIV/AIDS interventions and services (eg, ART and PrEP). In implementation science and operational research, the unit of analysis can be at the level of the HIV treatment setting, community organizations, institutions, or even states and nations. Substantial gaps in the effective provision of HIV/AIDS interventions and services have limited impact of proven approaches.[77] It is important to ask what training programs, infrastructure, and capacity building, and policy approaches could be designed and enhanced to better enable these entities to optimize outcomes. Improving outcomes such as the adoption and uptake of evidence-based interventions, as well as the successful scale-up and delivery of services with cultural competency and fidelity, will increase the number of individuals effectively reached and served, ultimately leading to goals such as reductions in community viral load and HIV incidence rates.

The concept of combination prevention maintains that multiple multimodal approaches across key and varied levels of intervention must be undertaken to effectively address the HIV epidemic.[78,79] This concept is also rooted in the analogy of combination ART. Just as combination ART uses multiple drugs to intercept HIV at various junctures in its replication life cycle, combination prevention uses multiple modalities to interrupt HIV transmission at various junctures.[53,79] A combination prevention approach therefore seeks to deploy a constellation of integrated behavioral, biomedical, and structural approaches to prevent HIV infections and ultimately mitigate the scale of the HIV/AIDS epidemic.

An integrated approach to prevention, treatment, or cure accomplishes several aims. First, it recognizes that the HIV/AIDS epidemic is sustained by many complex and interlocking factors that require a complex, multifactorial response.[53] Such an understanding corresponds to current understandings about HIV risk, which increasingly underscore the concept of HIV risk at the community level.[80] HIV transmission is not strictly the product of particular sexual practices but is importantly informed by complex contextual determinants that increase or decrease risk; this includes such dynamics as biologic susceptibility; sexually transmitted infections other than HIV; other risk behaviors and comorbidities; social and sexual mixing patterns; as well as HIV prevalence, incidence, and viral load at the community level. Second, it recognizes that many strategies are only partially effective, and that their integrated use in combination may be required for maximal impact.[78] As noted by Coates et al,[53] "Failure to show that a specific strategy reduces HIV infection does not render it useless in a comprehensive program or a multilevel behavioral strategy for HIV prevention. The combination of strategies might be relevant to the end result." In addition, integrated or combination approaches factor in the behavioral and social processes that are integral to the effective uptake and use or biomedical prevention and treatment strategies.

The integrated approach can act as a "force multiplier." A modeling study found that biomedical prevention strategies will have limited impact on HIV incidence among MSM in China without concomitant condom use promotion, which would greatly speed and magnify the collective preventive impact.[81] As noted earlier, models also indicate that rapid expansion of both behaviorally focused and biomedically focused interventions are necessary to realize and end the HIV/AIDS epidemic before 2030.[46]

The integrated approach can further identify and illuminate the "essential elements" that are missing from current approaches. For example, in the United States, decades of widely available access to ART has not slowed the increasing incidence of HIV among key groups such as young black MSM. Modeling studies indicate that any ambitious achievement of high ARV uptake and adherence in these groups will still not bend disparities in the incidence curve.[82] Multilevel research and intervention addressing the social contextual factors that continue to drive HIV risk and resilience in these groups—factors such as economic opportunities, racial discrimination, and HIV stigma— are among the critical and missing pieces in the prevention mosaic.[83] Research designed to understand and address the social and structural determinants of HIV risk provide necessary insight and make vital contributions to the efforts to end the epidemic.

Further research to evaluate social factors and structural interventions, policy, and laws is needed in the advancement of HIV/AIDS prevention, treatment, and cure. For example, the vast preponderance of HIV prevention research to date has been conducted at the individual level. This represents important, foundational research— but its impact may ultimately be constrained by resource limitations for the wide-scale delivery of individual-level interventions and by the increasing recognition that HIV transmission is importantly influenced by broader contextual factors, such as community viral load, social networks, and mixing patterns. Continuing this example, the next generation of HIV prevention, treatment, and cure research should therefore seek to better address social, structural, and environmental factors that drive HIV incidence and influence prevention. This will require additional focus on

contexts that may promote transmission risks or prevent effective treatment from taking hold, including social networks, venues, neighborhoods, and political and legal systems. Structural-level factors need to be taken into account and can be powerful targets for intervention and part of an integrated strategy to prevent, treat, or even cure HIV/AIDS.

It has been postulated that combination prevention approaches are most likely to succeed if they simultaneously use behavioral, biomedical, and structural approaches to address multiple junctures that facilitate HIV transmission.[77] Fundamental questions remain such as how much effort and resources should be invested in any single strategy, and whether there are particular combinations that would be more effective than others, for specific populations. In addition, it is important to determine how local epidemiological and contextual issues can best inform the selection of combination prevention approaches. Issues and questions also emerge when particular strategies are combined. For example, in the current era of antiretroviral-based prevention, how much of a prevention benefit might be provided by PrEP if one's HIV-positive relationship partner already maintains durably suppressed viral load through ART treatment? New research is needed to help target, field, and evaluate such combination prevention approaches. The use of modeling as a tool and an approach can be highly advantageous in this regard, along with efforts to leverage national, state, community, and clinic-level data, as well as "natural experiments" that may be underway when prevention services are scaled-up and rolled out in a sequential or stepped fashion.

