
A GUIDE TO BEHAVIORAL AND SOCIAL SCIENCES IN HIV PREVENTION CLINICAL TRIALS:

Points to Consider when Undertaking Research

2009-2014

National Institutes of Health

National Institute of Allergy and Infectious Diseases
Division of Acquired Immunodeficiency Syndrome
Vaccine Research Program and Prevention Sciences Program

National Institute of Mental Health
Division of AIDS Research

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FOREWORD

“Let’s talk about sex and a possible vaccine for HIV.”

When the first phase III study of human immunodeficiency virus (HIV) vaccines in the U.S. was launched, I was an active volunteer at a community-based grass roots clinic in Chicago (Howard Brown Memorial Clinic). It was a guerilla storefront operation, where people hung sheets on clotheslines as room dividers. The group worked with the Centers for Disease Control and Prevention (CDC) and the Health Department to provide sexually transmitted disease (STD) testing and care for gay men who could not admit to their physicians who they were and what they did. Often men still went to their family physician whom they would never tell about anal or penile discomforts, because that would mean coming out to their entire family about their sexual activity.

This group had been very helpful in testing Hepatitis B (HBV) screening tools and early generation vaccines. So a few years later, when large billboards appeared with a hot shirtless guy, three foot high letters saying let’s talk about sex and an 800 number to call, I anxiously phoned, gave my zip code, and was set up with a contract research clinic near my home for eligibility screening. My excitement about the possibility of participating in this study with other sexy men was phenomenal. All my friends knew about my appointment and were anxious to hear if I got in, what was it like, and would they too be eligible to participate.

I knew they might take a medical history and draw blood because the phone scheduler encouraged me to allow about an hour for the first visit. It was also clear there might be some financial compensation, but I just wanted to be part of the next big thing and help find the vaccine that would end this epidemic. The medical screening seemed pretty routine, but I was somewhat disappointed to learn they were also screening for studies of diabetes, asthma, sleep disorders, and other conditions. It was also clear that the guy on the billboard was nowhere to be seen that day.

After an hour of procedures, I was put in a room and told the social worker would join me in a minute. A nice thirty-something man came in, shook my hand, and verified my identity. He then sat down armed with a clipboard and said “today and at each visit you are going to tell me about your sexual activity: what you have done, how often and with whom.” I replied “Oh really? Why would I do that? I just met you...you didn’t even tell me your name. Why would I talk to about my personal life? I came here to volunteer for the vaccine.”

“Because I am the social worker,” was the response, which apparently was supposed to bring me closer to divulging the most intimate details of my personal life. In that moment, my vaccine study career tanked. He didn’t provide me an acceptable reason to disclose to

a perfect stranger, a single detail of my personal life in such a stark, clinical, impersonal environment. I can only guess that I am among many who were deprived of the opportunity to be a trial participant due to a wholly ineffectual approach to gathering sensitive information centered on human behavior. Goodness knows, we need new tools for HIV prevention, and many very well-meaning, generous individuals yearn to help in this endeavor. If study personnel are not equipped with the technical skill and emotional intelligence to collect behavioral information from participants, we may compromise the studies and the progress toward new tools.

When I was first told of this body of work to address the theory and practice of integrating behavioral and social science into the trials, my first thought was, "It's about time!" The field has needed a guide like this to better understand the theories behind highly-nuanced behaviors around sex, and one that could suggest best practices in this area. *Behavioral and social Sciences Points to Consider in Clinical Trials of New Prevention Technologies* is a welcome addition to the collection of tools needed to conduct HIV prevention trials with competence and some grace. My hope is that this work will allow the HIV Prevention research field to be more confident in the study-outcomes that are dependent on self-reported behaviors. I can also hope that it will mean that volunteers will not be lost to insensitivity but be proud participants of an informed, caring, and competent process.

-Steve Wakefield, HIV Vaccine Trials Network (HVTN) External Relations

April 2014

PREFACE

“If you want to change attitudes, start with a change in behavior.”

William Glasser, M.D.

The NIAID/DAIDS in support of and in collaboration with AIDS researchers is committed to innovations of research and strategically pursuing the long-term goal of ultimately eradicating HIV/AIDS from the planet. Over five million people are being treated, and people in many countries are accessing therapy. Simultaneously, prevention activities are being linked to the treatment of HIV and HIV-associated co-morbidities. Pre-exposure antiretroviral prophylaxis (PrEP) has been shown to be an efficacious HIV prevention strategy in people at high-risk for HIV infection. Great efforts are extended to gather information about the behavioral and social determinants that affect the spread of HIV and future directions in HIV vaccine research. That is excellent progress.

However, approximately 35 million people are currently living with HIV; the majority of people infected with HIV are unaware of their status; and most people living with HIV or at risk for HIV lack access to prevention, healthcare, and therapy; and a cure has not been realized. The prevailing model utilized in HIV clinical trials, particularly in introducing new prevention technologies, is evolving. The goal to expand access to care needs to visualize the cure in terms of behavioral and social components.

Studies have indicated HIV risk behaviors can be reduced in targeted populations by providing preventive interventions in the context of individual adherence counseling and community engagement. NIAID/DAIDS supports research leading to a better understanding of the effects that behavioral and social factors have on HIV acquisition and transmission. Funded research encompasses the development of novel behavioral prevention strategies to address dynamic transformations in the HIV pandemic; in primarily non-behavioral clinical prevention and therapeutic trials, NIAID/DAIDS stresses the inclusion of behavioral and social science (BSS) expertise to improve the implementation of effective interventions.

The BSS comprise a vital part of HIV prevention research, because behavioral components influence the acceptance of every specific approach, and in turn, its efficacy. Stemming from the recognized importance of the BSS to non-behavioral clinical prevention and therapeutic trials, which culminated in cross-disciplinary workshops over several years, DAIDS staff and outside consultants have labored to produce an authoritative and exhaustive report containing practical applications and functional knowledge.

This Points to Consider (PTC) document has been developed for clinicians, researchers, and other stakeholders to use as a reference for recommended strategies to enhance the melding of the BSS with new HIV prevention technologies. These “Points” are neither regulations nor guidelines but represent the current thinking that the NIAID/DAIDS and collaborating agencies believe should be considered.

It is our intention to periodically update and revise this document in order to maintain its usefulness. We hope the readers of this document, particularly those involved in clinical prevention and therapeutic trials, will use the BSS strategies offered here and drive forward the goal of eliminating HIV. As a civil society, as researchers, and as healthcare providers, the challenges of the HIV pandemic compel us to employ all the scientific ammunition at our disposal, and chief among the devices in the armamentarium are the behavioral and social sciences.

Carl Dieffenbach, Ph.D., Director of DAIDS/NIAID/NIH

April 2014

Abbreviations and Acronyms

AAAQ	Available, Accessible, Acceptable and Quality
AIDS	Acquired Immunodeficiency Syndrome
ACASI	Audio Computer-Assisted Self-Interview
AETC	AIDS Education and Training Center
ART	Antiretroviral Therapy
ARV	Antiretroviral
AVAC	AIDS Vaccine Advocacy Coalition
BSS PT	Behavioral and Social Sciences Project Team
CAB	Community Advisory Board
CAPRISA	the Centre for the AIDS Programme of Research in South Africa
CASI	Computer-Assisted Self Interview
CBT	Cognitive-Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Science
CROI	Conference on Retroviruses and Opportunistic Infections
DOT	Directly Observed Treatment
DSMB	Data Safety and Monitoring Board
FHI	Family Health International
GBV	Gender-Based Violence
GEM	Gender-Equitable-Men
GNP+	Global Network of People Living with HIV
GPP	Good Participatory Practice
HANC	HIV/AIDS Network Coordination
HIC	High-income Countries
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IAPAC	International Association of Providers of AIDS Care
IAVI	International AIDS Vaccine Initiative
ICASO	International Council of AIDS Service Organizations
ICRW	International Center for Research on Women
ICT	Information and Communication Technology

IMB	Informational-Motivational-Behavioral
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
IOM	Institute of Medicine
IPrEx	the Chemoprophylaxis for HIV in Men Study
IRB	Institutional Review Board
JHU/CIR	Johns Hopkins University/Center for Immunization Research
LMICs	Low-and Middle-Income Countries
MEMS	Medication Event Monitoring System
MERG	Monitoring and Evaluation Reference Group
MSM	Men Who Have Sex with Men
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Diseases
NIMH	National Institute of Mental Health
NPTs	New Biomedical Prevention Technologies
NSC	“Next Step” Counseling
OBSSR	the Office of Behavioral and Social Sciences Research
PEP	Post-exposure Prophylaxis
PEPFAR	the United States President’s Emergency Plan for AIDS Relief
PLHIV	People Living with HIV & AIDS
PrEP	Pre-exposure Prophylaxis
PRS	Prevention Research Synthesis
PRSC	Prevention Review Sciences Committee
PTC	Points to Consider
PUD	People Who Use Drugs
RCTs	Random Controlled Trials or Randomized Clinical Trials
RPAR	Rapid Policy and Assessment Response
SBRA	Behavioral and Social Risk Assessment
BSS	Behavioral and Social Sciences
STIs	Sexually Transmitted Infections
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNGA	United Nations General Assembly
UNGASS	United Nations General Assembly Special Session
VOICE	Vaginal and Oral Interventions to Control the Epidemic

WHO

World Health Organization

1. KEY MESSAGES

1.1. Actions to plan, implement, and reward team science that include behavioral and social scientists should become the norm, rather than the exception.

In HIV prevention research, there are voices calling for “team science,” that include specialty cadres of behavioral and social scientists in HIV New Biomedical Prevention Technologies (NPT) trial teams. The goal is to gather best practices to advance the NPT research field. The NPT redirection marks a shift in paradigms from one where behavioral and social science (BSS) issues and experts are “squeezed in” to traditional biomedical trials, to the new model of “team science” in which behavioral and social scientists are embedded as co-equal team members, so as to achieve productive trial outcomes.

1.2. Community contributions are multifaceted and must be considered in the overall study planning and budgeting.

Host communities have central roles to play throughout HIV clinical trials. Ethical requirements have long codified the responsibilities of investigators to obtain consent from trial volunteers. In addition, the Good Participatory Practice (GPP) guidelines developed by UNAIDS and AVAC (2011) point out that trial funders and sponsors, including government authorities, implementers, and organizations – from faith-based communities to mass media – should be proactively consulted and engaged, from trial planning and funding to implementation and completion.

1.3. Drivers of HIV risk encompass social, economic, organizational, and political factors that contribute to healthcare inequities in access and delivery.

Individual HIV transmission risks should be contextualized within social and structural drivers of the epidemic to guide practice, research, interventions, and policy development. In clinical trials, the host of behavioral and social issues involved in risk behavior and in HIV care and support – from individual knowledge and attitudes to community norms to national health and legal system policy development – are critical to all phases of NPT clinical trials.

1.4. The behavioral and social sciences are focused on understanding the individual and contextual causes of varied human experiences and actions.

The BSS are repositories of theory and knowledge concerning the sources and underlying reasons that motivate people to think and interact as they do, and how they act differently with different people (e.g., their children versus their employers), in different settings (the family hearth versus the clinical waiting room), and in different cultural and geographical locales.

1.5. Incorporating behavioral and social science within NPT trials offers an extraordinary opportunity to build local and global understanding of human health management.

The bulk of behavioral and social science research has been conducted in high income countries, leaving important gaps in the HIV prevention workforce and knowledge base, particularly in the countries hardest hit by HIV.

1.6. The behavioral and social sciences offer a myriad of quantitative analytic methods for exploring and identifying patterns within complex, multifactorial studies.

Rather than seeking to define factors that predict binary outcomes (e.g., infection versus no infection), sophisticated quantitative methods seek to define combinations of variables (factors) that explain significant amounts of variance in complex outcomes. New methodologies are being refined for exploring complex systems in which multiple and multi-directional relationships are among the variables and where systems have emergent properties.

1.7. Behavioral and social sciences recognize the limitations in accuracy of self-reported behavior.

Researchers still have not devised ethical and practical means of directly observing levels of risky sexual behavior, drug use, or adherence to prophylactic products, such as topical or oral Pre-exposure Prophylaxis (PrEP). Thus, measures of proximate behavioral determinants rely on self-report. However, if the self-reported behavior deviates from established assumptions, erroneous inferences may follow.

1.8. The Working Group has identified several areas where better integration of behavioral and social sciences will improve HIV clinical trials, including risk, adherence, and communications/stakeholder engagement.

A number of special challenges are presented in HIV prevention clinical trials and trials of NPTs in particular, which would benefit from behavioral and social science expertise. The populations of most interest epidemiologically tend to be socially, economically, and politically vulnerable. Exploring sensitive topics with vulnerable populations requires developing and maintaining empathetic rapport in addition to real partnership and trust, specifically, in the areas of risk adherence, local communication, and stakeholder engagement.

1.9. Risk reduction interventions can be designed for use in study contexts or in the context of ongoing services.

Extensive literature is available on the development and testing of interventions to reduce HIV risk. Understanding characteristics of the research setting, including the interests, talents, and challenges of site staff, is an important part of designing and monitoring risk reduction interventions.

1.10. Continued involvement of community stakeholders is a dynamic process and needs to be re-addressed throughout the trial.

Research teams should begin early to advocate for newer and better prevention strategies with local community members and stakeholders during the research design and development processes. It is the obligation of research teams to assist with building local capacity and partnerships by assessing the current prevention strategies offered by the local communities.

1.11. In HIV risk assessment, research teams should anticipate and monitor challenges in recruitment, retention, adherence, so as to minimize anxiety and maximize success.

Behavioral and social assessments in clinical trials of biomedical HIV interventions have a critical role in recruitment and retention, as well as in the analysis and interpretation of results. In addition to calculating individual risk, HIV prevention investigators should characterize the context, correlates, potential causes of HIV risk in the study population, and variations among sub-populations for a number of purposes, including recruitment, retention, and adherence.

1.12. Counseling content that is refreshed and updated at every stage of the study complements HIV prevention strategies.

Every circumstance implies different causes and consequences. Anticipating these causes through ongoing and updated counseling at each stage serves to advance maximal understanding and empowerment in efforts to reduce the probability of disease transmission and to improve treatments when transmission does occur.

1.13. Contextual issues have a critical bearing on trial ethics, progress, and outcomes.

HIV prevention trials can no longer afford to marginalize contextual issues. Coping styles, learned resourcefulness, and social support (particularly family relationships and partner support) can influence resilience and the health impact of HIV.

1.14. The role of adherence and factors influencing it, should be included in the trial's overall conceptual framework.

Efforts to plan an adherence support strategy should occur collaboratively and early in the course of designing a prevention trial. The formative research should be guided by theoretical understanding of proven approaches to product adherence; the best available biomedical, behavioral, and social science evidence; and by experts in adherence science. It is critical for teams to study adherence challenges and to develop socially and culturally relevant strategies for reducing individual and structural barriers.

SECTION I

FRAMEWORK

CHAPTER 1. BEHAVIORAL AND SOCIAL ISSUES IN CLINICAL TRIALS OF BIOMEDICAL HIV PREVENTION INTERVENTIONS

Point to Consider 1. “Information is necessary but is not sufficient to effect and sustain behavioral change in large segments of the population.” (Coates et al, 1988)

End of Point to Consider 1

INTRODUCTION

The importance of behavioral and social sciences to HIV research, including HIV clinical trials, has been clear since the first efforts to grapple with the epidemic (Coates et al, 1988; Haynes, 1993; Van Devanter, 1999; Blank et al, 2013) and is widely acknowledged today (Underhill et al, 2010; Kim et al, 2010; Ryan et al, 2012). However, three decades since the HIV epidemic began, HIV prevention trial researchers and clinical research scientists still often struggle with the role behavioral and social sciences play in the development of **new biomedical HIV prevention technologies (NPTs)**. Explicit and unspoken questions linger regarding when, how, and how much to complement basic, clinical, and epidemiological elements of clinical trials; scientific attention should be given to the beliefs, practices, and social and economic contexts that mediate behaviors that are integral to the testing of potential new technologies such as microbicides, preventive vaccines, pre-exposure prophylaxis (PrEP), and the early initiation of antiretroviral treatment (D'Cruz & Uckun, 2004; MacQueen, 2011; Newman et al, 2012; Vermund & Hayes, 2013). Thus, the question is not *whether* to expand the behavioral and social sciences into HIV prevention trials, but *how* to do it; and how to do it so that study findings are definitive. Actions to seek, include, and reward high-quality Behavioral and social components of clinical trials should become the norm, rather than the exception.

Background. In 2009, the Vaccine Research Program, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health convened a diverse group of scientists involved in domestic and international HIV clinical trials to provide practical advice gleaned from their experiences with behavioral and

social sciences, (Lau, Swann & Singh, 2011; see Annex I – Overview of the Initiative). The goal of this effort was to gather best practice experience and expert advice on anticipating and addressing behavioral and social issues that influence biomedical HIV prevention trials in the advancement of the research field on NPTs. The project affirms a shift in paradigms from one in which behavioral and social science issues and experts are “squeezed-in” to traditional biomedical trials, to a new model. This new model requires “team science,” (Creswell et al, 2011; NIH OBSSR, 2007) in which the necessary specialty cadres of behavioral and social scientists are embedded along with biomedical scientists as co-equal team members, to achieve more productive and clear trial outcomes.

Audience and Structure. This document is aimed primarily at researchers and clinical research site staff who are engaged in the planning, execution, and/or evaluation clinical trials of biomedical HIV prevention technologies. It shares a variety of perspectives meant to be meaningful to additional key audiences, including community advocates, communicators, and, very importantly, funders. It is an evolving resource, with practical examples, lessons learned, useful tips, and links to relevant texts and tools – all meant to help investigators and other stakeholders meet the challenges of new, more multi-disciplinary approaches to NPT trials. A few **guiding principles** govern the points to consider that are presented throughout the document [see below]. Finally, the document presents the important perspectives of trial volunteers and other key stakeholders which serve to illustrate how and why the points to consider really matter.

Importantly, this document is not a comprehensive review of the behavioral and social sciences literature; nor is it a manual for designing HIV prevention programs. Excellent resources are available for these purposes (Peterson & DiClemente, 2000; Global Health Learning, 2013, <http://www.globalhealthlearning.org/course/designing-hiv-prevention-programs-key-populations>). It does not constitute formal NIH guidance.

Guiding Principles. In the diverse world of global HIV research, a “one size fits all” approach does not work. However, there are over-arching commitments that should guide decision-making and prioritizing by research teams throughout any study, from conceptualization to dissemination. The guiding principles highlighted by expert groups that contributed to this guide are behavioral and social.

- All HIV prevention research should manifest an overarching commitment to ethical and rights-based research practice.
- HIV prevention clinical trials should build fundamental knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. They should include diverse populations and local determinants, and develop products and strategies that will be widely affordable, accessible, and practical in the social and economic contexts where they are to be used.

- Due to the diversity and social embeddedness of HIV risk and HIV services, good research practice and efficient use of resources require heightened investment in Behavioral and social sciences in NPT trials.
- The guide should contribute to the specific mission of the National Institute of Allergy and Infectious Diseases (NIAID) “to conduct and support research on infectious and immunological diseases that contributes to the health of people everywhere.”
- Researchers and site staff should collaborate with and respect host communities’ customs and laws. Research methods, approaches, and budgets should demonstrate commitment to put study volunteers and their communities first, and to listen and respond to stakeholders throughout the study process.
- Studies should enhance and build on the in-country research capacity of low and middle-income countries.

Clinical Trial Stakeholders and the Protocol Development Process

Trial participants and their communities have central roles to play throughout HIV clinical trials. Ethical requirements have long codified the responsibilities of investigators to obtain permission from local authorities before studies can be considered, and to obtain and maintain informed consent from trial volunteers (Kagan et al, 2012; Rosas et al, 2014; CIOMS, 2002). Experience with HIV clinical trials of NPTs emphasizes that community contributions are much more multi-faceted, and must be considered in overall study planning and budgeting (see Section I Chapter 2). In addition, the Good Participatory Practice (GPP) guidelines developed by UNAIDS and AVAC (2011) point out that trial funders, sponsors including government authorities, implementers, and interested groups and organizations - from faith communities to mass media – are stakeholders who should be consulted and engaged proactively.

Effective engagement begins when research ideas are formulated, but it should not stop there. Stakeholders, specifically the communities that host the clinical trials, should be engaged systematically and consistently throughout the life cycle of protocol development and study conduct. The social, economic and political circumstances of the lives of individuals living in these communities are as integral to a successful clinical trial as are laboratory conditions, product supply chains and other traditional concerns of biomedical research practice (see Figure 1.1 Behavioral and social).

Diversity in the Global HIV Pandemic

A myriad of social, political, economic, and historical differences among the world’s populations have led to a highly diverse and dynamic global AIDS pandemic and response. Because of this diversity and the pace of change within and among countries each country and community benefits from taking steps to investigate the

HIV situation in their own setting – who is most affected, how are they affected, why, and what is being done about it – in order to mount appropriate responses. This diagnostic approach to national and sub-national diagnosis and response has been referred to by the slogan, “Know Your Epidemic, Know Your Response” (Wilson, 2006; UNAIDS 2007).

Figure 1.1 Phases in The Life Cycle of a Clinical Trial



HIV prevalence and incidence rates in populations most at risk vary based on routes of HIV transmission and on social, cultural, political, health and economic conditions in the communities where these populations live. Thus, potential new biomedical prevention approaches must be tested in a variety of affected communities within and between countries before general claims of efficacy can be made. In addition, locations where the incidence of HIV is high are found world-wide, and the majority of people living with HIV (PLHIV) dwell in low and middle-income (LMI) countries. Therefore, the sites of current and future new prevention technologies (NPT) clinical trials can be expected to differ in terms of the national health systems, research infrastructure, politics, and a host of cultural, political, health, legal, environmental and economic factors. Such diverse social factors are not external to biomedical research. They can make or break a study and influence public reactions to an entire prevention strategy.

For example, factors ranging from ethnicity and cultural tradition, to religion, to media responses, had to be taken into account in order to test the efficacy of voluntary medical male circumcision in reducing the risk of HIV acquisition for men (Ngalande et al, 2006; Weiss et al, 2008;) in countries with generalized epidemics. Investigators found it challenging to deploy the protocol for testing PrEP with men who have sex with men in the six sites of the iPrEx trial without first accounting for

local conditions. (Carlos Cáceres, personal communication [comment made during PrEP Demonstration Project meeting in Washington, DC, July 2012]).

Issues of diversity are particularly central because in order to observe enough study endpoints within a reasonable study period clinical trials of NPTs must be conducted in populations at high-risk of HIV exposure and infection. In countries where HIV is rare in the general population, HIV may be concentrated in “key populations”¹, groups such as men who have sex with men, sex workers and people who inject drugs. Whether these key populations are in high income or LMI countries, the groups who have most to contribute to the research tend to be underserved, or actively marginalized by mainstream institutions, and economically and politically vulnerable. Despite similarities in the “risk environments” (Rhodes & Simic, 2005) of key populations, investigators need to understand the specific dangers and resources that frame the life conditions of prospective trial volunteers, as these vary widely at the community and national levels.

Comment 1.1 A Stakeholder viewpoint on research with vulnerable communities.

“While vulnerability may leave research participants and their communities open to exploitation, [these] data indicate that clarity about the fairness of research practices within the local context can be achieved through dialog among researchers, sponsors, participants and community stakeholders.”² **End of**

Comment 1.1

Since the early days of the WHO Global AIDS Programme most countries have developed medium term plans for responding to HIV that followed a common template. The Declaration of Commitment drafted during the unprecedented United Nations General Assembly Special Session (UNGASS) on HIV in 2001 and the Political Declaration signed in 2006 both established a global commitment to Universal Access to HIV prevention, treatment, care and support, and a common framework of measurable goals, targets, and indicators (UN General Assembly, 2006). Despite this common framework, there remain large differences in the economies, health systems, justice systems and the health and social policies that create the foundation for HIV prevention research.

Thus, the specific national context, leaders and guidelines in key sectors should be taken into account when planning HIV prevention trials. In addition, knowledge, attitudes and behavior of participants and study staff members differ from community to community which contribute to trial dynamics. Behavioral and social sciences, including anthropology, economics, sociology, political science and psychology, provide theory and methods to anticipate, explore and rigorously

¹UNAIDS, The Strategic Information and Monitoring Division, Methodology-Understanding the HIV estimates. 2013.

²MacQueen KM, Namey E, Chilongozi DA, Mtweve SP et al. Community perspectives on care options for HIV prevention trial participants. *AIDS Care*, April 2007; 19(4): 554-560.

document these kinds of diversity, and to predict and prepare for their impact on study design and outcomes.

Behavioral and Social Factors in Clinical Trials of Biomedical HIV Prevention Interventions

An enormous scientific effort over the past three decades has gone into understanding sexual, drug use and reproductive health behaviors in order to inform interventions to prevent HIV transmission. Behavioral and social scientists and historians have emphasized that complex, culturally constructed and mutually reinforcing beliefs, meanings, attitudes, aspirations, roles, relationships, social norms and informal and formal policies and laws shape sexual and drug use practices and networks (Sabatier, 1988; de Zaluendo, Msamanga & Chen 1989; Sweat et al, 1995; Auerbach & Coates, 2000; Baral, 2012).

Epidemiologists have sought to cut through this complexity and quantify sexual and drug use behaviors as events that can be tallied objectively, and to estimate their roles as risk factors or “proximate determinants” (Boerma, Weir et al, 2005) of HIV transmission. Aligned with this approach, a focus on individual-level knowledge, attitudes, motivations, skills, and partner types in health promotion and behavior change dominated the first two decades of HIV prevention research (see Chapter 3 for further details). More recently, consensus has emerged that multi-level models, which also examine structural factors (see Box 1.2) are needed to account for the proximate biological and behavioral factors that shape HIV risk and risk reduction, including those in clinical trials of NPTs (Gupta et al, 2008; Auerbach et al, 2009; see Phillips and Pirkle, 2011).

Comment 1.2. Structural causes of HIV vulnerability and risk.

“Structural” - when juxtaposed with the “biomedical and behavioral” – refers to the broad range of social, cultural, economic, political, legal and physical environmental conditions that operate outside the individual; that directly and indirectly influence HIV vulnerability and risk; and that individuals alone cannot change (e.g. Sumartojo, 2000; Gupta et al, 2008; UNAIDS, 2010). Some researchers distinguish “social” and “structural” factors reserving the latter for macro level, societal systems such as a body of laws, or the global economy (e.g., Sweat & Dennison, 1995; Koblin, Andrasik & Austin, 2013).

“Structural interventions refer to public health interventions that promote health by altering the structural context within which health is produced and reproduced.” (Blankenship et al, 2000). **End of Comment 1.2**

Recognition that biomedical, behavioral and structural factors interact at multiple levels and should be considered jointly is a key feature of “combination prevention.” Government guidelines now advise implementers not only to “know your epidemic” and “know your response,” but also to “know your context” and “know your costs.” (PEPFAR 2011 guidelines for prevention of sexual HIV transmission). The influence

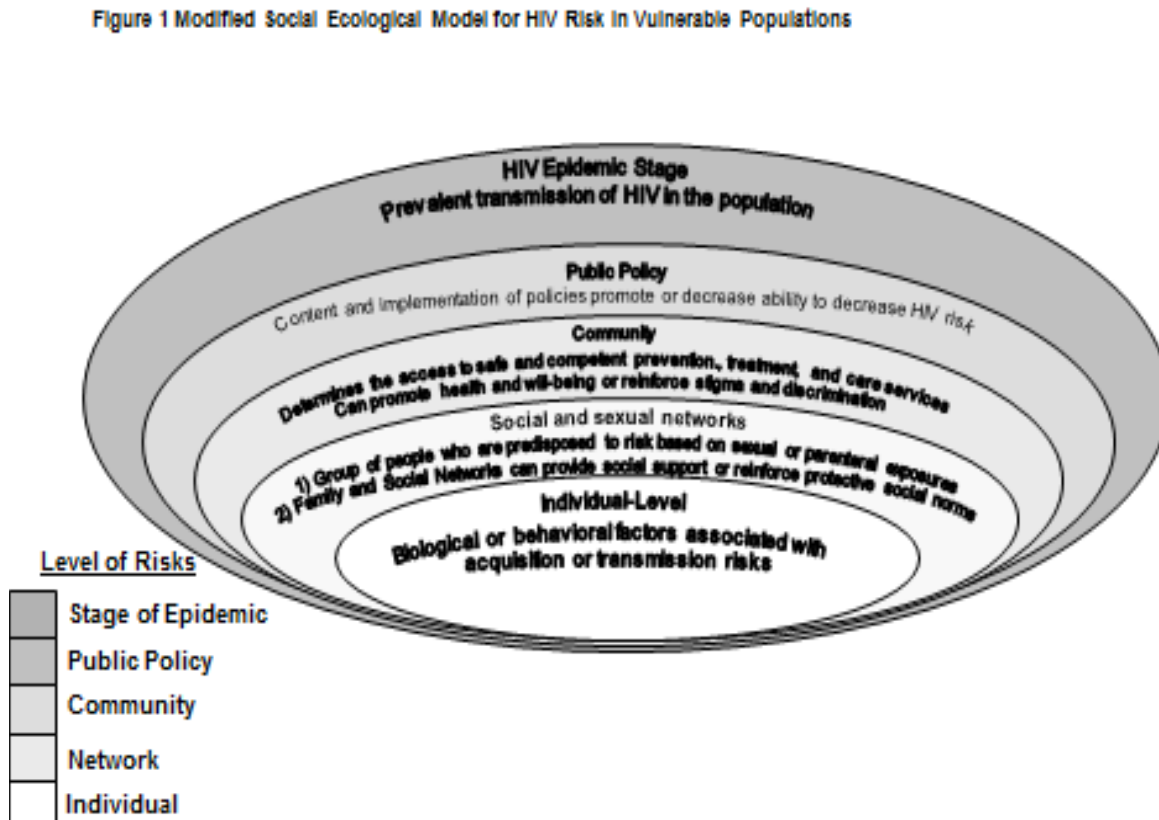
of epidemiological, social, cultural, economic, legal and political, and physical environmental factors is represented in socio-ecological models such as the example provided by Baral et al, 2013 (see Figure 1.2).

Regarding “know your context,” behavioral and social science approaches highlight three tenets to inform biomedical-oriented HIV studies:

- Structural drivers of HIV risk include social, cultural, economic, organizational and political factors that contribute to social inequities and influence HIV risk at the individual, network and community levels;
- While clinical trials of biomedical products are not focused on changing social and economic conditions, those conditions influence the conduct of research, so they must be adequately assessed and addressed in the development and implementation of clinical trials, to optimize chances of a successful outcome;
- Investigators and funders have an ethical obligation to identify and address structural conditions that can be reasonably expected to harm study participants, staff and/or their communities, or to put them in danger.

Study design, stakeholder engagement and communication, recruiting, and retaining eligible volunteers, promoting adherence to study procedures/regimens/, training and supervising culturally competent researchers including site staff, monitoring study impact, trouble-shooting, interpreting and disseminating results, promoting research translation, and dealing with local and global mass media (see Figure 1.3) are profoundly affected by the social, cultural, economic, political and historical backgrounds and expectations of researchers and host communities.

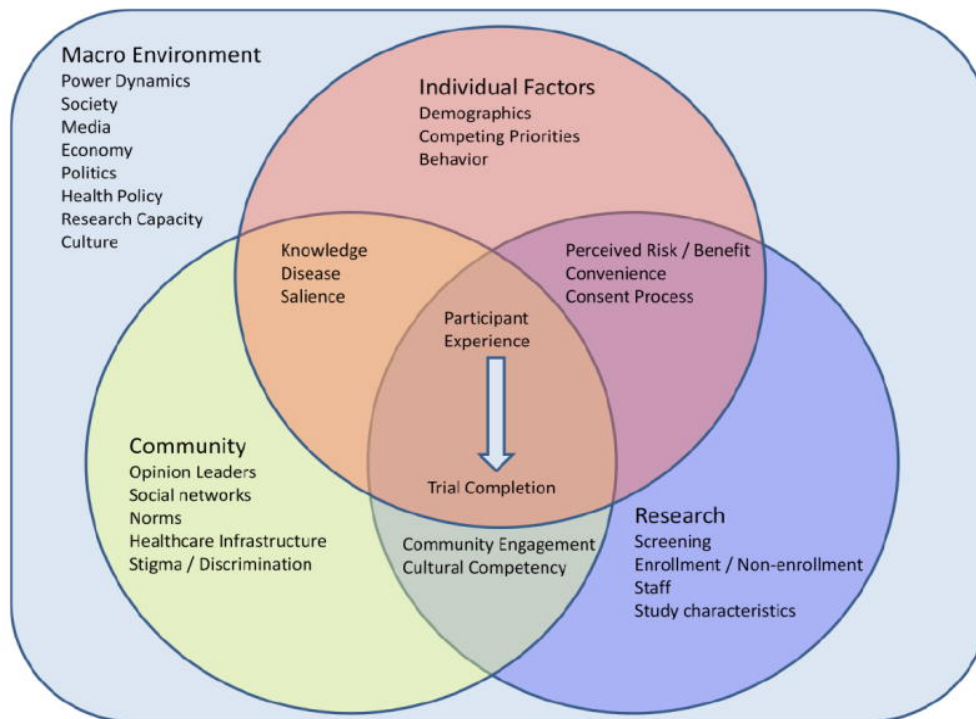
Figure 1.2 A socio-ecological model of factors influencing HIV risk and vulnerability of people who inject drugs. Source: Baral et al, 2013



Building on prior research and theory about the interaction of behavioral and social factors, Lau, Swann, Singh, Kafaar, Meissner, and Stansbury (2011) offered a heuristic, socio-ecological framework for HIV vaccine trials. Their review refers to the interacting factors at play, operating at individual, community and “macro” levels, to influence sexual and drug use practices. Unlike many other heuristic HIV prevention frameworks, in addition to including HIV risk behavior and the community and macro level factors that affect it, they call attention to the importance of the health care infrastructure. At a potential study site, communities’ knowledge and beliefs about health, disease and healing; their history with health service providers and researchers; socioeconomic characteristics of, and power relations between, volunteers and site staff; and other issues affect how and

whether a clinical trial gets done, and with what social and scientific impact (see Box 1.3).

Figure 1.3 Individual, Community and Research Setting, and Macro Environment Factors Affect HIV Vaccine Trials (Lau, Swann et al, 2011)



Contributions of Behavioral and Social Sciences to NPTs

Social and behavioral sciences can be considered by scientists and implementers from various technical backgrounds. What, then, are the behavioral and social sciences, and what are their specific contributions, or added value, in conceptualizing and collecting data on them? How can engaging behavioral and social scientists improve the outcomes of NPT clinical trials?

The behavioral and social sciences

Boundaries between behavioral and social sciences are permeable, but in general, **the behavioral sciences** deal with *psychology*, its biological bases (e.g., neuropsychology, psychiatry, human growth and development), inter-individual factors such as relationships and networks, and cognitive factors from information processing to memory and decision-making. **The social sciences**, principally *anthropology, economics, geography, political science* and *sociology*, deal with culture, social organization, economics and politics, addressing how the physical environment, and/or social structures, processes and systems, shape individual and

community experience and behavior over time (e.g., the experience of illness and healing, socialization, religion, the subsistence system, and how individuals and groups catalyze social change).

Social-ecological models of health remind us that biomedical and behavioral, and individual and social factors are interdependent and interacting. Numerous sub-disciplines have emerged to focus on these intersections, such as social psychology, behavioral economics, or medical anthropology, as well as thematically focused specializations, such as child and adolescent psychiatry, psychiatric epidemiology, or women's studies. Communications is a problem-focused specialty that is founded in behavioral and information sciences, with broad applications in the HIV world, from social marketing to media relations. Problem-focused, integrative training in socio-behavioral sciences and communications is increasingly available in public health, but there are inevitable trade-offs of depth for breadth.

Comment 1.3 – Clinical Research Challenges

1. Prioritization of research questions
2. Divisions between clinical research and clinical practice
3. Clinical trial globalization
4. Clinical trial funding
5. Low incentives for practitioner participation
6. Dwindling clinical research workforce
7. Navigating convoluted administrative and regulatory requirements
8. Recruitment and retention of subjects.

Source: Transforming Clinical Research in the United States, Challenges and Opportunities: Workshop Summary; Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Washington (DC): National Academies Press (US); 2010. ISBN-13: 978-0-309-15332-4 ISBN-10: 0-309-15332-8. **End of Comment 1.3**

Five benefits that BSS can provide to NPTs

1. An explicit conceptual framework is essential to explore the impact of BSS on NPTs. Behavioral and social scientists have mastered the rich body of theory and data in their respective fields that concerns HIV risk behaviors, health beliefs and behaviors, health inequalities, and their behavioral and social determinants. Behavioral and social scientists can also outline causal frameworks and formulate hypotheses about the potential pros and cons of a study for specific populations and settings in terms of their “sociological plausibility” (Goldthorpe, 2000; Auerbach et al, 2009).
2. The behavioral and social sciences are repositories of theory and knowledge concerning how and why individuals think and interact as they do, and why they act differently with different people in different settings, and in different cultural and geographical locales.

Comment 1.4. Stakeholder Viewpoint. What is “social” and what is “behavioral”?

“... the term “behavioral” refers to overt actions; to underlying psychological processes such as cognition, emotion, temperament, and motivation; and to bio-behavioral interactions. The term “social” encompasses sociocultural, socioeconomic, and socio-demographic status; to biosocial interactions; and to the various levels of social context from small groups to complex cultural systems and societal influences.”

Source: National Institutes of Health, Office of Behavioral and Social Science Research, 2010. **End of Comment 1.4**

Biomedical-oriented researchers often see their knowledge and procedures as objective and uncomplicated, whereas medical sociologists and anthropologists view both local, traditional medicine and biomedicine as complex social and cultural systems (Kleinman, 1978). A range of basic constructs from each of the behavioral and social sciences have wide relevance to HIV prevention trials.

For example:

- Anthropology contributes the concepts and evidence of insider (“emic”) and outsider (“etic”) points of view, which are crucial for understanding local perceptions of HIV and HIV prevention (Helman, 2000);
 - Psychology contributes cognitive models (selective organization of perceptions and memory according to normative or idealized models of situations or events, which affects recall and reporting of HIV risk behavior (Grenard et al, 2013; Wagner et al, 2010).
 - Sociology contributes theory and evidence on social norms - descriptive and prescriptive rules about how people are supposed to behave in specific situations (Parsons & Shils, 1951), and which provide a “grammar” of social interaction (Bicchieri, 2006).
3. People trained in the Behavioral and social sciences expect that the causes of health behavior are complex, multi-factorial and often non-linear, and that knowledge, meanings, experience and behavior will vary in patterned ways from place to place, and society to society.
 4. Behavioral and social scientists provide necessary bridges to systematically elicit and address local meanings, knowledge and history that affect clinical trials and that can contribute directly to development of sampling, data collection and analysis plans, as well as to interpretation of quantitative results. Establishing a common language among site staff, volunteers, community leaders and investigators takes time and effort but can avoid major misunderstandings on all sides (Kagan JM et al, 2012; Rosas SR et al, 2014).

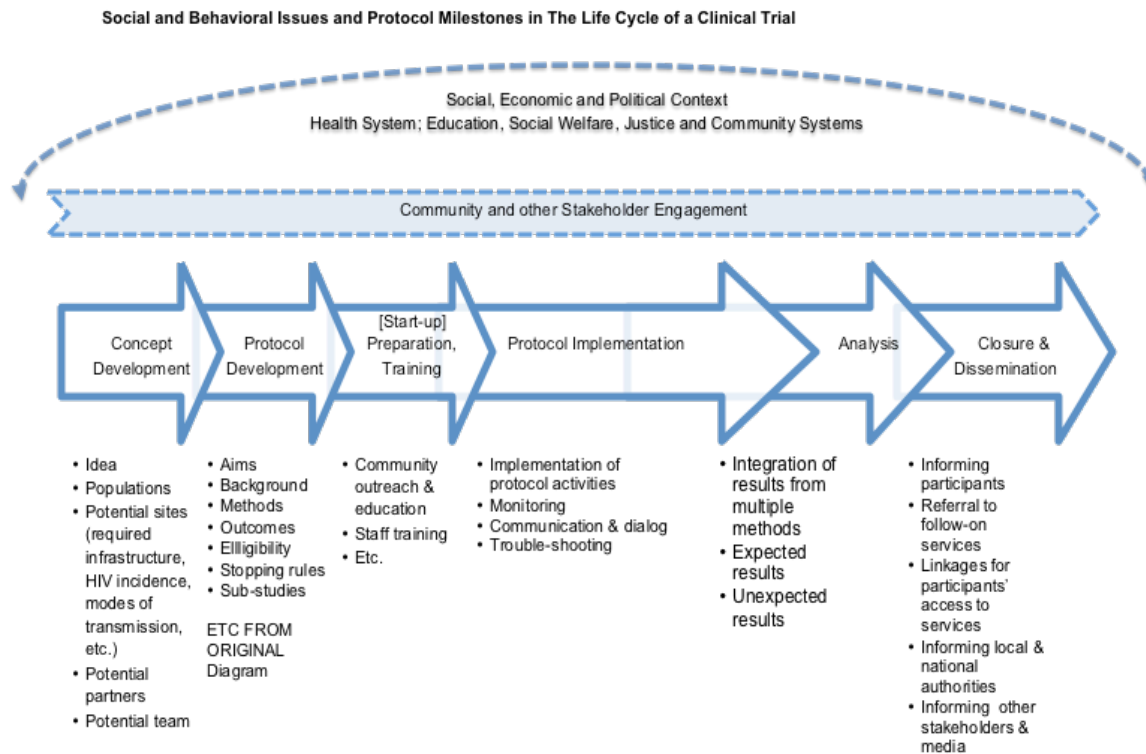
Comment 1.5. Practical Tip

The behavioral and social sciences supply different levels of analysis, and their respective theories and methods. Specifically, in a multi-site trial it is important to complement the individual-focused theory and methods of psychology with sociological or anthropological expertise to lead planning and data collection on the social contexts of HIV risk. Communications specialists focus on how to frame and deliver a study's messages to different audiences. Thus when forming a protocol development team, it is practical to recruit different specialists to handle these three important areas. **End of Comment 1.5**

Importantly, the knowledge base of sociologists, anthropologists and medical geographers will combine a common core of general theory and method with specific knowledge of the history and prior research in their own region and thematic area of expertise (examples from NPT trials). For example, all medical anthropologists will bring knowledge of the social embeddedness of healing and care and the cultural construction of illness categories and etiologies (Helman, 1984) and may bring specific local knowledge.

In Port-au-Prince, Haiti, for example, a long-established health research team, following a decade of research practice in the region, translated 'sexually transmitted infection' into "illnesses a person can get when having sex." The anthropologists on the team found, however, that study participants considered tuberculosis an STI under that definition, given that in sexual relationships "you sleep together, and he can cough in your face" (de Zaldondo & Bernard, 1995). This ethnoscientific observation may or may not apply in another culture or country. In contrast, in the biomedical sciences, the starting assumption is that theory and knowledge are universal (e.g., all people have an endocrine system that works the same way in all people).

Figure 1.4 Behavioral and social issues affecting phases of a clinical trial



5. Incorporating specialists who will build good behavioral and social science into NPT trials offers an extraordinary opportunity to build local and global understanding of human health and behavior. The vast majority of behavioral and social science research has been conducted in high income countries, leaving important gaps in the HIV prevention workforce and knowledge base in the countries hardest hit by HIV.

The Role of Theory

A theory is an explicit statement or model of cause and effect that has been or can be subjected to empirical testing and falsification. Theory helps to focus behavioral and social components of research to address the “how and why” questions, before, during, and after the study endpoints have been measured. Good behavioral and social science uses existing theory and knowledge, and applies these to frame hypotheses and data collection plans that both contribute to the study outcomes and also build general knowledge by confirming or disconfirming their hypotheses.

For example, there are theoretical frameworks (and sometimes competing ideas) from a range of disciplines regarding gender inequality, adolescence, sexuality, identity, health beliefs, stigma, capacity development, social stratification, governance and conflict resolution, and many other topics that can help predict barriers to recruiting and retaining women and girls in NPT clinical trials, and barriers and incentives to their adherence to NPTs. Based on gender theory, Gupta

et al. (2008) famously juxtaposed two pathways whereby gender inequality influences the ability of women and girls to negotiate safer sex with their male partners: fear of gender based violence and economic dependence. Noting that research was tending to focus on one or the other of these pathways, they recommended that interventions to reduce HIV risk for women should address both.

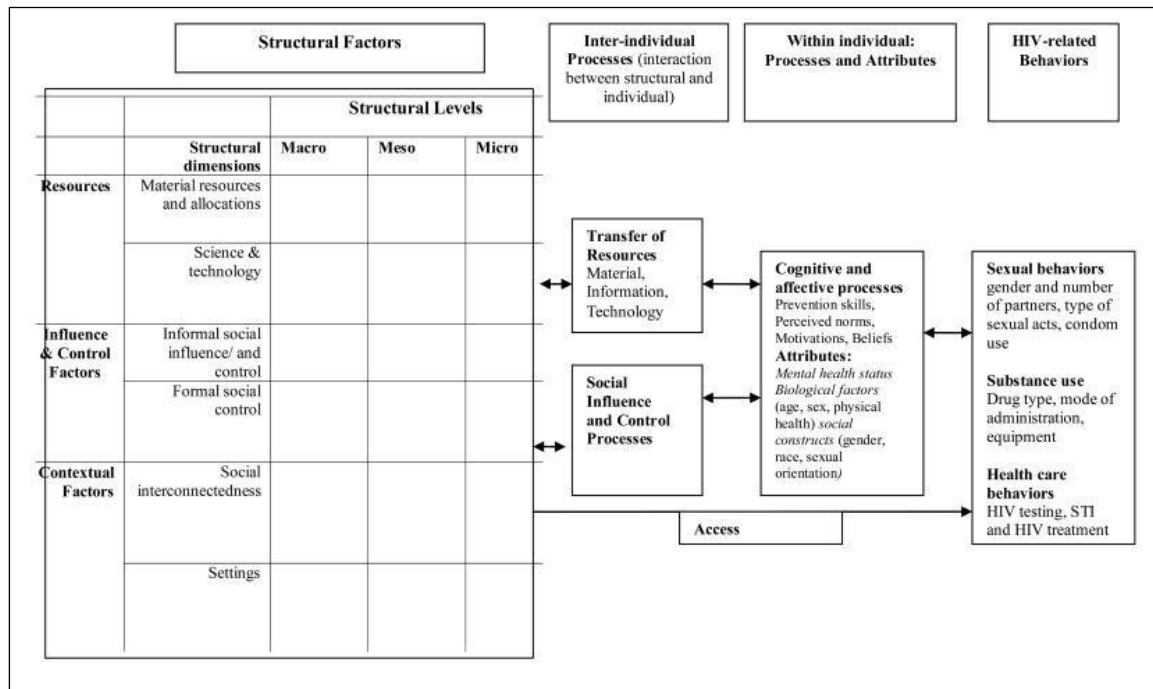
This kind of theory-based analysis, complementing local knowledge, can support plans to enhance participation of women in clinical trials of NPTs, and to support their retention and adherence. Because of their scale and duration, biomedical HIV prevention trials afford an opportunity to embed and evaluate behavioral and social intervention strategies that will illuminate HIV and other health behavior while they improve trial outcomes. This integration can be accomplished through ancillary studies, or by building theory-building questions directly into the trial design itself.

Multi-level causation. In a significant effort to improve the comparability and cumulative knowledge building about these complex issues, Latkin et al. have offered a comprehensive, “dynamic social systems model” (Latkin & Knowlton, 2005; Latkin et al. 2011). It builds on earlier, individual focused theoretical models and pays special attention to unpacking the contextual, or structural factors that too often are left undefined in NPT clinical trial design (see Figure 1.5). This trans-disciplinary, synthesis model identifies six categories of structural factors to consider when explaining or assessing HIV prevention and related behavior. The right-to-left arrows depict the causal cascade through which these factors are expected to influence HIV-related behaviors:

- Material resources (food, money, land, etc.)
- Science and technology, including scientific knowledge, and types of prevention technology available (for example, condoms, PrEP)
- Informal social control (for example, social norms, influence of opinion-leaders)
- Formal social control (laws and policies, the organizations that formulate and implement them)
- Social interconnectedness (including formal and informal social networks, associations).
- Settings (e.g. clinics, schools, neighborhoods, cities, etc.).

Latkin, et al, (2010) illustrated how these six dimensions operate and interact at different levels (using terms micro, meso, and macro), and provide concrete examples of how these dimensions influence harm reduction interventions, and HIV testing and counseling.

Figure 1.5. The Dynamic Social Systems Model of HIV- related behaviors.
Source: Latkin et al, 2010.



In every study, there are many behavioral and social factors that may affect the trial that need to be considered in order to provide an explicit conceptual framework of the key factors in the lives of the study participants. These factors define “what is going on” outside the clinic, beyond the view of the clinical staff.

Given this, the study team can define the key structural conditions, the study inputs and activities, and the expected short-term and long-term outputs and outcomes that are particularly relevant to the NPT trial, and that can be monitored and analyzed. The team can point to study recruitment criteria that will minimize loss to follow-up while avoiding selecting a population that is so different from the general population that conclusions will not be generalizable (MacQueen 2013). In addition, behavioral and social knowledge also supports effective “segmentation” of the study population (i.e., identifying sub-groups that are different enough to require different approaches), so that superficial similarities (e.g., age and sex, residence, occupation) are not the sole guide to tailoring outreach, recruitment and data collection (AETC 2013).

Behavioral and Social Science Methodologies

A methodology is a set of methods that are called for and justified in terms of a specific theory or approach. Each behavioral and social science discipline brings theory-based methods (i.e., methodology) to the research effort. For example,

Lundahl et al, (2010) explain that “Motivational interviewing is a counseling approach; it is a philosophy and a broad collection of techniques employed to help people explore and resolve ambivalence about behavioral change.” (p. 137).

HIV research has long since transcended squabbles about the relative value of qualitative and quantitative methods. Both have different critical functions (Bernard, 2000); the behavioral and social sciences offer a myriad of quantitative analytic methods for exploring and identifying patterns within complex, multifactorial study issues. For example, network analysis has been a powerful tool in the study of HIV transmission and prevention among people who inject drugs (Latkin et al, 1995; Friedman and Aral, 2001; Rhodes et al, 2005), and for explaining how very small differences in numbers of sexual partners can have an explosive effect on HIV transmission dynamics (Morris & Kretzschmar, 1997).

Rather than seeking to define factors that predict binary outcomes (infection/no infection), quantitative methods in the behavioral and social sciences are often used to define combinations of variables (factors or components) that explain significant amounts of the variance in complex outcomes (Cohen, 1968; Giri, 2004). New methodologies are being refined for exploring complex adaptive systems in which there are multiple and multi-directional relationships among variables, and where systems have emergent properties (Byrne, 1998; OBSSR symposium series).

Standards of evidence. There are no ethical and practical means of directly observing levels of risky sexual or drug use behavior, or of on-going adherence to prophylactic products such as topical or oral PrEP. Therefore, measures of proximate behavioral determinants of HIV risk rely on self-report. Behavioral and social sciences recognize that there are limitations to the accuracy of self-reported behavior, and use a variety of methods to reduce and quantify inaccuracies that stem from cognitive, emotional and social constraints on reporting (see Section II, Risk Assessment, Chapter 3). These are routine in behavioral and social research in high-income countries (HICs), where there is an extensive body of knowledge available to guide and streamline collection of self-reported data. That knowledge is only partially transferrable across populations and settings, and there is a large gap in behavioral and social science research on these issues in low and middle-income countries (LMICs).