THE CONFLUENCE OF BSSR IN HIV/AIDS RESEARCH AND OUTCOMES

A comprehensive multicomponent approach to HIV/AIDS BSSR through a functional framework of four primary domains has been presented (Fig. 1). Each domain serves a specific role and makes important contributions: "Basic BSSR" fosters knowledge of vulnerable populations and contexts of risk; "Elemental BSSR" advances uniquely behavioral and social science approaches to prevention and care; "Supportive BSSR" strengthens the behavioral and social aspects of biomedically based HIV/AIDS research; and "Integrative BSSR" addresses behavioral and social science aspects of proven biomedical interventions and promotes integrated and multilevel prevention, treatment, care, and cure strategies.

Basic BSSR should not be overlooked in the urgent response to HIV/AIDS. As illustrated in Figure 1, Basic BSSR provides the foundation for the other three domains. Basic BSSR advances knowledge of key populations and risk environments, identifies opportunities and targets for intervention, and improves measurement of social and behavioral phenomena. Each aspect strengthens the other BSSR areas. For example, Basic BSSR advances knowledge of key populations and risk environments that can inform the appropriate design and successful support of large-scale biomedically focused HIV clinical trials (Supportive BSSR). Basic BSSR also elucidates tools and targets for behavioral and social research and intervention (Elemental BSSR) by describing phenomena like cognitive biases, seroadaptive practices, and social stigma. Basic BSSR further develops valid assessments of risk behavior and product adherence and collects normative data that provide critical inputs for modeling studies that chart optimal combination prevention approaches (Integrated BSSR).

With Basic BSSR as the foundation for Elemental, Supportive, and Integrative BSSR, these four domains collectively steady and strengthen the figurative "tabletop" of HIV/AIDS prevention, care, and cure research and practice (Fig. 1). This "tabletop" represents the current landscape of HIV research and practice, and it could not have been built without the many extensive advances concomitantly provided by fields such as virology, immunology, and epidemiology. The model simply underscores that the basic, elemental, supportive, and integrative domains of BSSR undergird our many efforts to address the complex realities of HIV/AIDS.

FRONTIERS FOR BSSR IN HIV/AIDS

HIV/AIDS continues to be one of the most challenging health and public health crises affecting people around the world. While recent advances in research have provided optimism about making further significant gains against this global epidemic, the next action steps will prove critical. We highlight three of the many avenues where the breadth of BSSR is poised to make important impact in the future.

The first generates from the rapidly diversifying toolbox of biomedical prevention and treatment options. The mainstay of oral ART has been joined by oral PrEP, and future tools may include vaginal rings, injectable PrEP and ART, broadly neutralizing monoclonal antibodies, and preventive and therapeutic vaccines. All aspects of BSSR are required to optimize their development, delivery, and use. Supportive BSSR will strengthen the clinical trials testing these novel approaches. Basic BSSR will investigate the risk perceptions, choice architecture, and decision-making processes that inform product selection and uptake among key populations. Integrative BSSR will support and sustain use of proven products and identify effective service delivery strategies for improved impact. Elemental BSSR will provide companion risk-reduction strategies and social factor interventions.

Another future opportunity derives from the exceptionally novel capacities provided by mobile and connected health technologies, including smartphone apps, wireless devices, passive sensors, online social networks, and electronic medical records. These technologies offer the revolutionary capacity to transcend distance, deliver interventions precisely when most needed, and tailor care to individual needs and changing circumstances. Basic BSSR will create highly novel measurement approaches through these technologies, such as geocoding levels of HIV-related stigma through Twitter posts and monitoring medication adherence in real-time through wireless pillboxes and digital pill ingestion sensors. Elemental BSSR will use mobile and connected health technologies to develop and deliver a new generation of highly scalable HIV testing and behavioral risk-reduction interventions. Supportive BSSR will use wireless technologies to facilitate conduct of large-scale clinical trials and epidemiologic research cohorts. Integrated BSSR will use these technologies to improve HIV care

engagement and to increasingly move services out of clinics and into communities.

The third avenue concentrates on social and structural drivers of the HIV pandemic and researching our responses at the organizational, social, and structural level. HIV/AIDS is a social disease as much as it is an infectious one. Profound and persistent disparities in HIV infections, access to care, and treatment outcomes are apparent in every setting worldwide. These derive from HIV stigma and broader social and structural inequities that marginalize key populations. Research and interventions conducted at the individual level or by technology have an important role to play, but any mitigation of HIV/AIDS disparities will require a stronger complement of work conducted at higher levels of influence and analysis. Basic BSSR can interrogate and unpack the social dynamics behind deep structural drivers of HIV/AIDS such as socioeconomic inequalities, migratory patterns, gendered power relations, stigma, and racial prejudice and discrimination. Elemental BSSR will build on these understandings by developing appropriate social and policy responses. Supportive BSSR will facilitate clinical research that is mindful of these deep currents so that it neither perpetuates nor drowns in them. Integrative BSSR will advance implementation science at the clinic and community level and will model the best combinations of individual, biomedical, and structural interventions to achieve impact.

CONCLUSION

The BSSR contributions described in the functional framework will be necessary for our continued efforts to gain ground against HIV/AIDS. There is unprecedented opportunity to pool the collective power of the biomedical, behavioral, and social science disciplines to prevent HIV transmission, to treat and care for those living with HIV, and to structurally alter the course of the HIV/AIDS global pandemic. The behavioral and social sciences are key partners in this approach and resolve.

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