Debates about the credibility of self-report data often mask deeper, philosophical differences between scientists trained in positivist scientific traditions and those trained to view human behavior – including reporting behavior -- as socially constructed and embedded (Kippax, Holt and Friedman, 2011). This difference in philosophy and training explains the persistence of debates over the place of randomized clinical trials (RCTs) in HIV prevention research, long after the strengths and limitations of RCTs have been enumerated (UNAIDS/MERG, 2009a; Mermin and Fenton, 2012; Padian et al, 2010).

When developing a clinical trial, it is the responsibility of the behavioral and social science team to assess the available knowledge regarding each potential study site in relation to the priority issues that have been identified in the conceptual model of their study. Based on that combination of theory and available evidence they can recommend the appropriate range of data collection and analysis methods to consider. This includes assessing whether key constructs (e.g., “sexual partner;” “vaccine,” “randomization”) have been adequately explored in local terms, and if available data collection tools (e.g., focus group guidelines, questionnaire items, ACASI methods) apply, and have been tested successfully, in the planned site/s.

Cross-site comparability is essential for trial success and for building transferrable knowledge, and it takes expertise to adapt tools to local settings without losing comparability and external validity. Collaboration between behavioral and social scientists from each of the countries involved in a multi-site trial is a good way to mobilize the relevant data and refine the study’s theoretical framework and methods, as well as to build research capacity on all sides.

Multi-method research. Given the diversity of individual and contextual issues that can contribute to clinical trials of NPTs, multiple Behavioral and social science methods are almost always required to approach the issue from different perspectives (e.g., individuals, their sexual or drug use partner/s, family members, community, service providers). The NIH Office of Behavioral and Social Sciences Research recently released guidelines for multi-method research (Creswell, 2011), stressing the importance of a clear philosophical and theoretical basis for selection of the methods, judicious selection of qualitative and quantitative methods, according to the issues at hand, having a strategy for integrating the varied types of data (merging, connecting or embedding), and including the appropriate array of behavioral and social scientists on the team to provide an adequate breadth and depth of expertise (Box 1.9). Triangulation, or converging analysis of data from different sources and/or perspectives, to achieve a more complete and insightful picture, is an essential skill-set in multi-method research.

Comment 1.6. Multi-Method Research.

“Social inquiry is targeted toward various sources and many levels that influence a given problem (e.g., policies, organizations, family, individual). Quantitative (mainly deductive) methods are ideal for measuring pervasiveness of “known” phenomena and central patterns of association, including inferences of causality. Qualitative (mainly inductive) methods allow for identification of previously unknown processes, explanations of why and how phenomena occur, and the range of their effects (Pasick et al, 2009). Mixed methods research, then, is more than simply collecting qualitative data from interviews, or collecting multiple forms of qualitative evidence (e.g., observations and interviews) or multiple types of quantitative evidence (e.g., surveys and diagnostic tests). It involves the intentional collection of both quantitative and qualitative data and the combination of the strengths of each to answer research questions.” (Creswell, Klassen, Clark and

Smith, 2011 for OBSSR, page 5). **End of Comment 1.6**

Special challenges in HIV prevention trials

There are several special challenges in HIV prevention clinical trials, and trials of NPTs in particular, which benefit from Behavioral and social science expertise.

1. Topics involved in HIV prevention are sensitive, and mostly private. Some, such as sex work and injecting drug use, are also illegal in many settings. Intimate conversations are required, and conducting, documenting and analyzing these in a professional manner require the relevant expertise.
2. Populations most of interest epidemiologically tend to be socially, economically and politically vulnerable. Working on sensitive topics with vulnerable populations requires developing and maintaining not only courteous rapport, but real partnership and trust. The overarching medical dictum – do no harm – must shape all decision-making in HIV prevention trials, and where affected communities face legal sanction, this is especially challenging.
3. Benefits and motivations for participation and adherence in HIV prevention trials are difficult to explain and promote. Concepts of medical treatment are much more widely understood and explained than prevention, and the benefits of participating in prevention research are less obvious, especially for potential recruits who do not perceive themselves to be at high-risk of infection (AVAC, 2005; Tolley et al, 2014,).
4. Communication challenges in HIV prevention trials requires explaining technical concepts such as “risk” and partial protection. Working in HIV requires dealing with sensitive topics that may be taboo in polite conversation, and yet they attract media attention.
5. HIV NPT investigators are held to the highest ethical standards, but in some cases, there are inconsistencies that must be negotiated. Standards of care mandated by global guidelines may differ from those held and implemented in study locales and between study sites in high income and low-income countries. These issues need to be contextualized and negotiated locally, with a range of different stakeholders who have different knowledge and interests. Social sciences and communications offer models and methods for the needed policy dialog, community consultations and advocacy.
6. Finally, HIV prevention research is political. The topics, the funding, the populations most at risk, the asymmetries between researchers and volunteers, and the local-to-global advocacy around HIV research define the circumstances in decision-making (Crewe, 2007; Campbell/ Letting them Die; Nguyen, 2011; Altman and Buse, 2012). Social science expertise, along with a commitment to respect host communities and

invest in equitable relationships and benefits, can enable research teams to anticipate and better deal with local and global politics of HIV prevention research.

Comment 1.7. “The dilemma for HIV prevention researchers (as in other health areas) is that the more we learn about effective methods, the harder it will be to test new ones that might be even more effective (including cost-effective).” Auerbach and Coates, 2000. **End of Comment 1.7**

RECOMMENDATIONS

1. Behavioral and social issues are central to clinical trials of biomedical HIV prevention strategies. Behavioral and social scientists should be included as vital members of the protocol team to ensure that all aspects of the study use the best available science and contribute to ethically and technically sound research.
2. Protocol teams should develop a bio-psycho-social conceptual framework that includes the full range of proximate and distal factors that will influence participation in and outcomes of the trial. Using a socio-ecological model can stimulate planning and hypothesis formation.
3. The behavioral and social science sub-team should include experts from each country where the research will take place, and technical dialog and exchange among them will strengthen both the research and research capacity on all sides.
4. While many of the terms and constructs that feature in HIV prevention research are familiar to all health scientists, theory and methods from the behavioral and social sciences should be utilized to frame and document behavioral and social issues, such as participation, community engagement, gender equity, sexual and drug use, HIV-related stigma, risk perception, and adherence.
5. Current and historical issues regarding the research sites, and interactions between researchers, the communities, and site staff, should be considered early.

CONCLUSIONS

There are costs to integrating Behavioral and social sciences more effectively into NPT clinical trials, but it is important to resist short-term thinking and competition of zero-sum thinking. Neither affected communities nor research donors can afford the false economy of flat trials that do not yield clear information about what happened and why, or that lose community support. Social behavioral concerns play a fundamental role in the implementation and impact of HIV clinical trials, particularly in the integration with biomedical HIV prevention methods.

The current document focuses on three themes where the social and the biomedical are intertwined. The next chapter of this section addresses *Community and Stakeholder Engagement and Communication*, sharing perspectives from study

volunteers, investigators, site staff and others on the varied Behavioral and social challenges that arise in the phases of clinical trial design and implementation. Subsequent sections of the document address thematic areas of Behavioral and social science theory: Risk and Adherence.

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CHAPTER 2. COMMUNITY AND STAKEHOLDER ENGAGEMENT – THE HEARTBEAT OF CLINICAL TRIALS

Stakeholder Perspectives on Stakeholder Engagement

Good Participatory Practice (GPP) guidelines define stakeholder engagement as “processes through which trial funders, sponsors, and implementers build transparent, meaningful, collaborative, and mutually beneficial relationships with interested or affected individuals, groups of individuals, or organizations, with the goal of shaping research collectively” (UNAIDS-AVAC, 2011).

From the outset of the HIV epidemic, HIV clinicians, epidemiologists and other biomedical research staff around the world have established powerful bonds of trust and mutual respect with people living with HIV and their communities. These bonds, often forged over years, have provided insight into the behavior and life context of study populations which has enriched the planning and design of HIV prevention research. Active and informed participation by volunteers is the *sine qua non* of clinical trials. Today, HIV research experts recognize that the behavioral and social sciences have a large place in planning and measuring community and other stakeholder engagement in clinical trials of biomedical HIV prevention strategies (Dieffenbach, 2012, speech at Microbicides 2012; Fauci, 2012 – speech at VAX2012 in Boston). In addition, HIV research is building broader theory and knowledge about health behavior, health systems and community development that have practical applications beyond HIV (IOM 2008; Campbell and Cornish, 2012).

This chapter highlights the importance of community and stakeholder engagement and communication with new biomedical prevention technologies (NPTs) research teams throughout the life of a protocol. The chapter is structured according to the protocol phases in Figure 2.1, which depicts the continuing importance of stakeholders from the beginning to the end of a clinical trial. Study stakeholders include the communities where the trial will take place; the volunteers and their relatives and friends, local opinion leaders; the researchers; the clinical teams; national regulatory authorities; local experts including academics, health service providers, HIV advocates and funders. People living with HIV are especially vital stakeholders who are in a unique position to contribute insights into what works, and what has not worked, in HIV prevention (UNAIDS-GNP+, 2013).

Proper stakeholder engagement strives to ensure that key groups genuinely understand and support a study’s objectives and contribute to a well-run trial. The knowledge and support of a diverse array of participants can optimize many aspects of a given trial including: ethical study design; community education; volunteer recruitment, counseling and retention; self-reported information; the analysis and sharing of information about the trial and other crucial procedures.

Because every community is different, and differences are multiplied when multi-country research is involved. Study design must include rigorous and realistic site

assessments of the issues that matter to stakeholders in their own settings, including “macro” sociocultural, economic and political issues and the “meso” or community and organizational environments of study participants (see Chapter 1). Only through dialog about the study in its “real life” contexts can community members and other stakeholders establish firm common ground for collaboration, and specific, empirically grounded strategies for internal and external communication throughout a clinical trial.

Stakeholder engagement is a sustained process that should occur throughout the lifecycle of clinical trials (UNAIDS-AVAC, 2011). There is an extensive literature in the social sciences, including sociology, anthropology and political sciences, on community participation in HIV programs and more broadly, in health and human development activities (White, S. 1996; Hickey and Mohan, 2005). Social science expertise in this area can help study teams to investigate the local context systematically, using rigorous participatory methods and complexity science, in addition to traditional descriptive and analytic methods (Plsek & Greenalgh, 2001; Byrne, 2007).

Stakeholder engagement serves the important goals of empowering affected communities and enhancing partnerships between researchers and communities. Genuine engagement entails transparent two-way communication throughout the trial. This is fundamental to the successful implementation of biomedical HIV prevention trials (Newman et al, 2009; Slevin et al, 2008).

Comment 2.1. Stakeholder Perspectives

“Women and men are physiologically different, so results and conclusions from male-only studies cannot be assumed to be applicable to women...

“It is both ethically and scientifically sound to enroll women in adequate numbers to be able to provide answers pertinent to them in all stages of human subject research.” (Catherine Hankins, 2007; <http://www.unaids.org/en/Resources/PressCentre/Featurestories/2007/December/20071205roleofwomenHIVtrials/>). **End of Comment 2.1**

Since HIV risk behavior, including sexual and drug use practices are culturally constructed, and individual behavior is embedded in a web of social, economic, and political relationships, structures and constraints (see Chapter 1), each protocol team should investigate and unpack these behavioral and social issues in a systematic way. Culture influences everything from underlying constructs of health, medicine, sexuality, gender, individual autonomy and risk, to the language used and understood in study interactions. Designing and carrying-out clinical trials in HIV requires site-specific social as well as biomedical knowledge. For example, in settings where women and girls have subordinate social status, or have limited access to health information, special efforts are required to inform and engage them in HIV research (UNAIDS, 2007,

<http://www.unaids.org/en/Resources/PressCentre/Featurestories/2007/December/20071205roleofwomenHIVtrials/>).

Inclusion and research literacy. In many cultures around the world, including the global south and diverse ethnic minority cultures in the global north, the individual is not at the center of decision-making. In the case of what may be major decisions, such as participation in an HIV prevention trial, an individual's choices are embedded in family and community systems (Newman et al, 2006). Women and girls in some settings have limited autonomy to travel to a research site, much less to engage in a trial, and they may fear censure or physical abuse if it emerges that they are living with HIV (Modie-Moroka, 2009; Greig et al, 2008).

HIV prevention trials often work with participants from marginalized populations who may face legal as well as economic threats. As a result, it is crucial to be knowledgeable about the social norms and power relations that structure community life outside the research site. These issues should be examined at the concept development stage, as well as by including formative research in the study protocol.

Many populations that are of interest for biomedical HIV prevention trials are “virtual” rather than geographic or kin-based communities. For example, people living with HIV (PLHIV), female and male sex workers, people who use drugs (PUD), men who have sex with men (MSM) and transgender people sometimes represent virtual communities. Whether the population of interest is geographic or virtual, needs assessments should determine whether education regarding health, HIV, and health research is required for them to meaningfully engage in dialog and decision-making around the benefits and risks of clinical trials, including providing informed consent (ICASO, 2006; Nutbeam, 2009; Fisher, 2010).

Tools are available to build the capacity of various stakeholders to participate as partners in the research (AVAC 2014). However, meaningful engagement strategies must be built on assessment of the desire and the capacity of various stakeholders to be involved (Essack et al, 2012; AVAC-GPP, 2011). Community engagement involves mutual assessment of, and respect for, stakeholders' strengths and contributions.

Stakeholder engagement plan. Each study's site assessment and formative research should provide the protocol team with the knowledge to formulate an explicit stakeholder engagement plan (AVAC Webinar Series, 2014). Representatives of host communities should be consulted from the concept stage, and soon as a trial is approved and funded, a community advisory board (CAB) should be in place (IAVI, 2012).

The following process and steps are recommended for research teams and trial sponsors/funders to obtain stakeholder/community input (see AVAC-GPP, 2011):

- Identify key stakeholders at the regional, national, and international levels;

- Designate trial site staff responsible for management of stakeholder engagement planning; ensure all research and site staff understand the importance of stakeholder engagement and their own roles in fostering it;
- Discuss and negotiate stakeholder engagement plan across the lifecycle of the trial with all stakeholders, including the CABs, representing the range of volunteers and key activists in each site;
- Ensure sufficient funding to implement the engagement plan is included in the project budget. (Please see AVAC-GPP (2011) section 3.3. for details);
- Monitor and report on the roll-out of the stakeholder engagement plan, and share the reports in the protocol's periodic reviews.

Comment 2.2. Practical Tip on Communications Plans

Every protocol team should have a communications plan that addresses the following kinds of questions (see PATH and FHI, 2010 Communication Handbook)–

- How best to communicate information outward to participants, community and other stakeholders?
- How do people communicate about “risk” and prevention in local terms? What local metaphors and analogies accurately convey challenging concepts such as partial protection?
- What forms of media involvement and preparation are needed?
- What forms of communication and/or community engagement are traditionally relied upon in the setting?
- Who are the trusted local sources of information for each stakeholder group? How can they help in moments of controversy or conflict?
- Do we have a schedule of consultations that enables the team to stay abreast of local politics and to inform and educate key stakeholders? **End of Comment 2.2**

Clear, focused and goal-oriented stakeholder engagement, commitment to transparency and other ethical principles, and consistent monitoring by and dialog with the CAB, local authorities and HIV advocates requires investment and expertise are investments well worth their cost (see Box 2.3, Case Study).

Comment 2.3. Case Study

In July 2004, after significant investment by the NIH and Bill and Melinda Gates Foundation and work by trialists, the Cambodian Prime Minister closed down a PrEP trial of Tenofovir among female sex workers before its initiation. At the 2004 International AIDS Conference in Bangkok, high profile protests at the Gilead exhibition against the Cambodian trial made international headlines. Demonstrators alleged inadequate prevention counseling and lack of medical services and insurance for those who seroconverted or experienced adverse events due to the trial drug. Activists argued that overall there was limited engagement of local stakeholders, including sex workers themselves, in the design and setup of the trial.

The investigators, after the shutdown, identified difficulties in engaging sex workers on a community advisory group and broad mistrust among intended participants (Newman, 2006; Singh & Mills, 2005). **End of Comment 2.3**

Stakeholder Perspectives on Research Concept Development

Research concept development takes a protocol team from an initial study idea, to a well-elaborated concept paper that contains explicit, testable hypotheses, and potential sites and partners. The initial idea may be to test a new HIV prevention biomedical tool/product or delivery system, a new application of a proven product, a combination of products or a delivery approach that will meet a clear need for a defined population. This phase involves convening the multi-disciplinary team, conceptualizing the range of designs that could test the idea, identifying suitable populations and locations where the study could be conducted, identifying the range of partners who will be essential to the study's success, and seeking to engage key partners to join the study team.

Given the importance of HIV prevention trials to global health, community good-will and resources are global public goods. Community leaders, investigators and funders should use them strategically, productively, and with respect. New trials should be conceptualized as part of national and global research efforts to control and end AIDS (Snow, 2013 – VAX plenary; AVAC, 2013) and to achieve zero new HIV infections, zero discrimination and zero HIV related deaths (UNGA 2011). Biomedical, behavioral and structural expertise will be required to develop the idea to the point where a study protocol can be designed to test it. Many biomedical study ideas never progress beyond this stage because it is not possible to identify suitable sites, methods and partners or to meet basic ethical requirements, such as firm commitments to provide post-trial access to the trial product if it proves efficacious (AVAC-GPP 2011).

1. *Issues, tips and participant voices*

- The first obligation a researcher has is to the communities where the research will take place. Focused dialog between research team, national authorities and the community should explain the value of the study to the local population as well as to the broader national health and the global scientific agenda.
- National and community leadership should be engaged and consulted via the National AIDS Program (UNAIDS 2004 /The Three Ones; http://data.unaids.org/una-docs/three-ones_keyprinciples_en.pdf and included in decision-making. This will enhance alignment with national guidelines, access to unpublished background information, and access to local political and technical support. Relationships and regular

- communication with national authorities insure that researchers learn early of impending social and political changes that may affect a clinical trial.
- Concept notes will be judged against the guidelines on Good Participatory Practice (GPP) in HIV clinical trials, (UNAIDS-AVAC, 2011) as well as on their technical merit, so they should be reviewed early and often.
 - The deliberate inclusion of bona fide behavioral and social scientists as a vital part of the multi-disciplinary protocol team may enable the prediction and avoidance of many of the behavior-related missteps that have plagued recent HIV prevention trials. They can facilitate development of a conceptual framework for mapping and working through the many individual, community, and macro level features of the planned study sites that are likely to affect the trial (MacQueen, 2012; Koblin, 2013). The National AIDS programs of study countries, HIV/AIDS Network Collaboration (HANC), or UNAIDS can link researchers with a range of people who can provide the needed expertise.

Comment 2.4. Researcher's Perspective – from HVTN 907

“HVTN 907 was a prospective observational cohort study conducted in Haiti, PR, and DR to determine the feasibility of recruiting and retaining Caribbean female CSWs at high-risk of HIV infection into HIV vaccine efficacy trials...

... Challenges in identifying, recruiting, and retaining CSWs include constant migration, socioeconomic limitations, and stigma associated with CSW and HIV. Despite these difficulties, having a good understanding of these factors and the local epidemic and working effectively with CBOs who understand these sub-populations resulted in relatively low screening to enrollment ratios. “

Source: Deschamps et al., 2013: 97 **End of Comment 2.4**

2. Key Points

- ***Investigators should consult with*** national authorities, local health and HIV experts, community members and other key stakeholders at the earliest phase of protocol development to ensure that they can honestly buy-in to the objectives. They should be sure not to over-promise.
- ***Study protocols should include a Stakeholder Engagement Plan***, one that embraces an inclusive and well-rooted Community Advisory Board, and actively communicates with potential volunteers, local authorities, opinion leaders, scientists, service providers and funders.
- ***Behavioral and social scientists should be a part of an integrated protocol development team*** at the earliest stages and throughout the trial process (e.g. Koblin, 2013; Tolley et al, 2014), and they should frame and

facilitate dialog with stakeholders to refine the protocol's socio-behavioral theoretical (causal) model (see Chapter 1).

- **Research team should utilize HIV research networks and coordination mechanisms** to refine study objectives and their theoretical base, to design the most strategic and productive possible study, and to enhance coordination and efficient use of HIV research resources across the field.

Stakeholder Perspectives on Protocol Development

Comment 2.5. Funders/National Authorities Perspectives

"Science has a critical role to **play in ending the AIDS epidemic**. The potential returns on investments are hugely important and I strongly urge donors to make funding for research and development a top priority." Luiz Loures, Deputy Executive Director, UNAIDS.

"...the HIV vaccine field has been a leader in catalyzing innovative partnerships across the public, private, philanthropic and academic sectors. Such partnerships can help integrate new funders and help enhance the information exchange and collaboration that is required as we tackle remaining critical questions in immunology as we move forward **to develop even more effective prevention options**." Margaret McGlynn, President and CEO, International AIDS Vaccine Initiative.

Source: The Wallstreet Journal. Source, AVAC. June 2013.

<http://www.wsj.com/public/page/archive-2013-6-30.html> **End of Comment 2.5**

Protocol development begins with the finished concept paper and continues through the submission of fully elaborated protocol documents to the sponsor and national authorities for review and approval. Protocol development iteratively clarifies and focuses the research problem and questions to be answered by the study. It details the rationale, population(s), sampling strategy, data collection and analysis methods, and expected results, as well as the contribution the study will make to the national and global scientific effort and to participating communities.

1. Issues, tips and participant voices

- Clinical trials require substantial resources justified by public health need. Community participation and the enormous effort invested by volunteers and site staff are critical and limited resources. Not all new biomedical prevention technologies (NPT) candidates will be found efficacious, but protocol development should ensure that every HIV prevention trial makes scientific advances (biomedical, Behavioral and social) commensurate with their investment. The study's stakeholder engagement plan must be a component of the trial protocol and budgeted accordingly.

- During protocol development consultation with local and national stakeholders can have the greatest impact on a study. The CAB, national authorities, advocates for PLHIV and other vulnerable groups, and other stakeholders can advise and strengthen the study design. As in the concept phase, objections from community members and other stakeholders can stop further development of a protocol.
- Protocol development requires addressing a range of tradeoffs involving behavioral and social procedures such as counseling, education and client support. Disagreements may arise between site staff and investigators over the time it takes to develop rapport with participants. For example, investigators may consider electronic communications efficient and likely to reduce data transcription errors, whereas site staff may know that local communication norms require face-to-face contact. These issues should be voiced and resolved or explored empirically through formative research and/or embedded sub-studies (IOM, 2008).
- Early engagement of national government and private sector partners is key to obtaining commitments to provide referral services during and after the trial, and to produce the study product or service at an accessible price if it is proved efficacious. For example, the CAPRISA 004 trial was the first efficacy study of an ARV in the form of a vaginal gel for HIV prevention. It also represented the first microbicide trial in which a developing country led a multi-national partnership - the Centre for the AIDS Programme of Research in South Africa (CAPRISA), based at the University of KwaZulu-Natal in Durban, South Africa (Abdool Karim and Baxter, 2010).
- Participants are the experts on their own lives and can offer insight into potential barriers, facilitators, and mediators of sampling, enrollment, retention, data collection methods, and adherence to protocol, so that the design can address these systematically across study sites. The gender and age of prospective recruits play key roles in defining appropriate methods in every research site.
- Insider perspectives on local life conditions and health systems can inform the generalizability of results, and the degree of effectiveness that could be anticipated in a real-world scenario.
- The views of volunteers and site staff are particularly important in a multi-site study, where procedures such as behavioral and social risk assessment and adherence assessment will be implemented in vastly different environments. For example, computer-assisted interviewing and other non-face-to-face methods have been found to increase reporting of HIV risk behaviors in Asia but not in other regions (Phillips, et al., 2010).

Comment 2.6. Practical Tips

Every protocol team should consider the following kinds of questions when developing a protocol:

- How are Community Representatives and Stakeholders identified? What is the best way to obtain their input?
- How may their time, energy and expertise be engaged in an efficient and respectful manner?
- What are possible risks, constraints and opportunities for community engagement in a particular setting? (For example, laws criminalizing “homosexuality” and anti-gay violence may present obstacles to gaining bona fide input from men who have sex with men (MSM) and other sexual minority communities; laws and customs that systematically disadvantage women, as well as criminal statutes against drug users and sex workers, may present obstacles to safe and meaningful engagement.) **End of Comment 2.6**
 - The goals of community representatives and potential participants in a trial may be quite varied. People may volunteer for altruistic reasons, to earn money to meet critical family needs, to receive dignified and efficient health services, out of interest in something new, because of social pressure, or all the above (Tolley et al, 2014). Site assessments and the study design should identify stakeholders varying interests and priorities and align them as much as possible with recruitment criteria, incentives and other methodological decisions. Investigators can increase efficiency and quality and reduce risks of trial closure due to futility through sampling and recruitment strategies - such as using social media or advertising - that attract sufficiently large numbers of volunteers who meet psychosocial as well as biomedical enrollment criteria.
 - Avoiding undue financial and social inducements is an ethical requirement for clinical trial protocols (Grady, 2005; Tolley et al, 2014).
 - HIV prevention clinical trials can draw upon and contribute to research on issues such as HIV-related stigma, gender inequality, health literacy, and involvement of young people in health promotion, through use of standardized instruments and measures (e.g., PLHIV stigma index, WHO GBV scale, ICRW Gender-Equitable-Men (GEM) scale.
 - Participant time and patience are valuable resources, and participant burden must be considered when methods are decided. However, fear of participant burden should not lead to decisions *a priori* to limit counseling or critical data collection and services. Their time demands may be offset by perceived benefits to the individual and to their community.

Comment 2.7. Participant’s Voice

“Over the course of the three years of the study, I developed a bond of trust with the practitioner who handled my trial. (And risk-reduction counseling was introduced into the study protocol after, I believe, the first year--so he did both with me and with the others on his case load.) That bond would be harder to establish with

someone I only saw once, or maybe once a year.” - Anonymous VaxGen Volunteer - HANC Facebook blog respondent, Spring, 2012

"I've heard this said by so many volunteers! It's best to provide continuity when it comes to HIV risk-reduction counseling in the trials." Jim Maynard, Study Coordinator from Boston's Fenway site. **End of Comment 2.7**

2. Key Points

- Ensure that the CAB (or equivalent) is in place in time to consult meaningfully on protocol development.
- Align the level of visible community engagement with the recommendations of study volunteers first and then their families.
- Both the protocol team and institutional reviewers must assume responsibility for ensuring that the new protocol is designed building on previous, relevant studies -- published and unpublished – and makes a *strategic* contribution to addressing high priority gaps in prevention science.
- Consider including behavioral and social factors, including life context and research literacy, in participant screening processes to identify people who are likely to be able to adhere to the protocol throughout the trial, while recognizing that selectivity may limit generalizability of study results.
- Relationship-building is a key to successful collection of self-reported data and to promoting adherence, so activities that build relationships and trust should not be short-changed.
- The expertise of experienced behavioral and social scientists should be mobilized during the protocol development phase, built into the budget and incorporated as a critical part of the team from the outset. They should contribute their expertise within the context of the aims of the protocol.

Stakeholder Perspectives on Start-up and Site Preparation

Site preparation includes establishing or building on relationships with local authorities, assessments and formative research; community preparation, instrument testing and refinement, preparing lab and other biomedical systems and hiring and training study personnel. It often begins as regulatory approvals are being sought and involves widespread community outreach, identification of qualified study staff and all of the requisite training to properly conduct a given protocol.

1. Issues, tips and participant voices

- Community members and site staff need to understand the aims of the study and its conceptual framework. The more they are aware of the social determinants and mediators identified by the study's biosocial conceptual framework, the more they will advise and help to test and refine the guiding, explanatory framework.
- Prospective participants who have no financial pressure to enroll in a trial may nonetheless experience social pressure to do so (see Tolley et al, 2014). Neighbors and other community members may assume that participants in biomedical HIV prevention trials are HIV-negative and, thus, that trial participation may indicate that a person has a clean bill of health. Site assessments and other formative behavioral and social research should bring such risks to light.
- Data collection and counseling on HIV are challenging to staff as well as to participants. Staff training is required, as is supportive supervision to deal with stress and burn-out. These needs are intensified in resource constrained settings, where volunteers may report intimate partner violence or other conflicts, pertaining to their daily priorities (i.e., securing food etc.), and where gender inequality and low health literacy increase power imbalances between service staff and clients or volunteers.
- In sites that recruit diverse participants, translation into several languages/dialects may be necessary. Social scientists experienced in ethnoscience methods, as well as back-translation will be an asset in tailoring counseling and data collection while maintaining construct validity and cross-site comparability.
- Treating every volunteer with dignity and respect is essential in every setting and the environment should be inviting, safe and as comfortable as possible. This orientation may conflict with individual personalities and with local medical traditions. A combination of selective staff recruitment and careful training in the site preparation phase can be used to help all site staff have the inclination and the skills suited to this challenging job.

Comment 2.8. Practical Tip

The environment in which this delicate and private information is elicited may significantly influence study participants' willingness to be truthful.

"It really should be in an individual, one-on-one situation, and absolutely not in a cubicle or a common area where there might be other people present or in a position to overhear. If you're going to be asking intimate questions, you have to be given a safe space if you expect us to share that information." --Anonymous PrEP study volunteer. **End of Comment 2.8**

Comment 2.9. Participant's View

"When my husband found out that I was a volunteer here, he hurt me. He knows you provide some shillings and he thinks it 's only for him to earn the money in our family." -- IAVI Protocol C participant in Kenya. **End of Comment 2.9**

Comment 2.10. Stakeholder Perspective

"If you want to know what I do, you better be prepared to talk about sex the way I talk about sex, and not sterilize it." -- Anonymous VaxGen study participant - respondent to HANC Facebook Blog, 2012

"Familiarity & vernacular are key. If you want to ask me about what I do, you need to know what my community does, in the street, in the clubs, in the bars, and at the snotty places....the whole gamut. The more peer match we have, the better. Being professional is also important. You can't react badly to details you don't like. The biggest obstacle to getting good information is a lack of compassion. I assume you would never judge behavior, but don't be a cold, monolithic edifice to things you find weird. I think just more being human, and less robotic is key. Try to understand and empathize." --Anonymous VaxGen study participant - respondent to HANC Facebook Blog, 2012 **End of Comment 2.10**

2. Key Points

- Site assessments should examine the immediate behavioral and social context of the trial, including how research is perceived in the communities, and whether there are likely to be financial or social pressures to participate in the trial.
- Employ staff who are culturally competent, sensitive to status and power differentials, and trained and skilled in non-judgmental counseling approaches (e.g., motivational interviewing, next-step counseling).
- Include linkages to social welfare services and legal aid, as well as HIV related health services in staff training and outreach.
- Be certain that communications stay fluid and active while the study prepares to open. On-going and productive interactions between study leadership, personnel and study stakeholders while readying the site can strengthen and the site providing a solid foundation on which even the most complex trials can be successful and sustained.

Stakeholder Perspectives on Protocol Implementation

Protocol implementation is the phase when the protocol structures and procedures are carried out, including recruitment, enrollment/accrual, data collection and management, participant follow-up and support, monitoring, interim analysis and reporting, trouble-shooting, and on-going internal and external communication. The goal of the investigators is to have all stakeholders, including researchers, participants, sponsors, community leaders and others, in accord with respect to the

local and national importance of the trial, the enrollment criteria and methods, and the responsibilities of participants and their families. It also requires clear and active communication channels and the ability to respond rapidly to prevent and resolve any troubles that are identified. CABs need to show they can get results or they lose credibility with the community, the protocol team, or both.

1. Issues, tips and participant voices

Comment 2.11. Practical Tip

Study participants often appreciate being told how their volunteering may affect the “big picture” of discovering new tools to prevent HIV. **End of Comment 2.11**

- By the time implementation begins, the CAB and stakeholder engagement plan should be operational. Regular consultations are a must, should not be reserved just for trouble-shooting or crisis intervention. “Our role is to provide awareness to the community as a CAB for HIV/AIDS, vaccines and issues of science, and to look after the rights of the participants, their rights are not being violated. These are our roles as a CAB member. [CAB member]” (Buchanan, et al, 2010).
- Investigators, site staff and CAB representatives should be alert to pressures or changes in the research site or in the community or macroenvironment that reduce volunteer willingness or ability to faithfully report on their sexual or drug use behavior and life context².
- Building research literacy in communities (e.g., AVAC 2005) and explaining the importance of the protocol criteria, such as participating in only one biomedical technology trial at a time, can enlist families and other community members in supporting volunteers with adherence and retention, and can help reduce the frequency of double enrollment.
- Enrolling in a trial is a major commitment. There is a “social contract of study participation” that must be negotiated (Tolley et al, 2014). Enrollment procedures can help people envisage the constraints that trial participation may make on their person lives, and the range of possible situations outside the study context that could affect their commitment to the trial (pregnancy, serving in the military service, academics/education, marriage, or migration).
- There have been reports of community members who discern enrollment criteria in order to be able to join a trial – whether actually eligible or not. A person who is willing to lie to get into a trial may be more likely to report their risk behavior inaccurately during the trial. Study teams can reduce the “gaming” of the system to some extent by ensuring that sufficient time and effort are invested in explaining the importance of the trial and the full responsibilities of enrollment.

² Approaches to improve self-reported risk behavior and product use between trial visits is the subject of other parts of this resource (see Chapters 3 and 5).

- Staff responsible for enrollment and site supervisors must balance the drive to reach accrual targets with the aim of enrolling volunteers who are willing and able to follow their roles in the protocol through to the end. Selective recruitment of ideal volunteers will increase the efficiency of an efficacy trial, but may not provide enough insight into “real life” constraints that could affect the new biomedical prevention technologies’ (NPT) effectiveness (Kippax et al, 2011; Kippax and Stephenson, 2012) in a public health context.
- After enrollment, inaccurate reporting of personal risk behavior or product adherence is a critical risk to NPT clinical trials (see Chapter 3). Participants may also under-report some activities that they fear might trigger time-consuming extra counseling or lead to undesired labeling or treatment by study staff.

Comment 2.12. Stakeholder Viewpoint

“We lied.” “We were glad to have the diary cards so we would know how many applicators to empty in the trash before our next visit.”

The VOICE-C Qualitative Study in Johannesburg, South Africa. PLOS ONE 9(2): e89118. doi:10.1371/journal.pone.0089118. **End of Comment 2.12**

- Study participants must be sure that the information they offer during a given protocol will be held in strict confidence. During the informed consent process, it is useful to tell them how their information will be protected, e.g., how the source documents are organized so that participant identifiers do not reveal their names, exactly who is privy to this information, and how the information will be analyzed. It may be very useful to remind participants how behavioral data are collated and interpreted to serve study end-points, carefully conveying the potential negative impact of offering incorrect information, whether wittingly or unwittingly.

Comment 2.13. Participant’s Viewpoint

“I felt free to communicate details of my personal life relevant to the study in which I participated, thanks greatly to the open, non-judgmental, caring approach that the nurses displayed from my very first visit. They made me feel as if they related somehow, as fellow humans, to what I was going through at that particular time in my intimate life. They provided support and guidance for safer sex practices without showing disapproval or contempt for my sexual conduct.” --VaxGen Volunteer, JHU/CIR DC site. **End of Comment 2.13**

- Obtaining quality information is a give-and-take process. Providing the participant with adequate and respectful information about protection

from HIV, lab results, relevant study updates, safety issues, and referrals for needed social as well as health services, helps establish all-important solid and trustworthy rapport. It can also be useful to recognize volunteers for their conscious role in contributing to advancing medical research and global health.

Comment 2.14. Participant's Viewpoint:

"I remember being told about risky behaviors, but not really as they relate to the study and its protocols. I think that would be helpful. I also was never told the impact of dishonesty. That should be clearer, without being foreboding."

— Anonymous HVTN Volunteer **End of Comment 2.14**

- Investigators should avoid the trap of short-changing behavioral and social procedures in order to conserve funds or reduce participant burden.
- Monitoring fidelity to a protocol is a key part of quality assurance. It should be presented as an opportunity for improvement and for a reality check, not as a punitive or bean-counting exercise.
- Many dynamics are at play during a study visit. Both the staff and the study participants may have competing priorities that drive their need to compress or save time, so it is important to avoid allowing an "us versus them" atmosphere to emerge (Tolley et al, 2014). The tone of study visits can seem routine, burdensome, or it can build trust with participants while accruing the data required of the given protocol.

2. Key Points

- Community engagement, through education and communication about health, research, HIV prevention and treatment, and the trial itself, is an important asset in clinical trials for biomedical HIV prevention.
- Needs assessments and formative research before implementation can effectively lay the foundation for success. Formative research and pre-testing can anticipate and prevent many but not all problems. Regular monitoring of community and volunteer perspectives, through outreach, CAB input, and listening to site staff, is essential. If staff, volunteers or CABs say something is not working, something is not working.
- Ongoing staff training is useful to ensure study participants feel heard, understood, respected and valued. It is a rich source of information for study directors on risks and opportunities for improvement in study procedures.
- The onus is on study staff to respectfully and competently elicit and protect study data, whether it is regarding highly sensitive information about participants' sexual activity or their adherence to a drug regimen.
- From recruitment to enrollment and then throughout the study, participants must be assured that staff are not seeking what "sounds right"

or what meets study inclusion criteria – but rather just their real life experiences.

Stakeholder Perspectives during Trial Data Analysis

The analysis of a trial is an on-going process of utilizing the data collected during each study visit. This includes both the clinical data generated by biological makers like tissues and serum samples and the psychosocial data on behaviors reported by the trial participants.

Comment 2.15. Practical Tip

It is the responsibility of study staff *at every visit* to ensure that participants gain an *on-going* understanding of the crucial role of the integrity of the information they provide and how it affects arriving at optimal trial results. **End of Comment 2.15**

1. Issues, tips and participant voices

- Donors and participants alike want to know that the end-points of a trial are sufficiently answered. This requires rigorous attention to both the ethics and methods of gathering the information that generates trial data.
- It is not unusual to discover valuable complimentary data during the analysis phase. Staff should be encouraged to be vigilant for these serendipitous and sometime pivotal findings, including the various impacts a trial may have on communities as a whole.
- When thorough stakeholder engagement is accomplished, communities can be prepared for study results whether they are expected or unexpected. Trials that produce disappointing results, i.e., the inability of a given product to protect against HIV infection, cannot be labeled a “failure” if/when the study is conducted according to Good Clinical and Participatory Practices.

2. Key Points

- Although the analysis phase of a given trial involves the study staff more than its participants, there are many points at which an understanding of the data by all stakeholders can be beneficial.
- Carefully shaped messages and complete transparency in communicating the analysis of study data can result in a lasting and sustained trust between researchers and at-risk communities.
- Meaningful individual and institutional capacity can be built during a well-designed, conducted and analyzed trial.

Stakeholder Perspectives during Study Closure and Dissemination of Results

Trial closure occurs when all participants have completed all trial procedures. Results dissemination involves providing trial results to participants, community stakeholders, and the public at-large, while unblinding the participants to whether they were in the experimental or control arm. The events are related but distinct; in some cases they may be many months apart. In this section, we primarily discuss results dissemination.

Comment 2.16. Participant's Viewpoint

The Phambili trial of a candidate HIV vaccine in South Africa was terminated early to avert possible unforeseen risks that had affected volunteers in other settings in which the same candidate vaccine was tested (in the STEP Study). Nevertheless, many Phambili participants indicated strong resolve to continue to volunteer and press-on in testing new candidate vaccines (Essack et al., 2012).

" ... 'I'm already involved in it and I don't want to stop; I might find out there is a real cure out there...and I'll take the risk again (STEP Study participant, Toronto; Newman et al., 2011a) **End of Comment 2.16**

1. Issues, tips and participant voices

- It is essential to effectively prepare relevant stakeholders and engage them about trial closure and results dissemination in a transparent process that to builds trust, while laying a positive foundation for future research.
- It is critical to understand the best methods to communicate with different groups and to develop a communications plan to detail timing, messages, and appropriate language well before trial closure and results dissemination. The communication plan and staffing should be covered in the study protocol and budget. It should be aligned and coordinated with the stakeholder engagement plan.
- It will be difficult to explain complex results to external audiences at the end of a study or when study results are collated and delivered to both the scientific community and public at-large, unless biomedical and cultural concepts have been identified and bridged in earlier phases of the trial.
- The behavioral and social research that was carried out in the concept and protocol development phases of the trial should provide the needed background on the prevailing sexual culture(s) and health beliefs in the range of study sites. It also should cover the site historical experiences with research. This contextual information will help to anticipate the possible barriers to interpretation and comprehension of trial outcomes.
- Expert communicators from global HIV prevention trials networks and AVAC have developed tools to guide and build capacity in this key area

(AVAC Communication Handbook, 2013, and AVAC Blueprint, 2014) These tools should be launched in the concept or protocol development phases and implemented as needed throughout the trial.

- From study outset, prevention clinical trial teams should work with local and/or national HIV education and outreach organizations. These groups can share lessons and practices regarding locally acceptable language, appropriate terminology, and effective messaging that can best be used to communicate sensitively about behavioral and social issues linked to HIV risk, infection, and sexual practices in general.

Comment 2.17. Participant's Viewpoint

Experience shared from VOICE trial volunteer: 'We must take responsibility and tell the study staff the truth - that we didn't use the gel - we may have ruined the possibility of ever knowing if the gel works against HIV. Maybe if we promise to tell the truth next time, they'll give us another chance.' (Reported at USAID's Microbicide Partner's Meeting – March 26, 2013). **End of Comment 2.17**

- Community members may feel a sense of loss or disappointment at the closure of a study, which may affect how they perceive study results. In cases where the trial outcome is that a product did not show efficacy, it is important to allow key stakeholders to assist in shaping the messages. It is important to not focus on failure or to leave an impression that participants are to blame for unfavorable trial results
- Competing news stories, national crises and varied governmental responses need to be considered in the context of a trial because they have the potential to influence the political and socioeconomic landscape within which trial results are disseminated and they can have a major impact on how results may be interpreted.
- Throughout the trial, the social scientists in the protocol team should be tracking the social, economic, and political conditions that may influence perceptions of study results. They may also advise accordingly on project communications. For example, if economic constraints make product adherence more difficult for the poor than the rich, this should be understood early, so steps can be taken to avoid "blaming the victim."
- External audiences want to be able to draw clear conclusions from trial results. While researchers talk in terms of risk and risk reduction, these terms may have different meanings to different people. Research teams should work with communications experts and primary stakeholders drafting language to convey trial results.
- Communications should emphasize the importance of arriving at a rigorously validated outcome -- that there is an answer, even if it may not be the one

desired – and that the participants and community played essential roles. The plan should prepare for all possible outcome scenarios.

- Face-to-face meetings with stakeholders should take place whenever possible to discuss study results, with follow-up communications carefully planned on a regular and consistent basis throughout the results dissemination period. This process will build trust and mitigate misconceptions and controversy.
- HIV clinical trial teams should be in regular contact with other ongoing and planned HIV trials and interventions in the region. These not only create opportunities to identify and minimize co-enrollment, but they also have the potential to influence public perceptions of trial results.

2. Key Points

- Planning for study closure and dissemination of results begins during protocol design with investment in understanding the social, economic and political context and research history of the study sites.
- A communications plan, including plans for communicating about closure and dissemination of results, should be included in the study protocol and budget. It should be coordinated with the stakeholder engagement plan, and developed with input from participants, former participants, CAB members, and other key stakeholders.
- There are many concepts in HIV prevention trials that need to be explained in simple, understandable ways – from risk and partial protection, to confidence intervals, to blinding and random assignment. AVAC maintains a network of communicators for HIV clinical trials that can share information and advice on these challenges. Further advice can be found in the Communications Handbook for Clinical Trials:
<http://www.avac.org/resource/communications-handbook-clinical-trials> .
- It is important for communications to emphasize that no well-conducted trial is a “failure,” and that every trial provides the field with valuable lessons, whether hoped for or not.
- Engaging with media throughout the course of a trial is important since it increases the chances of more fair and balanced reporting and may help minimize the impact of any potential controversy related to socio-behavioral issues.

CONCLUSIONS

Proper engagement of community and other key stakeholders is critical to trial success, and it should be carried on from the first stage of developing an HIV prevention protocol. Stakeholders in HIV prevention trials include the study community/communities, but there are others who can help or hurt the study. Their perspectives on the study should be sought in earnest, as far in advance as feasible,

and considered seriously by the team of investigators as sources of insight as well as political support.

Study participants are the priority stakeholders to whom investigators are obligated, first and foremost. Their voices and views should be sought and taken to heart, including how their families and communities may perceive the trial, and the potential participant burden, particularly if sensitive personal information is to be collected.

Theory and methods from the social sciences, including good participatory methods, network analysis, community mobilization, and cross-cultural communication, enable protocol teams to include and use information from stakeholders in a rigorous manner and can strengthen HIV prevention. The unique and privileged perspectives of former trial participants should be sought methodically and taken into consideration while moving forward with new trials.

Participants can benefit from a full understanding of the weight of the behavioral and social factors in a given study and how this subjective data may affect study results. Researchers would be wise to explain clearly the possible ramifications of providing poor quality information about risk behavior and/or product adherence, including the potential for jeopardizing a trial's likelihood of generating accurate and reliable trial results.

Most importantly, showing genuine care for the general welfare of study volunteers, over and above what they offer to the given trial contributes immeasurably to building a trusting rapport with study volunteers, which is essential to their willingness to report their private behaviors.

Comment 2.18. Stakeholder Perspective

“Effectively engaging participants throughout the trial is as much an art as it is a science; eliciting highly sensitive information depends first and foremost on the human element to create the trust necessary for this dynamic. Truthful sharing can only be expected once this trust is established, which takes time, genuine compassion and active listening.” Brenda D. Larkin and Margaret M. McCluskey, Clinical Trial Nurses, Vaccine Research Center, NIH **End of Comment 2.18**

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Section II

Risk Assessment

CHAPTER 3. HIV RISK AND RISK ASSESSMENT

Point to Consider 2.

“..a renewed focus on effective risk assessment by providers will be essential to implement PrEP and other novel biomedical prevention interventions for which individualized risks and benefits need to be weighed when making prescribing recommendations (e.g., topical microbicides, voluntary medical male circumcision).”Source: Krakower D, Mayer KH. Engaging healthcare providers to implement HIV pre-exposure prophylaxis. *Curr Opin HIV AIDS*. 2012. Nov;7(6):593-9.

End of Point to Consider 2

Behavioral and Social Risk Assessment:

Characterizing and documenting, through qualitative and/or quantitative methods, the types of behaviors and conditions known to increase risk of HIV infection, their frequency and distribution, and their proximate and distal causes.

INTRODUCTION

Risk assessment in HIV prevention research is a process designed to characterize and document the types and frequencies of behaviors and conditions that can lead to exposure to HIV, so as to determine the likelihood of acquiring HIV infection for a given individual or population (Pisani et al, 2003). Since it is now recognized that structural factors are integral to HIV risk, it is necessary for HIV prevention research to identify both the individual level, proximate behaviors and the key social structural conditions that promote, inhibit, and are associated with risk behaviors in a particular population and setting, or that make certain individuals or groups *vulnerable* to HIV risk.

The concepts of vulnerability and risk, while linked, are nonetheless distinct. Risk is defined as the probability that a person may acquire HIV infection. Certain behaviors create, enhance and perpetuate risk. Examples include unprotected sex with a partner whose HIV status is unknown; multiple unprotected sexual partnerships; injecting drug use with contaminated needles and syringes. Vulnerability results from a range of factors that reduce

the ability of individuals and communities to avoid HIV infection. These may include: (i) personal factors such as the lack of knowledge and skills required to protect oneself and others; (ii) factors pertaining to the quality and coverage of services, such as inaccessibility of services due to distance, cost and other factors (iii) societal factors such as social and cultural norms, practices beliefs and laws that stigmatize and disempower certain populations, such as women and girls, or men who have sex with men, and act as barriers to essential HIV prevention messages. These factors, alone or in combination, may create or exacerbate individual vulnerability and, as a result, collective vulnerability to HIV.

Use of non-sterile medical equipment, and contact with infected blood products can cause HIV exposure, as can transmission from mother to child during pregnancy, birth, or through breastfeeding. However, the overwhelming majority of HIV transmission occurs through sexual exposure, and unsafe injecting practices (Kilmarx, 2009; Vermund, 2014). Thus, these are the main focus of behavioral risk assessment in clinical trials of new biomedical prevention technologies (NPTs).

As noted earlier, experience has led to a broadening of risk assessment, from consideration of individual risk to attention to the contextual factors that augment or reduce individual risk. This creates a more comprehensive view of Social and Behavioral Risk Assessment (SBRA). The bulk of risk assessment research has focused on assisting HIV negative individuals to avoid infection. However, today, attention to people living with HIV is also advised, to have a balanced assessment of the risk of both acquiring and transmitting HIV (GNP+, UNAIDS, 2013).

Goals of HIV Risk Assessment

SBRAs in clinical trials of biomedical HIV interventions have a critical role in recruitment and retention, as well as in the analysis and interpretation of results. The major goals of HIV risk assessments are:

1. To estimate study participants' potential HIV exposure, and changes in exposure across study sub-groups and across time;
2. To characterize the context and causes of HIV risk behaviors in populations under study.
3. To anticipate and monitor challenges in recruitment, retention and adherence, so as to minimize these.

Estimates of potential HIV exposure are used during biomedical HIV intervention trials:

1. To determine if study participants assigned to the different arms of the study have equivalent levels of potential exposure at baseline and during follow-up;
2. To determine if participants lost to follow-up may have differed in their levels of exposure;

3. To determine if there are changes in potential HIV exposure associated with the treatment assignment (i.e., among participants assigned to one group or arm of the study and not another);
4. To be able to determine the effects of variation in the level of potential HIV exposure, when evaluating the efficacy of the NPT that is being tested.

Comment 3.1. Estimating HIV Risk

Risk of infection is a complex, compound estimate of several effects but can be simply assessed. Aggregate risk of infection is a function of donor challenge (e.g., risk that source is HIV positive, viral load, presence of cofactors including sexually transmitted infections and bleeding), recipient susceptibility (e.g., genetically defined host characteristics, route of infection, presence of cofactors), and frequency of exposure. (Robb et al, 2012) **End of comment 3.1**

Risk assessment at study baseline aims to identify, and ideally to avoid, introducing bias into the test of the safety and efficacy of the biomedical agent under study. Randomization and blinding are in place in clinical trials to eliminate imbalances in exposure by treatment arms (Schulz et al, 2002). However, randomization does not preclude a systematic or differential shift in risk occurring during the course of the study. Unblinding treatment assignment while on study or perceptions of treatment assignment while blinded may contribute to changes in risk behaviors, leading to changes in exposure to HIV (Bartholow et al, 2005).

Individual Level Theories

Variables for HIV risk assessment that are called for by most of individual-level health behavior theories include knowledge of HIV, knowledge of prevention methods, sexual history, sexual partner types, condom use and other risk reduction methods with each partner type, drug use and risk reduction practices, and drug use partners. The **Information-Motivation-Behavioral skills (IMB) model** and subsequent approaches also include motivation and skill variables or scales to assess self-efficacy for risk reduction. Additional individual level variables of interest could include STI history, HIV testing history, perceived social support, childhood history, and factors such as depression and anxiety. Some also include individual life conditions such as economic pressure, gender inequality, housing and employment, which are discussed further in the next section.

Many risk assessment tools focus on the individual levels of causality of HIV risk – the innermost levels in socioecological models (see, e.g., Figure 1.3 [Baral, et al 2013 in Chapter 1]), or the micro-level factors in a dynamic systems model (see Figure 1.6 [Latkin et al, 2010 in Chapter 1]). Building on decades of research in psychology and health promotion, several theoretical approaches to individual-level behavior change have been developed and used in conceptualizing HIV risk assessment and

to develop risk assessment tools (see Petersen & DiClemente, 2000, for further details).

The Health Belief Model (HBM) (Rosenstock, 1974) underscores the importance of perception to risk behavior. Perceptions of vulnerability to HIV is some joint function of the subjective perception of the risk of HIV infection (perceived susceptibility) and perceptions of the physical and social consequences of HIV infection (perceived severity). Perceived vulnerability determines health behavior. Health behavior options are evaluated based on perceived benefits and costs and perceived self-efficacy to perform the behavior.

The Theory of Reasoned Action (TRA) (Fishbein & Ajzen, 1975; Ajzen & Fishbein, 1980) asserts that risk reduction behavior involves three factors: (1) attitudes toward a risk reduction behavior; (2) intention to engage in HIV prevention behavior; and (3) subjective norms or perceptions of how others view the HIV prevention behavior.

The Theory of Planned Behavior (TPB) (Ajzen & Madden, 1986; Ajzen 1991) is an extension of the TRA and adds an additional behavioral risk reduction factor- perceived behavioral control-which is an individual assessment of the ease or difficulty of performing a preventive behavior. Perceived behavioral control is influenced by an individual's control beliefs as well as assessments of necessary resources and opportunities for effective preventive behavior.

The AIDS Risk Reduction Model (ARRM) (Catania et al, 1990) is a stage model of behavior change that lays out how people progress through different cognitive tasks (Prochaska & DiClemente, 1986). To reduce risk behavior the individual must pass through three stages: (1) Labeling actions as risky for HIV infection; (2) making a commitment to reduce HIV risk behavior and increase safer behavior; and (3) seeking and enacting strategies to reduce HIV risk behavior and increase safer behavior.

Table 3.1. Common Variables Used to Assess HIV Risk

Individual Level Factors	Structural Factors
Knowledge of HIV	Culture of medicine (medical beliefs, learned health practices)
Knowledge of HIV Prevention Methods	Health system coverage
Perception of personal HIV risk	Communications, including health information
Sexual History <i>for example: Sex of sex partners, Transactional Sex, Concurrent Partners</i>	Education system, including sexuality and reproductive health education
Sexual Partner Types	Citizenship and rights education & practice
Condom Use	Social gradient/inequity

Other Risk Reduction Methods	Community systems – degree of organization and political space
Injecting drug use (IDU)	Justice system (access to justice, enforcement of constitutional protections, etc.)
Other Drug and Alcohol Use	Incarceration
Incarceration History	Education
STI History	
Partners' Sexual History <i>for example: Transactional Sex or Concurrent Behavior</i>	
Partners' Incarceration History	

The Information-Motivation-Behavioral Skills Model (IMB, Fisher & Fisher, 1993) builds on other theories and evidence to provide a parsimonious model of behavior change. It asserts that for individuals to initiate and maintain HIV preventive behavior they must be well-informed, motivated to take action, and possess the necessary skills to act effectively.

The Social Cognitive Model (SCT, Bandura, 1994) posits that effective behavior change requires (1) information to increase awareness and knowledge of health risks and to help people believe that they can effectively engage in prevention; (2) the development of self-regulatory and risk reduction skills; (3) Self-efficacy (sense of control of motivation and environment); and (4) Social support.

The Transtheoretical Model (TM, Prochaska & Velicer, 1997) is another stage model of behavior change and identifies six stages of change in individuals who change behavior on their own. The stages include: (1) Precontemplation (no intention to change behavior; (2) Contemplation (intentions to change behavior in the next 6 months); (3) Preparation (intentions to take action in the next month); (4) Action (effective risk reduction behavioral modifications have been made in the previous 6 months); (5) Maintenance (work to prevent relapse generally begins 6 months after initiation of consistent behavior change); and (6) Termination (absence of temptation to relapse and complete self-efficacy regarding maintaining healthy behavior).

In addition to calculating individual risk, HIV prevention investigators want to characterize the context, correlates and potential causes of HIV risk in the study population, and variations among sub-populations for a number of purposes:

1. To provide evidence for eligibility criteria for trials (e.g., to identify participants who are in higher risk vs. lower risk situations);

2. To inform recruitment and retention strategies, to reach out to potential participants who are most likely to be exposed to HIV, and thus are most likely to benefit from the product, without putting them at risk of social or legal harm;
3. To inform counseling content at every stage of the study (e.g., informed consent procedures, retention and adherence counseling);
4. To identify contextual, mediating factors that may explain differences in risk and protective behavior, and/or to contribute to the development of improved HIV prevention strategies.

Life Context and HIV Risk

Life context refers to those historical, political, economic/resource, and group/population forces and dynamics which to a greater or lesser degree impinge upon and determine a person's functional potential and status, and their decision-making abilities and actions—thus, it impacts a person's 'reality'.

Depending on the population of interest and goals of the intervention trial, a number of contextual factors may be examined to assess HIV risk. These include health care access, access to education and material resources, informal and formal social control, prevalence of substance use (as exposure or correlate of sexual risk), perceived stigma, experiences of stigma and discrimination, childhood history, history of violence, degree of community mobilization and support and other forms of interconnectedness, history of research trials in the area, and socio-economic and factors such as access to transport, vulnerability to arrest, detention or deportation. Because the range of potential influences is so vast, it is essential to work with a conceptual model that posits key pathways in the complex causal cascade from macro to micro level factors (for examples see [Figure 1.4](#)).

Assessment of individual risk in HIV prevention trials must contend with cultural differences in conceptualization and language of risk, especially if the study includes sites in different countries. They also must contend with the fact that individuals frequently under-estimate or over-estimate their own risk of exposure to HIV. Lack of recent local HIV data, psychological denial regarding sanctioned practices (e.g., non-marital sex), folk theories of health and illness (Helman, 2007) and misconceptions about HIV (e.g., that infection carries visible signs) all easily distort people's perception of their own risk of acquiring or transmitting HIV.

Since all HIV prevention (risk reduction) theories begin with the individuals' cognitive appraisal that the dangers of HIV are relevant to them personally, differences between perceived risk and risk computed based on probabilities of exposure to HIV are at the heart of many failed HIV prevention strategies. Thus, while interviews and other methods for obtaining self-reported risk are important tools, they are best complemented by independent assessment and efforts to understand the prevalence of HIV among potential sexual and/or drug use partners,

the life contexts within which trial participants live as well as the context of the trial itself.

Comment 3.2. Stigma and Social Marginalization Impact HIV Risk

Health outcomes for transgender and gender non-conforming individuals show the appalling effects of social and economic marginalization, including much higher rates of HIV infection, smoking, drug and alcohol use and suicide attempts than the general population (Injustice at Every Turn: A Report of the National Transgender Discrimination Survey, Executive Summary, 2011). **End of comment 3.2**

These contexts have the potential to shape, and in some cases, determine, participants' beliefs, perspectives, and actions, which in turn, may influence their participation in the trial as well as the ability to interpret and ultimately understand its outcomes and implications. HIV prevention trials should not marginalize contextual issues, as they can have critical bearing on trial ethics, progress and outcomes. For example, in trials that seek to enroll key populations, including people who inject drugs and/or who sell sex, or men who have sex with men, the political and legal context, and especially relationships with the local authorities, drastically affects the risks of participation and the standard of prevention for individual participants.

As another example, one trial participant may drop out of the study due to a lack of autonomy and failure to obtain support from family decision-makers, another participant may drop out due to a lack of resources to cover transportation costs and time off from work. These are entirely different dynamics. Each circumstance implies different causes and consequences. Anticipating these causes at the risk assessment stage sets the stage for potentially different interventions to match the real needs of study participants (Gupta et al, 2008)

Social science theory may be used elucidate structural dynamics. (Haour-Knipe et al, 2013), including the interaction of macro level factors, research setting factors and community factors. This, is necessary to the analysis of individual level psychological, behavioral and biomedical factors that influence behaviorally mediated HIV prevention trials. In [Table 3.2](#), Latkin et al (2013) detail the six types of structural factors, called for in their **Dynamic Social Systems model**, to examine in an intervention to enhance HIV testing and counseling.

Comment 3.3. Example of Interacting Individual and Contextual Influences on HIV Risk.

Pantin, Prado, Schwartz, and Sullivan (2005) and Wetherill and Fromme (2007) identified the risk and protective factors that related to immigrants in the US as: (a) contextual or eco-developmental variables (acculturation, education, social assistance, and employment dynamics), (b) intrapersonal or social cognitive variables (risk perception, attitudes, beliefs, and intentions) about drug use and unsafe sex, and (c) one's sense of personal invincibility. **End of comment 3.3**

The following variables illustrate the complex interactions biomedical, behavioral and structural influences on HIV risk, and the importance of using socio-behavioral sciences in our efforts to reduce the probability of disease transmission and to improve treatments when transmission does occur.

1. **Mental Health.** HIV/AIDS and mental health are interconnected. The prevalence of mental illnesses in people living with HIV may be considerably higher than in the general population. Higher rates of depression and anxiety have been seen in HIV-positive people compared with HIV-negative control groups, with distress linked to the severity of HIV symptoms can interfere with HIV/AIDS treatment (Bing et al, 2001; Morrison et al, 2002; Weiser, Wolfe & Bangsberg, 2004; Tegger et al, 2008;). Conversely, some mental disorders result from HIV infection. The World Health Organization (2008) asserts that prevalence of mental illnesses among HIV-infected individuals is substantially higher than in the general population in both low- and high-income countries.

Several studies have indicated that among people with severe mental illnesses, 30% to 60% report behavioral risk factors (multiple partners, injection drug use, sexual contact with injecting drug users, sexual abuse, condomless sex between men, and low use of condoms) for HIV transmission (Hutton et al, 2004; Paul et al, 2003). The ability to acquire and/or use information about HIV/AIDS and subsequently practice safer sexual behaviors may be compromised by mental disorders and increased psychological distress.

Increased psychological distress among people with HIV infection is common and relates directly to internalized and anticipated stigma, and the experience of discrimination (Cooper et al, 2003; Kessler et al, 2001). Coping styles, learnt resourcefulness and social support (particularly family relationships and partner support) can influence resilience and the health impact of HIV (Trevino et al, 2010; Boonpongmanee, et al, 2003; Kalichman et al, 2003). However, these issues have been studied more in high income countries than in the LMICs where the HIV epidemic is taking the greatest toll.

2. **Violence & Trauma.** Extensive research has been conducted on sexual violence against women, both domestically and internationally. NPT study teams should be alert to signs and rates of violence and trauma during recruitment, retention and on-going data collection. The World Health Organization (WHO, 2010) reports that globally, between 10% and 69% of adult women have experienced physical and/or sexual violence in their

lifetime. In some geographic areas prevalence rates of lifetime physical and/or sexual violence by an intimate partner are as high as 71 percent (Garcia-Moreno et al, 2005). People with disabilities are at elevated risk for violence, including sexual violence, and HIV (Disability International, 2011; Rohleder et al, 2009).

The association between violence and HIV acquisition has been well documented in the literature (Campbell et al, 2012; Cavanaugh et al, 2010; Dunkle, 2004; Garcia-Moreno, 2000; Jewes et al, 2003; Wyatt et al., 2002; Maman et al, 2002). The presence or threat of violence can impact perceptions of risk and self-esteem (WHO, 2010), reduce decision-making power impacting the ability to negotiate condom use, prevent disclosure of HIV serostatus (Zierler et al, 2000; Gielen et al, 2000) and increase engagement in risky behaviors that may be related to trauma from childhood abuse (Gielen et al, 2005).

Table 3.2. Structural Factors to Examine in a Study of HIV Testing and Counseling.
Source: Latkin and Knowlton, 2013.

	Macro	Meso	Micro
Material resources and allocations	Budget devoted to HIV testing and HIV testing promotion; resources allocated to the discovery of HIV treatment, new HIV testing technologies, and HIV surveillance	Cost of transportation to HIV testing services; outreach and community HIV testing programs	Hours of operations, alternative and complementary services; staffing and equipment for HIV tests
Science & technology	Research on HIV treatment and rapid HIV testing technologies; studies on the impact of undiagnosed cases in the course of the HIV epidemic	Impact of HIV testing community promotion programs	Studies on testing sites and client preferences in that site
Informal social influences	Informal leadership of city, province, country; positions of religious, political, and cultural leaders; prevalent stereotypes about HIV, risk behavior, and risk groups	Community norms; neighborhood monitoring; neighborhood opinion; leaders	Social norms in the setting about HIV, risk behaviors, and risk groups (staff and clients)
Formal social control mechanisms	Legal requirements to conduct HIV tests (informed consent and pretest counseling, anonymous versus confidential) and provide and communicate results (e.g. counseling, referrals notification requirements) HIV testing laws applied to specific groups (pregnant women, immigrants)	Interpretation and enforcement of laws	Formal mechanisms for HIV testing in testing sites (e.g., decision rules to recommend HIV testing to certain individuals, provision of results, partner notification procedures)
Social interconnectedness	Interaction of organizations involved in the development, prescription, and promotion of HIV tests, and organizations of potential users (human rights)	Networks of potential clients in a community (circulation of information and referrals, social incentives and deterrents)	Relationships among providers in the HIV testing facility in terms of competing activities, priorities, and resources; relationships between clients and staff; relationships among clients and their networks
Settings	Political and demographic boundaries; number and variety of testing sites within those boundaries	Local availability of HIV testing sites; HIV prevalence and density of educational programs in a community	Privacy, predominant norms, and competing activities in the site of HIV testing provision (community, outreach, and clinical sites)

Significantly less research has been conducted on sexual violence against men. The research on male same-sex partnerships suggest that men who have sex with men (MSM) experience abuse rates similar to, or higher than, those reported by women in heterosexual relationships (Greenwood et al,

2002; Pantalone et al, 2012; Seelau, Seelau, and Poorman, 2003) and an HIV-positive serostatus may place MSM at even greater risk. A review of physical abuse among MSM living with HIV indicated high lifetime frequencies of physical (15-39%) and sexual (8-33%) abuse (22-73%) across studies. These rates are three times higher than those reported by men involved in heterosexual relationships (Tjaden and Thoennes, 2000), based on data from a representative sample of the U.S. population.

The collection of data on physical and sexual violence as well as sexual power dynamics with partners may reveal situations wherein women and men have little negotiation power or control in their sexual relationships. A complete behavioral assessment may allow practitioners to identify harm reduction strategies in the context of coping with abuse-related distress. Trauma and abuse training for those working in HIV education and prevention may assist clinical staff who are collecting the data to be empathic to the needs of participants and cope with the emotions raised by violence and trauma disclosure.

3. ***Drug Abuse and Addiction.*** The case of drug abuse and addiction also illustrates diverse effects of life context on HIV risk. HIV/AIDS frequently coexists with drug abuse and addiction, and the structural factors which cause them (El-Bassel et al, 2014; Strathdee et al, 2013; Alegria, Strathdee, and Pantin, 2012; Rhodes, et al, 2010). Drug intoxication is conducive to risky behaviors including condomless sex, transactional sex for drugs or money or for other resources such as sustained or short-term shelter. Participatory and formative intervention research with people who use drugs has long established that people want to use clean injecting equipment if it is available and if accessing it does not pose threats to their freedom and safety (Rhodes et al, 2010; Strathdee et al, 2013). Affected communities, HIV experts and the World Health Organization advocate “harm reduction” -- nine complementary strategies that include evidence-based individual focused interventions and macro level policy changes to reduce HIV transmission and other ill effects of drug use. Protection from punitive laws and policies is essential to enable people who use drugs to participate in clinical trials of HIV prevention technologies.
4. ***Culture and Context.*** An individual’s ethnic background, cultural heritage, language and religion shape their health belief systems and ultimately health-related behaviors (Fabrega, 1973; Kleinman, 1978; Helman, 2001). Health beliefs are learned, and highly varied. In many cultures, concepts of hot and cold are as central to insiders’ views of “risk” as germ theory is in the US. Medical personnel in both high and LMI countries are often uninterested, and even supercilious and judgmental about indigenous health beliefs, which cuts off communication about them. People in marginalized groups, such as

sex workers, men who have sex with men, people who use drugs, and low-income migrants, may face linguistic as well as psychological, social and legal barriers to understanding and reporting risk behavior, and they are unlikely or unable to demand improved communication – especially when they are legally vulnerable as well (Aday, 1994). Migration in and of itself is not a risk factor for HIV and sexually transmitted infections (STIs) (Haour-Knippe et al, 2013). However, immigrants from particular regions have to deal with stigma and discrimination associated with their immigrant status as well as STIs (Anderson et al, 2008).

Comment 3.4. Stakeholder Perspective

One of weaknesses [in the development of behavioral risk assessments] is that we don't pilot test things. People are always fussing over wording and it is hard to get consensus because multiple people have different views, so we are right up against the deadline of when the protocol will open without any time for pilot testing. (Andrasik et al, 2013) **End of comment 3.4**

There is consensus on which individual level factors should be featured in SBRA for clinical trials and that contextual, structural factors should also be included. However, the exact mix of contextual, structural factors to be assessed will vary from trial to trial depending on its purpose and/or design. Choice of factors for monitoring throughout the trial should be derived through application of the kinds of theoretical frameworks listed earlier (see Figures 2, 3 and 6 in Chapter 1) and through professionally facilitated dialog within the study team and with knowledgeable local partners to develop an explicit causal model (see Figure 5, in Chapter 1). Researchers are also charged with balancing resource allocation and participant/site/staff burden with potential cost effectiveness of obtaining data on key impediments and facilitators to risk reduction and medical care. Integrated behavioral and social risk assessments can aid this process.

Methodological Considerations in HIV Risk Assessment

Levels of risk serve as proxies for estimates of HIV exposure, so there is a powerful incentive to maximize the accuracy of risk assessment in HIV clinical trials. Since the main behaviors that convey HIV risk are private and cannot be observed directly, measuring HIV risk relies heavily on self-reported behavior, reported HIV status and behavior of sexual and drug-using partners, and on triangulating data from complementary data sources, such as local demographic and social statistics, key informant interviews, and ethnographic observations. To date, the importance of risk assessment has not been matched by investment in science-based strategies for maximizing its accuracy (see Box 3.7). An informal survey conducted by the HVTN SBS Working Group found that many major HIV clinical trials simply imported SBRA tools from previous studies in other populations and regions, and translated, cut and reshaped items to suit the time they felt was available for behavioral and social

assessment. They squeezed SBRA into the biomedical protocol. Theory and methods from the behavioral and social sciences can improve on this approach.

Risk assessment is a burgeoning area in public health practice and research. A proliferation of “risk calculators” even makes do-it-yourself risk assessment possible for people interested in their risk of acquiring or having HIV, STIs and other health problems (e.g., EndingHIV.org.au; www.stdriskcalculator.com/index.php/chances-of-getting-hiv). Behavioral and social risk assessment almost always requires use of a strategic mix of methods, especially where studies aim to understand or explain differences in risk perceptions and risk behavior, in order to inform further research and services (Petersen & DiClemente, 2000; Fisher and Fisher, 1993; Latkin et al, 2010).

Some aspects of risk assessment may be conducted by pre-trial, household survey or questionnaire methodology, others by qualitative interviews conducted at trial sites before the trial at designated time points during implementation. As noted in Chapter 1, there are strengths associated with qualitative, quantitative and mixed methods approaches (For an outline of issues refer to Creswell/OBSSR, 2011).

Threats to accuracy of reported risk. Advanced training in behavioral and social sciences always includes specific attention to sources of error in self-reported data, and ways to address them. Sources of error include:

- Lack of understanding, or different understanding, of the questions. When conducting SBRA in a new setting, formative research is needed to determine how to say and convey the research variables in terms that will be understood by participants. For example, there are many famous examples of false self-reports of sexual conduct based on different interpretations of the term “to have sex.” (MTN example of “sex from behind” as opposed to anal sex)

Comment 3.5. Practical Tip

Free-listing and pile-sorting is a useful ethnoscience method for eliciting the full range of local terms for key risk assessment constructs, including slang and rough language, along with their informal associations and meanings. This technique can be used with site staff to desensitize them to street terminology. (Ryan and Bernard, 2000) **End of comment 3.5**

- Denial – a defense mechanism where an individual refuses to admit or acknowledge that something has occurred or is currently occurring. For example, those victimized by a traumatic event may deny that the event ever occurred.
- Inability to recall or to quantify events in the past.
- Reactivity to social cues, and impression management/ presentation of self. Presentation of self is “a goal-directed conscious or unconscious process in which people attempt to influence the perceptions of other people...by

regulating and controlling information in social interaction “(Piwinger & Ebert 2001, pp. 1–2). “

- Norms of politeness (not wanting to offend the interviewer).
- Social desirability bias, or the tendency to respond to questions in socially or culturally sanctioned ways (Marlowe & Crowne, 1961) is a very common threat to the validity of survey and experimental research findings (King & Bruner, 2000; Paulhus, 1991). When utilizing one-to-one, face-to-face interviewing techniques to obtain responses to sensitive questions response bias can be important, especially if the situation does not align with local norms (e.g., gender of the interviewer, privacy) or if there is insufficient trust and rapport. It appears that universally, participants are more likely to under report socially undesirable behaviors and over report socially desirable behaviors, although research on this outside of high income countries is sparse.
- Information sharing among trial participants, and information circulating from concurrent national and local studies or HIV education services, can shape participants ideas about what they should be reporting.
- Deliberate misrepresentation, including misrepresentation in order to avoid negative consequences from the researchers (e.g., being assigned for remedial procedures, or being excluded from the trial) or from significant others (e.g., pressure to stay in the trial for economic reasons; pressure to misrepresent behavior to protect family honor).

Comment 3.6. Practical Tip

Data accuracy depends on more than well-formulated questions and volunteers’ willingness to answer them fully and accurately. Errors can be introduced by study staff during transcription and data entry. Automated data collection methods help in some settings but not in others (Vodopivec-Jamsek et al, 2012; de Longh et al, 2012). When considering a trial in a new site, start out by doing formative research to know your population and talk to people about what kind of approaches are likely to establish trust and understanding. **End of comment 3.6**

It is important to underscore that these potential sources of error may be reduced by increasing one’s knowledge about the population and sociocultural setting. There are several common contextual factors that exacerbate errors in self-reported data:

- **HIV/AIDS Stigma** – stigma associated with most risky behaviors (e.g., drug use; anal sex)
- **Taboos and punitive norms** regarding knowing and talking about sexuality and sexual behavior that can make participants – and/or site staff – uncomfortable, and social norms sanctioning, adolescent sexual activity, non-marital or multiple sex partners, and sex work

- ***Gender and sociocultural context of social desirability***-Strong sanctions against early (for adolescents) or premarital/extramarital /non-marital sexual activity (for women) in many societies around the world (Cleland and Ali, 2004)
- ***Legal prescription of transmission-associated sexual and injecting risk behaviors*** – e.g., criminalization of HIV transmission, sex work, injection drug use, anal sex, or homosexuality.

Methods to Improve the Validity and Reliability of Behavioral Self-Reports

Measures of HIV risk behavior will always be imperfect proxies for actual exposure to HIV. Many have been developed and tested in a wide variety of populations and settings, in high income countries and in LMI countries (for examples see Annex III). No single method of data collection can resolve all the challenges to the accuracy of reported HIV risk. However, there are numerous methods that can be employed to improve the validity and reliability of self-reported HIV risk factors.

These include:

- Systematic formative research, including consultation with representatives of the study population/s.
- Use of memory and recall aids, such as timelines;
- Use of previously validated instruments;
- Investment in pre-testing and iteratively refining all instruments when used in new settings and populations;
- Intensive training of data collection personnel;
- Rigorous segregation of data collecting personnel from counseling and service delivery staff;
- Investment in and quality assurance of data entry, data reduction and analysis stages.

In all cases, the study population/s and setting/s, the study aims, and the study's resources must guide the selection of best possible data collection strategies.

Risk assessment is a dynamic area of HIV research, where conceptual frameworks and methods are evolving to address biomedical, behavioral and structural aspects of HIV risk. They include sampling methods, data collection techniques, and instruments or tools. A number of these are listed in Table 3.2 (sampling methods), Table 3.3 (data collection approaches) and Table 3.3 (methods to improve recall and reduce recall error). Additional tools and resources are available from the Office of HIV/AIDS Network Coordination (HANC) website (<https://www.hanc.info/Pages/default.aspx>).

Social and Behavioral Risk Assessments (SBRAs) should identify and document these and other relevant contextual factors to help guide recruitment, retention, staff training and supervision, and communication regarding the trial. Tools are available for exploring each of these factors (see below and Annex III).

Table 3.3. Sampling Methods to Consider in Behavioral and Social Risk Assessment.

Sampling Methods	Principle Use	Citations	Use in a clinical trial
Ecological Momentary Assessment	Repeated sampling of participants behaviors and experiences in real time and in real-world environments	Shiffman S, Stone AA, & Hufford MR. Ecological Momentary Assessment. Annu. Rev. Clin. Psychol. 2008, 4: 1-32.	Participants complete multiple assessments over a period of time to illustrate how experiences and behavior vary over time and across situations
Respondent-Driven or Participant-Driven Sampling	Use of peers to locate and recruit other members of a hidden population	Heckathorn D. Respondent-driven sampling: A new approach to the study of hidden populations. Social Problems 1997; 44: 174-99	Particularly useful for sampling populations who mistrust the research community (Broadhead, 2001) and for persons who do not frequent public venues
Nominated or Snowball Sampling	Research participants are asked to assist in identifying other potential participants	Patton MQ. Qualitative Research and Evaluation Methods, 3 rd Edition. Thousand Oaks, CA: Sage pp 230-242	Useful in studies of networks of drug users and sexual networks – particularly useful in hidden or hard to reach populations
Venue-Based or Time-Space Sampling	To reach hard to reach (or hidden) populations during specific times and days in public venues where they are known to congregate	Muhib FB, Lin LS, Stueve A, Miller RL, Ford WL, Jonson WD, Smith PJ. A venue-based method for sampling hard-to-reach populations. Public Health Reports. 2001; 116 Suppl 1: 216-22.	Recruitment of participants from a specific demographic or who are highly likely to meet inclusion criteria
Targeted Sampling	Use of quantitative and qualitative data to describe the target population, develop the sampling frame of locations where the target population may be found and characterize the sample	Bluthenthal R, Watters J. Multimethod research targeted sampling to HIV risk environments. In: Lambert Ey, Ashery RS, Needle RH (Eds). Qualitative methods in drug abuse and HIV research. Rockville, MD. National Institute of Drug Abuse 1995: 212-230. DHHS Publication 95-4025. Research Monograph 157	Targeted sampling better suited for recruitment of individuals at higher risk of HIV infection (Iguchi et al., 1994)

Table 3.4. Data Collection Approaches to Consider in Behavioral and Social Risk Assessment.

Data collection approaches		Advantages	Weaknesses
Interview Approaches	1. Face to Face Interviews	<ul style="list-style-type: none"> • May increased comfort in the presence of a non-judgmental interviewer • Interviewer able to explain, soothe, validate, etc. • Can Include aids such as pictures or cards 	<ul style="list-style-type: none"> • Intentional misreporting of sensitive behaviors
	2. Telephone Interviews		
	3. Tape-Recorded Interviews		
	1. Self-administered Questionnaires (SAQs)	<ul style="list-style-type: none"> • Increased privacy and anonymity 	<ul style="list-style-type: none"> • Literacy is an issue • Difficulty with complicated skip patterns

Self- Administered Approaches	2. Assisted self-administered questionnaires (ASCQs)	<ul style="list-style-type: none"> Can use pictures and other visual aids to address literacy and translation issues; Diary cards and calendars to enhance recall accuracy, etc. 	<ul style="list-style-type: none"> May be less internally consistent
Technology- Based Self-Administered Approaches	1. Computer-assisted self-interviews (CASIs)	<ul style="list-style-type: none"> Computer-based interviewing in the US dramatically increases reports of sensitive behavior. Reduces data reduction time, though quality checks still needed. 	<ul style="list-style-type: none"> Literacy issues Some may be inhibited by technology Requires some experience with technology or willingness to learn on site.
	2. Audio-assisted Computer assisted Self-Interviews ACASI)		
	3. Handheld Personal digital assistants (PDAs)	<ul style="list-style-type: none"> Includes the use of cell phones, voice response systems or SMS texts. Used to assess sexual and alcohol/substance use behaviors. 	
Anonymous Approaches	1. Informal Confidential Voting Interview (ICVI)	<ul style="list-style-type: none"> Secret voting procedures that allow for anonymity of participants Low technology Methods suitable for resource-poor settings Increased Confidentiality Greater propensity to disclose sensitive sexual behavior variables 	<ul style="list-style-type: none"> Greater disclosure of sensitive sexual behavior variables may reduce over time. Internal validity between different question responses cannot be assessed
	2. Polling Booth Surveys		

Table 3.5. Methods to Improve Accuracy and Minimize Recall Error in Behavioral and social Risk Assessment.

Methods to Improve Accuracy and Minimize Recall Error	<u>Advantages</u>	<u>Citations</u>
Diaries – With coital diaries, sexual practices are recorded on a daily or other periodic basis after each sex act. Can include pictures, tick boxes, etc.	<ul style="list-style-type: none"> Some success in minimizing recall bias in low- and middle-income countries 	<p>Katz BP, Fortenberry JD, Tu W, Harezlak J, Orr DP. Sexual behavior among adolescent women at high-risk for sexually transmitted infections. <i>Sex Transm Dis</i> 2001; 28(5): 247-51.</p> <p>Allen CF, Lees SS, Desmond NA, Der G, Chiduo B, Hambleton I, Knight L, Vallely A, Ross, DA & Hayes RJ. Validity of coital diaries in a feasibility study for the Microbicides Development Programme trial among women at high-risk of HIV/AIDS in Mwanza, Tanzania. <i>Sex Transm Infect</i> 2007; 83(6): 460-497</p>

TimeLine Follow-Back – uses a calendar and other memory aids to obtain retrospective estimates of behavior over a specified time period	<ul style="list-style-type: none"> • High test-retest reliability, high agreement with collateral informants and urine assays 	Sobell LC & Sobell MB. Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In RZ Litten & J Allen (Eds.), <i>Measuring alcohol consumption: Psychosocial and biological methods</i> . 1992: 41-72. Totowa, NJ: Humana Press. Carey MP, Carey KB, Maisto SA, Gordon CM & Weinhardt LS. Assessing sexual risk behaviour with the Timeline Followback (TLFB) approach: continued development and psychometric evaluation with psychiatric outpatients. <i>Int J of STD & AIDS</i> 2001; 12: 365-375.
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Lack of standardization. While innovations in methods are valuable, the field does suffer from a lack of consensus on the necessary minimum methodology to document and explain behavioral and social risk in HIV prevention research. Most up-to-date theoretical frameworks for HIV risk have expanded from a focus on proximate, individual behavior to include attention to the social context and structural causes or modifiers of individual risk (Rhodes et al, 2005; Friedman et al, 2006, Latkin et al, 2011; Coates, 2013). Validated tools are available to document many key structural factors, including stigma (ICRW toolkit; Stangl et al, 2010); gender inequality (ICRW, 2010; Pulerwitz et al, 2008), and punitive laws (e.g., Rapid Policy Assessment and Response, <http://www.temple.edu/lawschool/phrhcs/rpar/tools/index.html>). What is needed is more application and evaluation of tested tools in more populations and settings, to enable comparison, evaluation and more robust and transferable understanding of what works for behavioral and social risk assessment, with whom, and under what circumstances.

Comment 3.7. Practical Tip

Decades of experience with the HIV module in Demographic and Health Surveys has shown that sensitive questions about sexuality and sexual practice, drug use, sexual violence, and other factors affecting risk require a high degree of rapport between interviewer and interviewee, privacy, and interviewer preparation to deal with intense emotional responses. Understanding the “layering of the stigma” associated with HIV is essential to meaningful dialogue. (See Reidpath and Chan, 2005; Obermeyer and Osborn, 2007). **End of comment 3.7**

Additional Challenges in HIV Risk Assessment

Risk Compensation. As access to prevention technologies increase, individuals who use NPTs may reduce their protective behaviors (i.e., condom use) because they perceive themselves to be at lower risks of acquiring HIV (Eaton & Kalichman, 2007; Hogben & Liddon, 2008). For example, a high-risk individual who has initiated safer sexual behaviors might return to high-risk behaviors due to perceptions of lower risk because of biomedical prevention technologies.

Concern that NPTs may cause or augment risk compensation is a persistent theme in debates about PrEP.³ Hypothetically, these cognitive and behavioral responses could wash out the HIV prevention benefit of the new biomedical agent (Blower et al, 2003; Tangmunkongvorakul, 2013), so they need to be assessed and countered. Kalichman and Cherry et al (2010) found that participants' beliefs about their reduced infectiousness were significantly associated with greater numbers of sex partners, less condom use, and a greater likelihood of having HIV sero-discordant sex partners, and that one's belief regarding viral load, rather than actual viral load influenced behavior. However, RCTs of PrEP have found instead that trial participants had decreased numbers of sexual partners and increased condom use – the opposite of risk compensation.

Such concerns and findings point to the importance of stable and comparable measures of HIV prevention information, motivation and skills, and of contextual issues such as stigma and punitive laws, at baseline and during trials, that may help to explain changes in risk behavior, and over time.

³Disinhibition is a linked concept, which refers to an intrapsychic process whereby sexual or behavioral restraint is lowered or dismissed. (Riess et al, 2010; Guest et al, 2008)

They also highlight the importance of tailoring information and pre-enrollment counseling protocols based on a detailed understanding of individual participants' health beliefs, social and relationship context, as well as prevailing sexual norms and practices.

Investigations of risk compensation also underscore the value of checking and monitoring participants' grasp of the actual purpose and promise of participation in a study, to determine if respondents incorrectly interpreted information given regarding the benefits and risks of the prevention technology. Even brief, 30-minute information sessions regarding the nature of the product, and the fact that its benefits will not be known until the trial is over, can substantially improve understanding of concepts that are integral to informed consent (Fisher, 2010). This kind of information should be gleaned both before and after the informed consent form is signed. While concerns to avoid risk compensation are legitimate, they reinforce the importance of investment in high quality formative research, and necessary and sufficient pre-trial education, and counseling and communication throughout the trial.

Depth, Specificity and Participant Burden. Methodologies are available to gather highly detailed data on the nature and timing of sexual events and prevention behavior, but they can be labor intensive both for study participants and for investigators, especially when pre-testing and validation are required. These intensive methods are not suited to implementation with random samples of volunteers in community or in routine service settings³. When these detailed explanations of behavior are key to the overall study question, or if they can improve research and practice in subsequent studies, they can be included in sub-studies or parallel studies.

Prioritizing behavioral and social questions and data collection. The range of Behavioral and social issues in HIV prevention is vast, and yet study volunteers and site staff may have limited time. It is both a practical and ethical obligation to ensure that these invaluable resources are not wasted, and every variable and data point collected must have a purpose that is on the critical path to respond to participants/community needs and to meet the study's objectives. This principle applies to Behavioral and social data just as it does to socio-demographic and biomedical data gathered in a clinical trial.

SUMMARY

- Risk assessment is a critical component of clinical trials of NPTs.

³ This is evident in the contrast between the explicit and detailed questions on HIV risk that were needed and feasible in Behavioral Surveillance Surveys (designed for use with high-risk populations such as sex workers and people who inject drugs), and those in the AIDS module of the Demographic and Health Survey, which is designed for use in household-based surveys of the general population.

- Both individual and contextual sources of risk should be included in risk assessment procedures.
- Clinical trials need an explicit conceptual model of the sources of individual and contextual risk, in order to guide and prioritize data collection on SBR.
- There are inevitable sources of error in self-reported risk behavior and correlates of risk, but error can be reduced by investment in adequate SBRA methodology.
- Diverse methods are available for eliciting, defining and quantifying behavioral and social risks. Each has advantages and disadvantages.
- SBRA almost inevitably benefits from use of mixed methods and triangulation.
- The field suffers from the lack of an established, minimum approach to behavioral and social risk assessment.
- Behavioral and social scientists have the unique training and competency to guide protocol teams in decisions regarding risk assessment and other issues requiring considerations of the social context of trial participation and conduct.

CONCLUSIONS

Behavioral risk and its social context are so fundamental to trial success that they should figure in the overall study design, site selection, recruitment, protocol design and fine-tuning. In new populations and settings, essential to precede structured instrument development with research to explore a) local concepts and terms – emic perspective; b) social, cultural, political, economic and physical environment factors believed/said to influence study intermediate and outcome variables, especially gender, socioeconomic status, and experience with HIV; c) sub-populations to consider for special questions and terminology – possible need to segment/stratify the sample.

It is essential to invest in the interview and observational methods that provide best estimates of risk behavior, its causes and correlates. These factors are complex and involve, as well as evolve, within a social and cultural life context – a context that parallels the physical and biological contexts. To maximize our ability to benefit in understanding and in health and public health “payoff” for our research investments, we must understand, respect and incorporate this as a basic tenant and core principal in HIV clinical trials research. An integrated approach to risk assessment is thus a vital aspect of clinical trials, and needs to be incorporated into study team planning, study design, and budgeting in increasingly effective and efficient ways.

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CHAPTER 4. INTERVENTIONS TO REDUCE HIV RISK

INTRODUCTION

Behavioral and social sciences play an important role in HIV clinical trials by helping to reduce the risk of HIV transmission in participants. This is due to the ethical obligation to provide research participants with the “standard of care”, typically proven and approved prevention services (see Box 4.1, HPTN Guidance point 9). In addition, some HIV clinical trials may seek to evaluate the efficacy or effectiveness of biomedical, behavioral, structural or combination approaches to prevent HIV transmission. The standard of care may include both prevention and treatment services.

There is an extensive literature and guidelines on the development and testing of rights-based and evidence informed interventions to reduce HIV risk (PEPFAR, 2011 guidelines; UNAIDS 2007/Practical Guidelines for Intensifying HIV Prevention; UNAIDS 2012/Investing for Results). This chapter focuses on the subset of interventions that are relevant to clinical trials of new HIV prevention technologies, under the obligation to provide research participants with the standard of prevention and care.

No single HIV prevention strategy serves all people. Individual differences including age, sex, education, relationship status, risk behavior, social and economic context, knowledge, motivation, skills, history and temperament influence which prevention approach will be acceptable and affordable to specific people. In addition, to achieve efficient and lasting results, a combination of interventions must be provided including efforts to change the social, cultural, political, legal, economic and physical environmental factors that create population differences in the above factors (e.g., Commission on the Social Determinants of Health, 2008) and that impede individuals’ abilities to avoid acquiring or transmitting HIV (Auerbach & Coates, 2000; Gupta et al, 2008; PEPFAR, 2009; UNAIDS, 2010; Hankins & de Zaluondo, 2010).

Comment 4.1. HPTN Ethics Guidance, page 44

“Guidance point 9: In partnership with key stakeholders, HPTN should establish a package of effective, comprehensive and locally sustainable prevention services to be offered to participants in each HPTN study.

“Effective means of prevention” refers to those interventions for which good evidence of effectiveness exists and for which there is no reasonable basis for questioning the effectiveness of the method in the local research setting. HPTN investigators have a responsibility to keep current with new information and developments in HIV prevention research that may be relevant to the standard of prevention in a given HPTN trial, and make modifications where appropriate.

“Reasonably accessible” indicates that the services are free or at a cost within the means of research participants, can be implemented safely and legally within the research participants’ community, and that, if no other significant obstacles to access exist, they can be reasonably overcome by efforts of investigators and the CAB. In general, services may be provided through referral if the referring clinic meets these criteria for accessibility, if direct provision of the services would critically overwhelm the capacity of the research staff, or if the service requires expertise or specialized skills that go beyond what is reasonably necessary for implementation of the trial. **End of comment 4.4**

Evidence-based Interventions

Clinical trial protocols should draw upon appropriate, well-researched, and well-validated theory, tested interventions, and evidence regarding the local populations and settings when designing standard of care prevention packages. The CDC has developed a compendium of evidence-based behavioral intervention programs (EBIs), all of which have shown some efficacy (<http://www.cdc.gov/hiv/prevention/research/compendium/rr/complete.html>). Most of the listed programs and tools focus on individual-level behavior change, and were developed for specific populations ²). Socioecological models have been used as heuristic frameworks, and case studies have discussed the value of combination prevention strategies that address multiple layers and determinants of risk (Stack, 2009, AIDStar-One). Many researchers advocate “high impact interventions,” which include structural intervention strategies as “critical enablers” of individual risk reduction (Reference UNAIDS, 2012 and CDC, 2012). However, there has been a dearth of research on these broader, combination strategies.

Randomized clinical trials (RCTs) have long been considered the ultimate tests of prevention interventions (the ‘gold standard’). While the power of RCTs to establish efficacy is undisputed, it is now widely acknowledged that HIV prevention researchers must cast a wider net (UNAIDS 2009 – M&E guidance; Padian, McCoy et al, 2010).

Given the complexity of contributing factors, the high cost of efficacy trials, the scarcity of populations with sufficient incidence, and ethical considerations, a wider range of rigorous data now qualify as data for HIV program planning. (Baral, Wirtz, et al, 2012). (See Box 4.2 on HASTE). For example, Scott-Sheldon, et al, (2011) hypothesize that interventions will be more efficacious when they: 1) serve greater proportions of those who are most affected, 2) sample patients diagnosed with an STI or HIV at baseline, 3) target motivation and provide skills training consistent with motivational and skill-based theories of HIV prevention, 4) tailor the content to the individual, target content toward a specific group, or match facilitators to the gender or race of the participants for message relevancy, and 5) are long enough to provide participants with additional opportunities to practice skills (see also Johnson et al, 2009). In addition, Padian & Isbell et al, (2012) found that 1) planning for commodity procurement, 2) supply management, 3) recruitment and organization of human resources, 4) organization of clinical settings, 5) choice of delivery strategies, and 6) demand for services also were associated with higher efficacy or effectiveness. It is difficult to imagine how controlled experimental evidence could be obtained to measure the individual and synergistic contributions of these ten program factors, in addition to the contributions of factors cited in socio-ecological models of behavior change, in multiple populations and sociocultural settings.

²The web page lists tools alphabetically by study title, but it provides information using some of the following codes: RR=risk reduction; HS=Heterosexual; HIV+=HIV-positive; HCV+= Hepatitis C-positive; HR=High-risk; MSM=Men who have sex with men; DU=Drug users; CSA=Childhood Sexual Abuse; M=Male; F=Female; T=Transgender; W=White; AA=African American; AI=American Indian; H=Hispanic; API=Asian/Pacific Islander; O=Other racial/ethnic group; GLI=group-level intervention; ILI=individual-level intervention; CLI=community-level intervention

Rather, these program factors can be emulated as good or best practices when assessing and planning risk reduction interventions in the context of clinical trials, and data should be collected on their aims, activities, implementation fidelity and results, to build the evidence base through rigorous comparison. Gathering and assessing the quality of contextual data, and triangulating qualitative and quantitative data, benefits from leadership by a team of experienced behavioral and social scientists.

Key Issues When Developing Risk Reduction Interventions to Include in Clinical Trials of NPTs

Several additional points should be considered when developing a protocol to enable basic HIV prevention services to meet population-specific needs, and thus to facilitate optimal outcomes:

1. The services should be aligned with national and global guidelines for HIV prevention related to the study locales and populations (see Chapter 1 on Know Your Epidemic, Response, and Context).
2. Interventions should be attuned to the life context/s of study participants, and they must be appropriate, accessible, affordable, of high quality (Patel et al, 2003; AAAQ, WHO and OHCHR (2007) The Right to Health–Joint fact sheet 323), and sustainable after the infusion of research resources has ended. A combination of in-depth knowledge of the populations and settings, formative research, and baseline assessments are required in order to meet these criteria.
3. Investigators, prevention intervention staff and local and international funders should be aware of and observe the HPTN Ethics Guidance for Research (HPTN, 2009) and the UNAIDS/AVAC Guidelines for Good Participatory Practice (UNAIDS and AVAC, 2013). Many key decisions about the quality and scope of the standard prevention services in a clinical trial are based on the funding available, for the trial, and after it concludes.
4. The philosophy of prevention should be to empower communities and their individual members to develop and own their HIV prevention strategies.
5. Prevention activities are needed with people living with HIV as well as with HIV – people.
6. Prevention trials also are obligated to ensure that trial participants receive (or are referred) appropriate medical care including access to ART if they are or become HIV positive.
7. Prevention interventions need to be fully specified. The specific audience, the activities, the setting and the intended outcome/s should be described (Sweat, 2007) so that the intervention can be evaluated and replicated in other study sites.
8. Up-to-date education and counseling tools should be used which consider the integration of prevention and treatment, which do not imply or assume all clients are HIV negative, and which address partner and family support and social networks.
9. Basic prevention services can address structural barriers to risk reduction, and they must do so when structural barriers, such as punitive laws or threats from police or opinion-leaders threaten research participants. PEPFAR and UNAIDS HIV prevention guidelines includes structural interventions-including programs that promote human rights, remove

- punitive laws, and combat gender inequality and HIV related stigma and discrimination.
10. Multi-method approaches to HIV prevention interventions are recommended, both to match the diversity of individuals and contexts, and, if possible, to offer choices.
 11. Clinical trial protocols should build in adequate monitoring and evaluation of the standard of prevention activities, including both process evaluation and intermediate outcome monitoring, and periodic reporting to investigators, local authorities, and host communities (see Chapter 2).

Comment 4.2. Combining Biomedical, Behavioral and Structural Strategies

Biomedical technologies, behavioral strategies and social structures are not to be treated as separate entities, but used in combination to support/enable people's appropriation of available tools into their sexual and injection practices." (Kippax & Stephenson, 2012). **End of comment 4.2**

It is the task of social scientists on the research team to define local structural risks and incentives and barriers within the social systems in study sites that enable volunteers to enroll and sustain their participation in the trial, so that these can be monitored and boosted by the trial. For example, relevant social policies (e.g., social protection, health education, etc.) will be identified through the broad context in assessment and formative research carried out in the concept and protocol development phases and guided by the trial's conceptual framework and theory of HIV risk and vulnerability (see Chapter 3).

Many national HIV prevention program guidelines call for decentralized planning and development of prevention activities and performance objectives to suit local populations (the Zimbabwe and Kenya national AIDS programs are good examples). Where an HIV prevention clinical trial seeks to recruit volunteers in special populations, including high-risk populations, and where the national standard of prevention is not sufficiently tailored to their needs, the protocol team will need to undertake basic prevention programming. Also, national program guidelines are a key starting point, but on the ground, these may consist of diverse public and private projects/services with inadequate funding and little investment in joint planning to capture potential synergies and maximize impact. With the added resources available through a clinical trial, both technical and management gaps can be reduced, creating models that can "raise the bar," build local capacity, and generate evidence about combination prevention effectiveness.

Approaches to Prevention Planning

Called by various names (e.g., community planning, intervention mapping, HIV programming), design of effective HIV prevention responses (and other health programs) requires several basic steps. Their aim is to develop strategies that utilize available theory and evidence and that match the needs of the specified

populations and settings. For example, “intervention mapping” guides planners in: 1) identification of behavioral and environmental determinants related to the health issues of interest the target population, and 2) selection of the most appropriate theoretical methods and practical applications to address the identified determinants (Bartholow, et al, 2001, see Table 4.1). As with all health programming frameworks, this intervention mapping process is viewed as cumulative (each step is based on previous steps), iterative (there are feedback and improvement loops), and not rigidly linear, as it is often necessary to move back and forth between tasks and steps.

Table 4.1. The Intervention Mapping process (Bartholow et al, 2001; 2006)

Step 1	Needs and Asset Assessment	<ul style="list-style-type: none"> • Identify the at-risk population, assess quality of life, health, and behavior • Differentiate environmental from behavioral conditions • Review key factors affecting community capacity • Assess intervention impact and specify goals
Step 2	Environmental Matrices/Context	<ul style="list-style-type: none"> • Outline potential behavioral changes relative to environment • Establish measurable criteria for successful performance • Identify major and modifiable determinants/factors affecting the health of individuals • Specify matrices of change objectives
Step 3	Theory-based Methods and Practical Applications	<ul style="list-style-type: none"> • Review national and global guidelines and evidence • Check actual implementation in study sites • Conduct broad gauge context assessment and risk and adherence assessments • Identify gaps and improvements to meet global and national standard of care • Discuss with communities and authorities to agree on standard of prevention package for sites
Step 4	Program Plan	<ul style="list-style-type: none"> • Conference with participants, staff, and other stakeholders • Develop program components and translate documents in local terms while preserving cross-site comparability • Design and pretest materials with target audience
Step 5	Adoption and Implementation Plan	<ul style="list-style-type: none"> • Identify users and implementers • Organize strategies or interventions into a program • State program performance objectives • For each program level, cross matrix performance objectives with determinants
Step 6	Evaluation Plan	<ul style="list-style-type: none"> • Inspect program logic and outcomes • Develop effect and process questions • Quantitatively measure (indicators) program performance • Monitor variables and review data to improve care

Zule et al. (2010) utilized a modified intervention mapping approach to develop and refine a single session motivational intervention for Methamphetamine using men who have sex with men. In this study, the authors first gathered information on their study population and developed a table outlining and displaying their risk behaviors and barriers to reducing risk (see Table 4.2). They then proposed strategies to reduce the risk behaviors and barriers that would be acceptable to their specific population.

Table 4.2. Evidence-based Planning of a Prevention Program for Men Who Have Sex with Men (Source: Zule et al, 2010)

Another example is from van Empelen et al (2003) in which their study presented

Risk Behaviors	Intervention Needs
Unprotected anal intercourse is common among methamphetamine using MSM	Reduce unprotected anal intercourse
Methamphetamine using MSM often engage in unprotected anal intercourse with non-primary partners when using methamphetamine	Reduce unprotected intercourse with non-primary partners when using methamphetamine. Reduce methamphetamine
Barriers to Reducing Risk	
Men are not ready to reduce their methamphetamine use	Increase readiness to reduce methamphetamine use
Men do not feel that they are able to use condoms when they are using methamphetamine	Increase self-efficacy for using condoms when using methamphetamine
Men do not feel that they can use methamphetamine and not have sex	Increase self-efficacy for avoiding sex when using methamphetamine
Intervention Format, Content and Delivery	
Men are unwilling to attend multisession interventions	Develop a single session intervention
Intervention should be delivered by someone with whom men feel comfortable	Develop an intervention that can be delivered by former methamphetamine using MSM or similar person
Intervention should offer options for reducing risk	Develop an intervention that provides a menu of options for reducing sexual risk associated with methamphetamine use
Many HIV prevention providers do not have the resources to deliver multisession interventions that are delivered by highly trained professionals	Develop a brief intervention that can be delivered

the development of a theory and evidence-based AIDS prevention program for Dutch drug users aimed at the promotion of consistent condom use.

The formative research and review of theoretical methods led the authors to base the intervention on social cognitive theory (Bandura 1977), and diffusion of innovations theory (Rogers, 1983).

The proposed determinants of risk in this study included: awareness, attitude, social influence, and self-efficacy. Once the determinants were identified, the researchers identified possible theory-based methods to promote behavior change that fit with the objectives specified and ordered by the determinants (van Empelen, et al, 2003; see table below).

Table 4.3. Methods, Theories, and Parameters Specified per Determinant (Source: van Empelen, et al, 2003)

Determinant	Method	Theories	Parameters
Awareness	Threat Personalization	Risk Perception, Unrealistic Optimism	Individual, Undeniable, Congruent with Actual Risk, Cumulative, Presented both with Qualitative and Quantitative Examples
	Active Learning	ELM, SCT	Relative Comprehension
	Framing	Judgment under Uncertainty	Qualitative, Gain Frame (preventive behavior)
Attitude Change	Active Learning	ELM, SCT	Regret Theory–Relevant, Comprehension
	Active Participation	Cognitive Dissonance, Self-Perception Theory	Voluntarily, not justifiable by rewards
	Persuasion	ELM, HSM PCM	Adapting to Existing Beliefs Source, Message, Channel, Receiver
	Modeling	SCT	Coping Model, Reinforcement
	Anticipated Regret	Regret Theory	Must Stimulate Imaginary
Social Influence	Modeling and Vicarious Reinforcement	SCT	Attention, Remembrance, Skills, Coping Model, Positive Reinforcement
	Mobilizing Peer Influence	Diffusion of Innovations	Credible, Realistic
	Interpersonal Skill Building	SCT	Favorable, Capable
Self-efficacy	Modeling	SCT	Attention, Remembrance, Skills

NOTE: ELM = elaboration likelihood model; SCT = social cognitive theory; PCM = persuasion communication model; HSM = heuristic

Examples of socio-ecological frameworks and tools for addressing the structural factors in that are deemed essential to prevention interventions were outlined in Chapters 1 and 3.

Additional Components of a Standard Prevention Package

Established research policies require that the HIV risk reduction package provided to all volunteers in NPT clinical trials should be 1) up-to-date; 2) evidence based; 3) acceptable, accessible, affordable and of adequate quality; and 4) and aligned with the relevant national and global guidelines. Clinical trials designed today will be carried out in settings where some form of HIV prevention has been under way for over 20 years – nearly a generation. When existing services do not meet these criteria, international ethical guidelines require clinical trial protocols to build and support capacity to meet national and global standards.

The HPTN Ethical Guidance (2009) requires all HPTN research protocols to ensure access to voluntary HIV testing and counseling, HIV and sexually transmitted infections (STIs) risk reduction counseling, counseling to reduce risk from drug and other substance use, and provision of male and female condoms (HPTN 2009).

Comment 4.3. HPTN's Recommended Components for a Prevention Package:

1. HIV voluntary counseling and testing
 2. HIV and STI reduction counseling
 3. Access to all available HIV reduction methods (condoms, PEP, etc.)
 4. Interventions should be 'reasonably accessible' (free or low cost and can be implemented safely and legally)
 5. Interventions should be 'practically achievable' (can reasonably be implemented and sustained independent of the resources required for a clinical trial).
- End of comment 4.3**

Based on a series of global consultations with all concerned stakeholder groups, UNAIDS set even higher standards for “standard of prevention” in biomedical research:

http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf. They state that:

- Guidance point 13 states “Researchers, research staff, and trial sponsors should ensure as an integral component of the research protocol, that appropriate counseling and access to all state of the art HIV reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial.”
- New HIV risk reduction methods should be added as they are scientifically validated or approved by relevant authorities.
- Risk-reduction packages should include provision for family planning, pregnancy and childbirth services. Researchers should guarantee that all

- communities engaged in biomedical HIV prevention trials have state of the art reproductive health care services.
- All trial participants should receive HIV risk reduction counseling as well as access to proven prevention methods, including PEP in the likely event of known likely exposure.
 - All participants should be counseled at the start of a prevention trial regarding the potential benefits and risks of participation, PEP, antiretroviral therapy, and plans for the community to have access to the product, if it proves efficacious.

The UNAIDS Guidelines specifically recommend that study protocols include mechanisms for negotiation about enhancement of the standard risk reduction package, should new biomedical prevention technologies (NPTs) be scientifically validated or approved by national authorities during the study period.

Comment 4.4. Example

Rapid Policy Assessment and Response (RPAR) is an intervention that mobilizes local knowledge to tackle complex health problems and builds capacity to make interventions sustainable. It was developed originally as a tool to fight HIV/AIDS among sex workers, injection drug users, and members of other marginalized populations at the city level.

Burris & Davis (2009) provide an example of how HPTN 058 investigators sought an independent empirical investigation of social and legal risks to research participants at the study sites. They utilized the RPAR tool to generate reports provided to the responsible IRB's.

The 'Law on the Books' and literature review components confirmed the detailed and prohibitionist character of the legal regimes governing drug users in Thailand and China (Burris & Davis, 2009). **End of comment 4.4**

Given the diversity of people and contexts, and the sensitivity and potential risks to study participants, interventions tested in studies with one population should not be transferred to other settings and populations without formative research, pre-testing and adaptation (Bartholomew, Goli, et al, 2006; Auerbach, Parkhurst, Caceres, 2011; UNAIDS, AVAC GPP Guidelines, 2011; Seeley, Watts, et al, 2012; Auerbach et al, 2009). In addition, where risk assessment (see Chapter 2) has identified other sources of risk, the basic package must be expanded, either through direct provision of more services, or through advice and counseling, partnership and referral, to quality services that are available and accessible, affordable outside the trial.

For example, if the behavioral and social risk assessment has identified injecting drug use as an important risk factor, the protocol should include needle and syringe exchange and other harm reduction services through information and counseling, referral, or direct provision. Where threats or gender-based violence were found

significant, access to post exposure prophylaxis (PEP), community dialogue, media campaigns, and access to legal protection might be required. Through use of empirical risk assessment, and then dialog and partnership with community members, other service providers in the area, national authorities and other stakeholders, investigators can provide a comprehensive essential package of services, even when their own funding resource does not suffice or permit it.

Summarizing papers that were presented in a conference on social drivers in 2011, Seeley, et al (2012) reviewed studies that illustrate how gender inequality, gender identity, economics, rights, education and health beliefs and practices can be “necessities” rather than “luxuries” in HIV prevention. Ideally, the risk reduction package should seek to include support for critical motivators and local groups and institutions that can support the goals of reducing new HIV infections (Plowden, Fletcher, & Miller 2005). These analyses require professional behavioral and social science expertise and local knowledge, so work with local behavioral and social scientists is a significant advantage (see Chapter 1).

Rapid but systematic methodologies, such as Rapid Policy Assessment and Response (RPAR), illustrate that complex structural factors can be documented within the time frame of formative research (see Box 4.5). For at-high-risk populations who face multiple barriers to accessing HIV information and services, formative research is especially valuable.

Comment 4.5 Stakeholder Viewpoint

...so, when things get difficult and you need friends; or you have a hard time like when a trial closes early; you already have people who have a relationship with you, who are aware of your intentions; can be the voice in the community and with the media and with other stakeholders to help get the message out and do some damage control (N013).

Source: Koen et al, 2012. ‘IT LOOKS LIKE YOU JUST WANT THEM WHEN THINGS GET ROUGH’: CIVIL SOCIETY PERSPECTIVES ON NEGATIVE TRIAL RESULTS AND STAKEHOLDER ENGAGEMENT IN HIV PREVENTION TRIALS. *Developing World Bioethics* ISSN 1471-8731 (print); 1471-8847 (online). **End of comment 4.5**

For the first two decades of AIDS research, prevention was directed toward people who do not have the virus. Today, it is clear that risk reduction and health promotion for people living with HIV are also essential (UNAIDS and GNP+ on Positive Health, Dignity and Prevention). In addition, the review and framework provided by Lau and colleagues (Chapter 1, Figure 1.3) reminds us that HIV risk reduction planning should examine not just characteristics and context of the study population, but also characteristics of the research setting, including trial site staff and spaces. Interventions to upgrade facilities for privacy, to train staff in motivational interviewing, to improve confidentiality, to promote tolerance and compassion and to combat stigma from health care workers and other site staff, are

readily available (Mahajan et al, 2008; 2008 Report on The Global AIDS Epidemic; Golin et al, 2010) and should be built into protocols when formative research indicates that they are essential to recruitment, retention and data collection.

Prevention Intervention Sub-studies and Trials Nested in Clinical Trials of NPTs

While difficult to prove, it is sociologically plausible (see Chapter 1) that diverse and mutually reinforcing biomedical, behavioral and structural interventions, delivered together, will have synergistic effects. It is also plausible that integrated, program strategies that target a broader range of risk factors such as personal, relational, and sociocultural factors, will be more effective than individual risk reduction interventions alone in a 3 to 5-year time frame (Blanchard & Aral, 2011; Seeley, et al, 2012). Clinical trials of NPTs are likely to have the scale, expertise, infrastructure and longevity to build up the evidence base on these complex and important points. These opportunities should not be missed.

Ethical Considerations in Developing HIV Prevention Interventions

A key ethical obligation is to provide information and services that are appropriate to and effective for the population/s in question. Poorly researched, poorly tailored, poorly resourced, or half-heartedly delivered prevention services are an ethical violation as well as a waste of resources.

Community participation. As noted previously, the HPTN Ethics Guidance document (2009), UNAIDS and the Good Participatory Practice (GPP) guidelines (AVAC and UNAIDS 2012), have provided 12 guidance points that summarize the main issues and obligations stakeholders encounter when developing and executing a prevention package in the setting of a HIV clinical research trial. They recommend early involvement of all relevant stakeholders from early protocol development through implementation and dissemination of trial results.

Comment 4.6. - Stakeholder Perspectives on Dual Standards of Care in High and Low-Income settings

Discussions in the mid-1990s as well as separate consultations were held regarding the design of trials to evaluate antiretrovirals to prevent mother to child transmission in resource-poor settings where implementation of the effective but expensive and clinically-demanding 076 regimen was considered unfeasible. These consultations led to the design and implementation of placebo-controlled trials (with one exception) on the grounds that a comparison with the 076 regimen would not answer the question as to whether the experimental intervention was better than the existing host country standard, i.e., better than nothing. This decision precipitated considerable controversy centered on accusations that ethical relativism was being used to justify lower standards of care for vulnerable populations with exploitation of that vulnerability for research that would primarily benefit wealthier countries.

The sponsors and implementers of the trials felt blind-sided by these accusations and insisted that they were motivated by the overwhelming need for Prevention of Mother-to-Child Transmission (PMTCT) interventions that could be rapidly brought to scale in the resource-limited settings hardest hit by the epidemic. In parallel with these, the PMTCT trial controversy spilled over into ethics debates related to preparations for HIV vaccine trials in resource-poor countries, centered on concerns about exploitation and use of double standards for care. In the late 1990s, UNAIDS led development of ethics guidelines specifically for HIV vaccine trials. **End of comment 4.5**

Ethical Relativism and Dual Standards of Care

Profound dilemmas attend efforts to identify new HIV prevention technologies including defining the standard of care to meet in clinical trials of NPTs, and dealing with sustainability of services after study closure (Philpott, et al, 2011). Human rights specialists and bioethicists approach these dilemmas from diverse technical and political perspectives. Many of these have been outlined recently in debates around PrEP (Macklin, R; 2010; WHO and UNAIDS, 2012; Sugarman & Mayer, 2013). There is broad agreement that the basic bioethics principles must be respected,⁴ and community consultations and debate are needed to establish how the principles are best realized in specific instances (Resnik, 1998; Macklin, 2010; Cowan & Macklin, 2013).

Special vulnerability of many HIV study populations. Vulnerable populations face a range of constraints that make recruitment, retention and adherence difficult. These structural constraints need to be identified, and addressed with a coordinated combination of intervention approaches beyond the standard of prevention for study participants. International research can introduce life-saving resources for intervention development, treatment and care, but also can invite unwanted scrutiny and repression of individuals or whole communities. Such trade-offs should be discussed with local stakeholders and with international IRBs, and decided by local stakeholders.

Risks and costs to study staff. The caring, empathy and engagement that are sought in HIV research staff (see Chapter 2) can place staff under severe psychological stress. So too can time pressures, such as when interviewers are urged to listen attentively and respectfully, document fully, but also to meet unrealistic daily quotas. Staff may also jeopardize important personal benefits and relationships by taking on roles in a study (e.g., management of reimbursements, or medical supplies). Periodic participatory reviews can be built into protocols when such issues can be brought to light and resolved. Appreciative, or strengths-based

⁴ Resnik (1998: 293) listed these principles, which are encoded in the Helsinki Declaration, the Belmont Report, and CIOMS (1993) as: “1) informed consent; 2) beneficence to subjects (or cost/benefit); 3) privacy/confidentiality; 4) social utility; 5) justice/fairness; 6) scientific rigor; and 7) monitoring of study and subjects.”

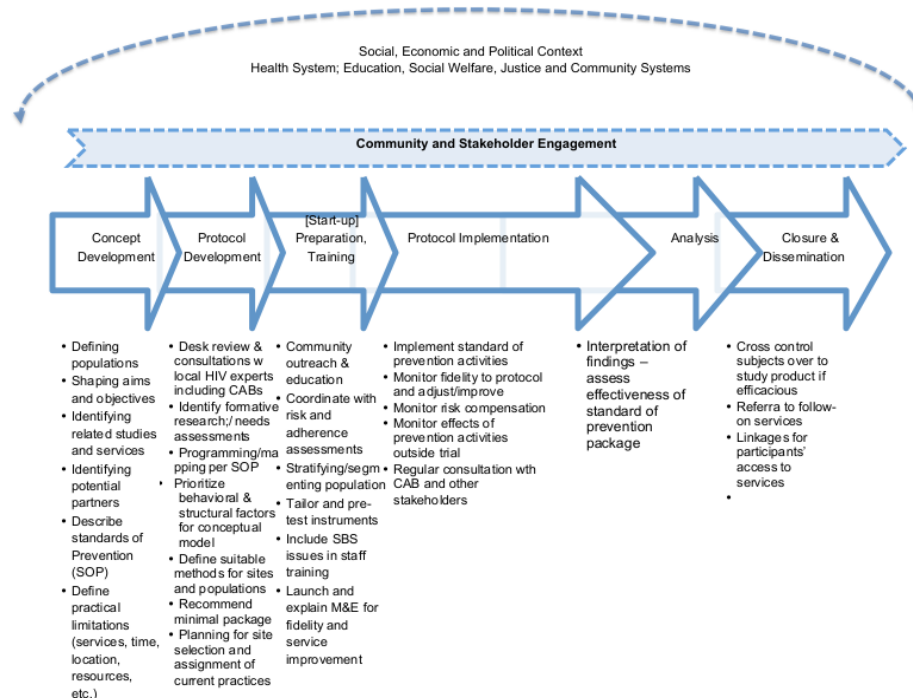
methods from organizational psychology can help make monitoring procedures productive rather than intimidating or punitive.

Risk compensation. As noted in Chapter 3, this is an on-going concern in HIV clinical trials of new biomedical prevention technologies (NPTs). It will be highly desirable for specific ethnographic and epidemiological activities to be included to alert investigators if suggestions arise that volunteers in any study population, including the control group, are increasing their risk behavior, and to understand how much, in what ways, and why.

The evolving standard of prevention. Finally, the field anticipates developing challenges in detecting treatment effects of new prevention interventions as they are tested against ethically sound standard of care prevention packages. Research teams can advocate for newer and better prevention strategies with local community members and stakeholders during concept and protocol development processes. They can assist by assessing the current prevention strategies offered by the local communities and including plans to build on the local standard of care when developing their prevention package. Building local capacity and partnerships for research is part of NIAID's mission (see Guiding Principles).

Resources. An extensive array of data collection and analytic tools are available that deal with HIV risk reduction interventions (See Annex III). As with interventions to promote adherence (see Chapter 5), risk reduction interventions can be designed for use in study contexts or in the context of on-going services. Links to some of these tools and resources may be found at:
<http://www.cdc.gov/hiv/dhap/prb/prs/index.html>.

Figure 4.1. Behavioral and social Issues in Interventions to Reduce HIV Risk (per Standard of Care) in the Life Cycle of a Clinical Trial



CONCLUSIONS

Clinical trials of new biomedical prevention technologies are obligated, by good practice and research ethics, to evaluate the NPT against existing, proven and approved HIV prevention methods.

- All prevention methods involve socially embedded behavior, from accessing health services to changing sexual and drug use practices. A wealth of expertise, approaches and tools that are grounded in behavioral and social sciences are available to support prevention program planning.
- Concept and protocol development should budget for the needed formative research, consultations, and services to provide the biomedical, behavioral and structural information required to plan the standard of care prevention package to be offered to all volunteers.

- The prevention interventions offered should be ethically sound, evidence-based, fully specified, and aligned with national and global guidelines, including standards of quality, intensity and coverage.
- Given the diversity among individuals and sites, standard of prevention packages require a strategic mix of components, tailored to local language and context. At the same time, issues of cross-site comparability have to be taken into account. Behavioral and social science expertise can improve tailoring without losing cross-site comparability.
- Standard of prevention tools and measures should be up-to-date, recognizing the interdependence of prevention and treatment, and the needs of people living with HIV for positive health, dignity and prevention, and the role of service providers in combatting HIV-related stigma and discrimination.
- Structural factors, including economic pressures, HIV-related stigma and discrimination, gender inequality, punitive laws, can be addressed in standard of prevention services, and must be addressed if structural factors put volunteers, host communities and research staff at risk.
- Monitoring and evaluation of the standard of care prevention services will both alert site staff and investigators to problems that can be corrected, and will contribute to needed evidence on the effectiveness of combination prevention programs.
- An on-going challenge for biomedical HIV prevention trials is the interpretation and application of guidelines in the real-world setting where numerous trials, wide range of modalities and policy requirements on prevention standards can vary over time and from the global to the local context.
- The ethical dilemmas of prevention research, including the evolving standard of prevention, are serious, and can only be resolved through pro-active, transparent consultation with stakeholders, beginning with volunteers and their communities.

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Section III

Adherence Assessment

Chapter 5. Adherence Assessment in Trials of New Prevention Technologies

Point to consider 3.

“I stopped taking my medication and my CD4 dropped to only 37 when I restarted my medication, my CD4 increased up to 200 and I felt that I am capable of changing the course of my life and doing things just like HIV uninfected people.....”
Adolescent FG

Source:

Mutwa PR, Van Nuil JI, Asiimwe-Kateera B, et al.

Living situation affects adherence to combination antiretroviral therapy in HIV-infected adolescents in Rwanda: a qualitative study. PLoS One. 2013;8(4):e60073.

INTRODUCTION

The MTN defines adherence as “Following a prescribed regimen correctly and consistently. In clinical trials, the term adherence usually refers to how well the trial participant followed the trial’s study drug or protocol.” Adherence is now a central concern in healthcare research and delivery due to the burgeoning array of effective treatments for many chronic diseases including HIV (Turner & Hecht, 2001). Most generally, “adherence” concerns both following prescribed medical procedures (e.g., follow-up visits, lab tests, data collection procedure) and also using prescribed medications according to the recommended regimen. *Product adherence* refers more specifically to use of a drug or other therapeutic product according to the prescribed regimen (Murphy et al, 2000; Williams, 1999).

Adherence reflects the problem-solving skills and active participation of the patient or study participant, and is a multidimensional process involving the person, the treatment or research environment, the health risk/condition, the provider and the person-provider relationship (Kennedy, 2000; Miller & Hayes, 2000). WHO provided an overview of behavioral science perspectives on adherence to medications. They noted that adherence strategies should address “the patient, the provider, and the health care system” (WHO, 2003:143). Patient and provider behavior and healthcare systems are shaped by community and broader structural factors such as economic resources, HIV related stigma, and social support (Amico

2013; Tolley et al, 2014). Thus, as in risk assessment, socio-ecological models are useful in planning studies and techniques to assess, predict and explain HIV new biomedical prevention technologies (NPTs) adherence.

Adherence profoundly impacts tests of the efficacy of biomedical HIV prevention approaches (IOM, 2008). A series of landmark clinical trials have recently demonstrated that daily oral pre-exposure prophylaxis (PrEP) can be highly efficacious in preventing HIV transmission. These trials indicated a clear dose-response relationship between adherence and reduced risk of HIV infection: clinical trials showing greater product adherence have produced greater estimates of PrEP efficacy for HIV prevention (Celum & Baeten, 2012). For example, among a subset of iPrEx trial participants who received active drug, a 95% reduction in the relative risk of HIV infection was observed in a controlled analysis that compared participants with and without detectable drug concentrations in plasma (Grant et al. 2010). In contrast, low adherence (low product use) was a key factor resulting in two large PrEP efficacy trials in East and Southern African countries being stopped for futility. Low adherence may also account for the failure of a proof-of-concept trial testing acyclovir suppressive therapy against genital herpes in Tanzania. (See Box 5.1). The data and outcomes from large-scale HIV prevention trials conducted to date collectively indicate that adherence may represent the “Achilles heel” of biomedical HIV prevention strategies (Bangsberg, 2014).

HIV product adherence has been studied extensively in the context of antiretroviral drug therapy (ART) (WHO, 2013; Amico, 2013 and Tolley et al, 2014, for review). Adherence to ART has long represented the strongest predictor of viral suppression (Arnsten et al, 2001; Bangsberg et al. 2000; Paterson et al, 2000), progression to AIDS (Bangsberg et al, 2001), and mortality (Garcia de Olalla et al, 2002; Hogg et al, 2002; Lima et al, 2009). Complex regimens that impede treatment adherence, and health disparities in prevention as well as treatment/care can lead directly to untoward outcomes including failure of viral suppression, progression to AIDS and death (Hsu, Saha, Korthuis, Cohn, et al, 2012; Schackman, Ribaud, et al, 2007; Lemly, et al, 2009).

The challenges of product adherence for prevention of HIV are different in crucial respects from adherence to medically indicated treatment. These challenges are further intensified in the context of clinical trials to evaluate the prevention efficacy of a NPT:

- Adherence is notoriously harder to motivate and sustain for prevention than for treatment;
- In a clinical trial, all participants must be advised and encouraged to adhere to already proven prevention strategies, including condom use, and they are cautioned not to rely on the test product for prevention as it has not been

- proven. This creates a “mixed message” about the value of the product for the individual (Tolley et al, 2014);
- People who take ART to control their HIV infection need to adhere to their regimen continuously over time, whereas complex patterns of use/non-use can be technically justified in the context of individuals taking PrEP to prevent HIV infection. For example, participants may reduce their potential exposure to HIV through abstaining from sex or by taking up consistent correct condom use and thus may not need to take PrEP continuously (WHO, 2013; Tolley et al., 2014).

Comment 5.1. Low Product Adherence Can Derail a Clinical Trial

FEM-PrEP, a large-scale prevention trial testing the efficacy of oral PrEP with at-risk adult women (FEM-PrEP) in Kenya, South Africa and Tanzania proved unable to demonstrate a protective effect and was halted early by the Data and Safety Monitoring Board (DSMB) due to futility. Trial participants evidenced low adherence based on drug-level testing, although high adherence had been indicated in participant self-reports and pill count data (van Damme, 2012).

VOICE, a large-scale prevention trial in Uganda, South Africa and Zimbabwe, tested the efficacy of tenofovir-based PrEP (daily use of oral tenofovir, oral tenofovir-emtricitabine, or vaginal tenofovir gel) in predominately young unmarried women with high HIV incidence. Although researchers estimated adherence at approximately 90% based on self-reports and unused pills and gel counts, the actual blood sample analysis indicated that adherence to study drugs was low, and none of the study drugs significantly reduced risk of HIV acquisition. The VOICE results are consistent with FemPrEP (JM Marrazzo, CROI 2013).

A proof-of-concept trial testing acyclovir suppressive therapy against genital herpes conducted with high-risk women in Tanzania failed to find evidence that acyclovir confers benefits for HIV prevention (Watson-Jones et al, 2007). Data from the trial suggested that shortfalls in product adherence occurred. A trial sub-study showed that a substantial proportion of participants in the active drug arm did not have detectable acyclovir in urine samples, even though product adherence as measured by pill count appeared to be high (Watson-Jones et al, 2007). Poor clinical response, in combination with the lack of widespread drug detection in the active arm, suggested that poor adherence compromised this trial. **End of comment 5.1**

Despite the importance of adherence to HIV prevention trials, use of adherence measures in trial design, implementation and interpretation has been inconsistent (Tolley, Harrison et al, 2010; Williams et al, 2010). Chesney observed that there is no “gold standard” methodology for assessing or supporting HIV product adherence (Chesney, 2006), and this remains true today. However, there has been progress. Over a decade of research and analysis has produced established models of adherence based on well-developed and tested behavioral and social theory.

Amico et al. (2013) recommended that “Shifting from a biomedical to bio-behavioral or rather a bio-psycho-social framework will help build the evidence base for effective PrEP adherence interventions.” An empirical and bio-psycho-social perspective helps to avoid false assumptions about who can and cannot adhere: in ART for prevention as well as for treatment, pejorative assumptions about vulnerable populations often are proven wrong (Beyer, Malinowska et al, 2010). When collected as part of a unified, socio-ecological framework that examines social determinants of HIV risk and risk reduction behavior (see Chapter 1), data collected about adherence in a clinical trial can not only quantify, but also explain and improve it.

Goals of Adherence

HIV prevention clinical trials use adherence assessments to:

- Estimate use of the investigational product, as a key variable in efficacy and effectiveness studies;
- Understand factors that increase and reduce consistent and correct product use, to inform and improve recruitment and service delivery;
- Identify low- and high-adhering individuals, for adherence support, and
- Build basic knowledge and test hypotheses about health behavior.

Comment 5.2. Participant’s point of view.

When I started ART treatment, I informed my brothers. One contributed some money, another one tray of eggs, another bought soft drinks, and another 3 kilograms of sugar, as well as asking the fish vendor to supply fish on Saturdays. They tried their level best. If it wasn’t for that support, I would have dropped out of (HIV) treatment at the very beginning. When I recovered, I started taking care of myself. I reared chickens in order to have a reliable source of eggs. I also grew vegetables. I also convinced my children to buy me a cow, which produces 3 litres of milk. I consume practically all that milk myself. Over a period of 3 months, I had regained weight. I started getting compliments from people about my bodily appearance. The more the compliments, the more I was encouraged to continue taking my medicine. (Male Key Informant, RPF)

Source: Dissertation, 2011; Title: Sustaining adherence to antiretroviral therapy among HIV/AIDS patients in Uganda; Author A. Ssewaya. Bibliographic details found at: <http://dare.uva.nl/record/400073>; Accessed: 22 April 2014. **End of comment 5.2**

The safety and efficacy of biomedical HIV prevention strategies cannot be adequately determined without clear measures of how and how much the investigational product was used. Masse (2009) has described how inadequate product adherence can “dilute” the outcomes of HIV prevention product efficacy trials by compromising their statistical power. In addition, the ability of people to adhere to recommended regimens will influence the effectiveness of products that

are approved for use. Efficient and accurate adherence measures can potentially help to identify high-risk individuals and populations for which adherence interventions can be targeted (Berg & Arnstein, 2006).

Understanding who was protected during the trial and under what circumstances has important implications for predicting how effective the product will be in real-world settings (IOM 2008 p. 119; Stirratt & Gordon, 2008). A wide range of biomedical, behavioral and structural factors have been found to influence adherence in HIV prevention trials (Miller & Hayes, 2000; Crane J et al, 2002; Stirratt & Gordon, 2008; Pelzer, et al 2010; Williams, et al., 2010; Amico, 2013; Tolley, et al, 2014).

Clearly there are major differences in the protocols for medical male circumcision and vaccines, where “use” is observed and administered by researchers, and in oral and topical PrEP, where “use” is user-dependent and outside the study site. There are also important differences between oral and topical PrEP. Certain product, individual, and “meso” level, life context factors arise in studies of adherence to these varied biomedical prevention technologies:

- Characteristics of the NPT protocol or product, including convenience and simplicity and flexibility of administration, time-frame of use, and side-effects (including perceived side effects);
- Individual level factors include health, education, perceptions about HIV/AIDS, concerns about disclosure, and other competing life priorities;
- Life context factors include access to health care, access to transportation, economic press including lack of insurance, cultural norms regarding gender, sexuality and health, and social support.

The challenges of assessing and promoting adherence to NPTs raise many of the key questions that are confronted in health behavior and health promotion, generally (Turner & Hecht, 2001).

Conceptual Models of Product Adherence

Models of health behavior and behavior change that were initiated in the pre-ARV era to explain HIV risk and risk reduction (see Chapter 3) are being applied and refined in the study of product adherence, both for HIV prevention and treatment (Munro 2007, Williams et al, 2013; Amico, 2013). Adherence to HIV NPT protocols is seen from a cognitive behavioral lens to reflect understanding, agreement, problem-solving skills and active participation of study participants (Williams, et al, 2010; van der Straten, et al., 2012). Study participants must have a combination of knowledge, motivation and behavioral skills in order to successfully adhere to, and report on, prescribed biomedical regimens for prevention (see Chapter 3 on the Information, Motivation and Skills model).

Comment 5.3. Example of Theory-based Adherence Assessment

“HPTN 067 will assess the feasibility of different intermittent dosing strategies, identify theory-based determinants of sexual and pill-taking behavior during PrEP use, maintain cohorts of participants interested in intermittent PrEP, and build interagency infrastructure that is essential for efficacy evaluation, regardless of whether it utilizes superiority or non-inferiority designs.”

HPTN 067, Final Version 4.0 Page 22 of 131 September 11, 2012; Found at <https://www.hptn.org/research/studies/hptn067>; Accessed 22 April 2014. **End of comment 5.3**

In a comprehensive review of adherence to medicines in general, the WHO advised that product adherence is affected by “the patient, the provider and the health care system” but that most research focuses on the patient (WHO, 2003:143). In addition, adherence assessment and subsequent adherence support interventions also should examine the research setting and broader health care system. Indeed, HIV product adherence raises many of the key questions in health behavior and health promotion, generally. A persistent question is how widely to cast the net in adherence assessment. For example, motivation to use the trial prevention technology hinges partly on understanding its risks and benefits, (Osborn, et al, 2007; Nutbeam, 2012), so health literacy should be included in causal models of product adherence.

Participant characteristics. A number of characteristics have been found to increase or decrease adherence to ARV regimens for treatment. These include information, education, comprehension motivation, access to providers/care, incentives, inclusion in decision-making and altruism. Correlates of non-adherence include; low perception of risk, forgetfulness, complex regimens, depression, and co-morbidities substance abuse, low health literacy, and poor social support (Gross, Bellamy et al. 2013). These factors are likely to be at play in adherence to NPTs as well.

The Provider/Research Setting. Expert opinion and experience with ART indicates that the quality of relationships between participants and study site staff play an important role in establishing and maintaining adherence. The strength of the patient/participant-provider relationship is associated with greater trust and self-efficacy which in turn can lead to better adherence to treatment regimens and achieving favorable virologic outcomes (Saha, et al, 2012; Beach, et al. 2006; Johnson, et al. 2006). Staff who measure adherence have very different roles in relation to study volunteers. Amico et al (2013) conclude that, all other things being equal, volunteers behave differently and report differently when they have a relationship of trust with the questioner. Thus, it may be useful to have different people play these different roles.

Comment 5.4 Practical Tip

To facilitate valid adherence assessments, the study personnel who conduct adherence assessments should not be the same personnel who deliver adherence support. **End of comment 5.4**

Structural influences. Multiple *community and life context factors* within and beyond the study sites combine to make it easier or more difficult to engage in and adhere to a product regimen. Urban/rural residence and other living conditions, partner and family support, perceived and enacted stigma, gender and sexual norms, community health beliefs and access to medications and health services, economic pressures and conditions of employment, and broader policies influencing such factors as transportation, housing and access to technology and communications, have been cited in various settings. To identify these site-specific factors, the formative research conducted during the protocol development and preparation phases should explore these conditions, and their variation within and across sites. A better understanding of the Behavioral and social determinants of adherence will enhance adherence and potentially maximize the translation of research into more effective adherence in public health settings (Stirratt & Gordon, 2008).

In sum, adherence has been recognized as a multidimensional process involving the 'patient/person', providers, environment, and disease and is a complex issue

involving social, cultural, economic and personal factors (Murphy, et al, 2000; Kennedy, 2000; Miller & Hayes, 2000).

Approaches and Methods for Documenting Adherence

HIV prevention trials have utilized a variety of methods to assess participant use of the biomedical agents under study. The principle approaches include; self-reports of adherence behavior, pill counts (in the case of oral medications) or counts of used applicators (in the case of microbicide) direct measures (including DOT), electronic monitoring, monitoring pharmacy refills, and detection of therapeutic drug concentrations in plasma or tissue (Berg & Arnstein, 2006; Stirratt & Gordon, 2008; Kagee & Nel et al, 2012; Castillo-Mancilla et al, 2013). Qualitative methods also play an important role in adherence assessment (Sankar, 2006). Since diverse participant characteristics, life contexts and research settings influence adherence, it is important to tailor the conceptual framework for adherence assessment to the local settings of trial site, based on pre-trial needs assessments, local knowledge and formative research.

In seeking to define 'best practice' approaches to matching methods to specific population and study needs (Williams, et al., 2010) outlined key assumptions and procedures associated with each type of adherence assessment method (see Table 5.1)⁵.

For example, self-reported adherence can be expected to be most accurate when the following conditions are met:

- Self-report participants understand the question as intended;
- They can reasonably answer the question
- There are no cognitive impairments or memory deficits
- The scale used to measure adherence is reliable and valid
- The scale used is culturally sensitive and worded clearly
- Social desirability bias is minimized or measured concurrently
- There are no implied or observed negative consequences of reporting non-adherence.

Comment 5.5 Stakeholder's Points of View

"I was never told the impact of dishonesty. That should be clearer, without being foreboding." (Source: Chapter 2) **End of comment 5.5.**

⁵ More detailed reviews and current examples of adherence assessment methods are being gathered and shared by a network of HIV adherence researchers at annual conference held by the International Association of Providers of AIDS Care (IAPAC) <http://www.iapac.org/>.

In addition, there must be consistent fidelity to protocol in the administration of the assessment by culturally competent staff. If any of these conditions is violated, distortions can be expected in the data from self-reported adherence (van der Straten, 2014). Of the listed reasons why inaccurate reporting could occur, only two concern volunteers' intent to "tell the truth." The rest place the burden of accuracy on the research instruments and procedures. These conditions set a very high bar for screening, instrument development, and counseling. They illustrate the importance of consulting with potential volunteers and site staff, and investing in community outreach to promote both understanding and buy-in to the study. They also illustrate the importance of having complementary data to cross-check self-reported adherence.

Because each method has limitations as well as strengths, studies should plan to use two or more methods, selected to complement each other (or to cover each other's weaknesses) and designed in a comprehensive methodology to improve the ultimate accuracy of adherence measurement (Berg & Arnstein, 2006; Tolley, Harrison et al, 2010; Munro et al, 2007). Combining methods requires sufficient mastery of the behavioral and social science background to devise a rights-based and science-based, integrated strategy, including detailed guidelines on the data collection methods, the timing of data collection, and the analysis of the data from the different sources (DiMatteo, 2004). Detailed knowledge of the study populations and sites, and of data collection methods previously used and validated there, will also contribute to effective design of adherence assessment. Many background items of interest for explanatory HIV adherence assessment and HIV risk assessment are the same, so coordinated or integrated planning of instruments and procedures can save time and reduce participant burden.

Given the many ways in which adherence is contingent on context, transferring measures from one setting to another should be done with skill and caution (Williams, et al, 2010). For multi-site clinical trials this implies allowing time in the protocol for cross-site consultation among risk and adherence experts, during protocol start-up and analysis, as well as during protocol design.

Table 5.1. Advantages, Disadvantages, Assumptions and Key Challenges of Commonly Used Adherence Measures.

Measurement Approach	Advantages	Disadvantages	Assumptions	Key Challenges
Self-report:	<ul style="list-style-type: none"> • No cost • Easily implemented in clinical settings • Moderate correlation with virologic outcomes • Allows discussion of reasons for non-adherence • Low participant burden 	<ul style="list-style-type: none"> • No standardized questions • Overestimates adherence • Relies on recall of forgotten events • Vulnerable to social desirability bias • Poor sensitivity 	<p>Participants can reasonably answer the questions (when doses were taken, how many, or provide general estimated).</p> <p>Cognitive deficits that impact memory/recall are not present.</p> <p>Immediate negative consequences (e.g., added procedures, reprimands, so on) of reporting non-adherence are absent. The scale used to measure adherence is reliable and valid. The scale used to measure adherence is culturally sensitive, worded clearly, and subjects know how to respond to the scaling response options with little difficulty. Social desirability bias is minimized or it is measured concurrently.</p>	<ul style="list-style-type: none"> • Mitigate ceiling effect • Include measurement of all aspects of adherence (e.g. dose-interval) • Continue to rigorously develop and test new measures (e.g. cognitive interviewing or item response theory)
Pill Counts	<ul style="list-style-type: none"> • Inexpensive • Moderate correlation with virologic outcomes 	<ul style="list-style-type: none"> • Time consuming • Inappropriate for most clinical settings • May overestimate adherence • Vulnerable to “pill dumping” • Difficult to determine refill start date • Assumes no medication stockpile or alternative supply 	<p>The number of pills prescribed minus the number returned equals the number of pills actually consumed.</p> <p>No pills have been discarded, lost, given away, sold or disposed of in any other way.</p> <p>Pill returns were accurately counted.</p> <p>The patient returned pill containers (either empty or with left over pills) at each study visit.</p>	<ul style="list-style-type: none"> • Manage logistic challenges of unannounced pill counts

Measurement Approach	Advantages	Disadvantages	Assumptions	Key Challenges
Electronic monitoring	<ul style="list-style-type: none"> • Best correlation with virologic outcomes • Allows analysis of dose-interval adherence and patterns of adherence over time 	<ul style="list-style-type: none"> • Expensive • Not feasible for most clinical settings • May underestimate adherence • Vulnerable to technological malfunction • Potential for selection bias • High participant burden (multiple visits to download data, caps are bulky, pillbox use problematic) 	<p>Each recorded opening equals one dose of medication consumed. The device is activated (e.g. cap is opened) once and only once when each dose of medication is taken. Multiple recordings at one time point are most likely artifact or improper use of the monitoring device. Periods when there is no recording of device activation indicate that the patient was not taking medication during that time; as opposed to other explanations (e.g., provider-directed hold; pocket dosing; borrowing medications).</p> <p>The novelty effect of using the devices wears off in</p>	<ul style="list-style-type: none"> • Understand intervention ("Hawthorne") effect • Accurately censor of data (e.g. standard questions about periods of non-use, "pocket doses," or "curiosity openings") • Develop evidence based guidelines for use, quality control, and data management
Therapeutic Drug Levels	<ul style="list-style-type: none"> • Only direct adherence measure • Plasma Concentration directly determines virologic response • May allow for detection or prevention of drug toxicity, which can lead to non-adherence • May be advantageous for populations at risk for altered pharmacokinetics (e.g. pregnant women, those with hepatic dysfunction, children, those taking drugs that interact with antiretrovirals) 	<ul style="list-style-type: none"> • Expensive • Invasive • Non-standard procedures for collection, testing and interpretation • Cannot routinely measure NRTI levels because active moieties are intracellular • Levels may be low for other reasons than non-adherence (e.g. diet, drug interactions) • Assumes no individual pharmacokinetic variation • Vulnerable to "white coat adherence" • Only provides a snapshot of recent adherence • Higher plasma levels may be necessary to suppress replication of resistant virus 		<ul style="list-style-type: none"> • Standardize of procedures for collection, testing, and interpretation • Develop protocols for quality assurance • Determine optimal monitoring frequency • Determine optimal parameters (e.g. minimum concentration, ratio of an individual's level to a population or expected level, or area under the concentration-time curve)

Measurement Approach	Advantages	Disadvantages	Assumptions	Key Challenges
Pharmacy Refills	<ul style="list-style-type: none"> • Data are easily obtained in “closed pharmacy systems” (e.g. VA, HMOs, Medicaid) • Moderate correlation with virologic outcomes • Allows for population level analyses • Immune to social desirability, recall bias and tampering 	<ul style="list-style-type: none"> • Feasible only in “closed pharmacy systems” • May poorly adherence • Cannot measure dose interval adherence • Cannot differentiate non-adherence from other forms of treatment interruptions (e.g. discontinuation by provider) • Assumes that patients have one source of medication • Assumes that medication acquisition reflects adherence • No standard method for operationalizing adherence (e.g. days covered vs. medication gaps) • Not useful if refills are mailed automatically or if several months' supply is dispensed at one time 	<p>Lack of a refill equals medication not consumed during that period. Pharmacy refill records are accurate. Medications are not purchased or borrowed from another person or venue. No health care provider-directed treatment interruptions occurred during the refill period.</p>	<ul style="list-style-type: none"> • Evaluate use in “open systems” (e.g. populations using numerous pharmacies with multiple payers) • Determine optimal method for operationalizing adherence

Adapted from Berg & Arnstein, 2006; Williams, et al 2010).

Self-report. Self-report of product use is the most commonly used approach to measuring adherence. This method requires respondents to report the number of missed doses during a specified time period of recall, or to estimate their overall rate of adherence on a visual analog scale (Berg & Arnstein, 2006, Williams, et al., 2010; Wilson, et al., 2009). There are large differences in method, due to variations in delivery method (e.g., face to face interview, self-administered checklist or questionnaire, ACASI, etc.). There are extensive differences in the content assessed, in terms of questions asked, question formats and sequence, response items, terminology used, and other elements of data collection.

An important methodological issue with self-report approach is how to mitigate the ‘ceiling effect’ or the tendency of self-reported adherence to be skewed towards highest values, which may be influenced by questionable misrepresentation, poor recall and bias, which results in overestimates of adherence (Berg & Arnstein, 2006; Wilson et al., 2013; Stirratt & Gordon, 2008; Williams, et al. 2010).

As with HIV risk assessment, a number of strategies have been developed to improve the accuracy of self-reported adherence by addressing specific participant, provider, life context and/or research conditions listed above (see Chapter 3). For example, formative research and pre-testing of interview questions reduces misinterpretation and misunderstanding of questions. Diaries or diary cards have been used to reduce recall errors (Miller & Hayes, 2000; Turner & Hecht et al., 220).

Telephone calls have been used to collect data and to remind participants to use the study product or to record their use (Williams, et. al. 2010). Self-administered methods including both paper and pencil and computer- assisted or telephone-assisted methods, have been used to increase privacy and reduce errors from desirability bias. However, none of these strategies is effective for all people⁶ and settings, so investigators usually combine self-report with other data collection methods.

Comment 5.6. Practical Tip

(Audio) Computer Assisted Self-Interview (ACASI/CASI) methods are not a panacea. They can increase privacy, reduce data entry errors, and may decrease social desirability bias in some settings, but they also have disadvantages. Some investigators have found the method can cause confusion, and it is challenging to build interview methods to detect and resolve misunderstandings. ACASI methods can get around literacy issues, but they may try participants' patience as they listen to questions being read out. **End of comment 5.6**

Pill counts. This approach to adherence measurement entails counting the number of doses remaining in a prescribed batch after a certain interval. Pill counting strategies rest on the assumption that the number of pills in a patient's possession at the time of the count reflects the number of pills dispensed minus those ingested (Williams, et al. 2010). This method is more objective than self-report of pill consumption. However, there are numerous ways that pill counts can be distorted, by participants, either intentionally or unintentionally. Announced or pre-scheduled pill counts may be inaccurate if study participants empty their pill containers (pill dumping) in the anticipation of the pill count procedure, without having taken the medications (Berg & Arnstein, 2006). Unannounced pill counts reduce possibilities for pill dumping and some studies have shown this approach to predict viral load slightly better than electronic monitoring. Given the various threats to validity of pill count adherence measures, pill counts and counts of returned microbicide applicators are used best in conjunction with other outcome measures (Williams, et al. 2010).

⁶For example, self-report may not be an efficient approach when there is impaired memory or cognitive deficit. Alternate methods of self-report may be necessary such as using shorter time intervals for recall, or use of estimations measures (Williams, Amico, et al., 2012).

Comment 5.7. Practical Tip.

Limit the time between unannounced pill counts to improve accuracy. **End of comment 5.7**

Direct measures. Assigning “buddies” or study personnel to witness product use has been successful in promoting adherence to ART, but has not been used or reported in biomedical HIV prevention trials.

Electronic Monitoring. This method utilizes monitoring devices such as the Medication Event Monitoring System (MEMS) cap (de Bruin et al, 2005; Shuter et al, 2012), whereby the cap of the bottle is embedded with a microprocessor that records the time and date of each time the bottle is opened as a presumptive dose. This information is stored and downloaded and enables the examination of patterns of adherence and dose interval adherence – assuming that the bottles are opened only when taking a dose, and that only one dose is removed at a time (no “pocket dosing”). There are other electronic monitoring devices such as the Med-e-monitor (Ruskin et al, 2003; Haberer et al, 2012), and Wisepill (Haberer et al, 2010; Haberer, et al. 2013). The latter is a real-time method of communication through transmission over a cellular network (Williams, et al., 2010). Some devices not only store adherence data, but also can be programmed to send reminder messages to enhance adherence.

Electronic monitoring methods are expensive, and they rely on an information and communication technology (ICT) infrastructure that may not be consistently or affordably available in all trial sites. Using electronic devices may improve adherence for a number of weeks, possibly due to the novelty effect, the particular intervention itself, or to the salience of being in a trial, but this effect is not well understood (Vervloet et al, 2012; Ownby, 2012).

Pharmacy Refills. Adherence rates from pharmacy refill records are determined by comparing actual to expected refill dates and/or by identifying ‘medication gaps’ or periods of time during which the patient’s supply of medication is assumed to have been exhausted (Berg & Arnstein, 2006, Williams, et al. 2010). Interpretation of pharmacy refill data relies heavily on the assumption that the pharmacy record is complete, comprehensive, exclusive and accurate (Williams & Amico, 2012). Interpretation of pharmacy refill data relies heavily on the assumption that the pharmacy record is complete, comprehensive, exclusive and accurate (Williams, et al, 2010), and that there is no substantial ‘carry over’ or ‘stock piling’ from previous refills. Where possible, pharmacy data should be linked with medical records.

Pharmacy refill assessment is the easiest and most likely to produce accurate data in prospective assessments where medications are provided by a single payer such as Medicaid or a universal health care system. When these systems are available, this method of assessment has the benefit of reflecting use in real-world settings (Berg & Arnstein, 2006, Williams, et al, 2010).

Drug levels. Measurement of the study drug levels in the blood and tissues has been considered a direct, objective measure of adherence that is feasible in both clinical and research settings. Drug level monitoring can be done through a variety of methods:

- Detection of drug metabolite in plasma
- Lab values: Viral Load measures, CD4 counts (ARV monitoring)
- Hair sampling to determine drug levels in hair root/shafts
- Vaginal fluid sampling (microbicide/gel use) (semen exposure)
- Mucosal sampling.

Measuring drug levels offers an objective crosscheck on self-reported adherence or pill counts. Therapeutic drug monitoring is most limited by a lack of technical standardization. Procedures for sample collection, cross-validation of analytic procedures and interpretation of results vary by settings (Back, Gatti et al, 2002; Burger, Aarnoutse et al, 2002; Acosta, Gerber et al., 2002). Additional factors may impact therapeutic drug levels detected in blood or tissues, including drug-drug interactions and diet (citations). Furthermore, serum drug levels mostly reflect adherence over the past 24 hours. While drug monitoring is not recommended as a cross-check in HIV treatment contexts monitoring drug levels is strongly recommended in clinical trials of PrEP (Amico, 2013).

Qualitative methods. The use of qualitative methods, ranging from a desk review of relevant research in the study site/s, and informal interviews to elicit insider perspectives, to ethnographic research, can provide information about participants' beliefs about medications, access issues, stigma, competing priorities, the risk environment, and other individual and life context factors that can influence adherence. Qualitative methods are not used to quantify product use, but are essential for eliciting the factors that should be counted. Better understanding of trial participant perspectives will also be relevant to future product introduction and delivery, as well as to the development of prevention strategies and realistic designs for future trials (Tolley, et al, 2010).

Considerations in Designing Adherence Assessment

Adherence assessment can be an ambitious, bio-socio-behavioral theory-building project where levels of product use are the primary outcome, and investigators are interested in all the individual and life context factors that explain it. Product adherence also can be viewed as one of several mediating variables in a phase II or

III clinical trial of a drug or agent, where new HIV infections are the outcome of interest. In the latter case, the investigators may prefer the most parsimonious method possible for obtaining accurate estimates of product use, and have less immediate interest in determinants of use, or in theory building to predict or explain observed use. In a clinical, service delivery setting, the time and resources available for assessing adherence to prevention medications are likely to be even more limited.

Table 5.2 illustrates the diverse approaches that would be recommended in research as opposed to a clinical setting, and in situations where adherence is the primary focus versus situations when adherence assessment is only one part of a study focused on HIV prevention or treatment (Chesney, 2006). Even if adherence is not the main focus of a trial, its adherence assessment process should provide enough information about adherence barriers and facilitators to inform the design of adherence support interventions.

Table 5.2. Diverse Adherence Assessment Strategies for Different Research and Clinical Settings. Source: Chesney, 2006.

	Research Project		Clinical Practice	
	HIV/AIDS General	Adherence Focused	HIV/AIDS General	Adherence Focused
Assessment Setting	RCT of a HIV/AIDS regimen	Prospective study of adherence barriers	Clinician patient visit	Adherence counseling visit
Suggested Assessment Strategies	Brief 4 or 7-day self-report scale, Visual analogue scale	Detailed self-report scale, EDM, Composite measure	Brief clinician-administered scale, Brief self-report scale	Detailed self-report of barriers and adherence, EDM, Computer-based self-report
Intervention	Intervention for an RCT of HIV/AIDS regimen	RCT of an adherence intervention	Clinician patient visit	Adherence counseling visit
Suggested Intervention Strategies	Brief individual adherence counseling, phone-based counseling	Extended individual/group, counseling, DOT + counseling, structural interventions	Brief individual intervention	Extended individual/group, counseling, DOT + counseling, structural interventions

Given the range of potential interests and research types, the best design and methodology for measuring and interpreting product adherence depends greatly on the goals, scope and scale of the study. It also depends upon the amount and types of evidence already available about the study population/s, adherence measures that have been used and validated in the study population/s, participant research literacy, buy-in to the study, recall and reporting practices, and life context/s. All studies should aim to maximize the external validity and comparability of their findings so as to build generalizable knowledge, but in multi-site studies, planning for comparability and data pooling is a special concern.

The resources available - funding, technical capacity and community and volunteer support - are another important design factor, but this point should not be misunderstood. Investment in high quality adherence assessment is as mission-critical to new biomedical prevention technologies (NPT) clinical trials as are traditional trial components such as recruitment or laboratory procedures. Measures of adherence must be efficient, practical, and as inexpensive as they can be while still accomplishing their mission-critical purposes.

Comment 5.8 Practical tip

Establish clarity of purpose a priori, on what is to be measured/assessed and why. Consider the 'what', 'how', and 'how often' of each assessment/measure, and how the data will be combined in the analysis. **End of comment 5.8**

Cost and logistics. There are several considerations regarding the potential or actual cost of implementing an adherence assessment. Costs related to actual measure of adherence will be dependent on the assessment methods used. If the methods have not been used before in the setting, essential formative research, pilot testing, and validation work will increase the costs. To provide a realistic picture, biomedical HIV prevention adherence studies should consider estimating costs related to non-adherence in the trial (i.e., possible inability to answer the trial's main scientific questions).

Schackman, et al (2006) conducted an economic study to determine the direct cost of HIV adherence to antiretroviral treatment interventions through a detailed assessment of the resources consumed by participants. The researchers assessed the incremental direct costs of conducting the adherence intervention that included the costs of provider time, participant incentives, adherence tools provided, scheduling appointments and provider adherence training. The cost of electronic monitoring appeared to be the most expensive approach with the cost ranging between \$10-\$29/month. Other non-electronic tools averaged between \$2.00-\$7.00/month. Direct provider labor costs represented two-thirds of the total direct costs, followed by incentives and finally adherence tools. Given the importance of adherence measurement, and the specificity of costing information in various countries and settings, more costing studies are needed.

The cost of adherence assessment, as for other components of biomedical trials of HIV prevention technologies, will depend heavily on background characteristics of the study sites, including the strength and reach of the health care system, levels of education, health, human rights and research literacy in the host communities and among site staff, the history of prior research in the sites, and levels of community participant and capacity development already done.

RECOMMENDATIONS

- It is essential to assess product adherence in a sound and appropriate manner in prevention trials. Adherence has been strongly associated with efficacy/outcomes, and sound adherence assessments are essential for appropriately interpreting trial results.
- Product adherence is contingent on participant characteristics, life context, and conditions in the study site, including the rapport and success of communication between participants and site staff. Design of adherence assessment procedures should begin with a theory- and evidence-based bio-psycho-social model of factors that contribute to adherence, linked into the trial's risk assessment procedures and the trial's overall design.
- Correlates and factors of non-adherence to ART include: patient/participant characteristics, provider and patient relationships, variables related to treatment regimen or disease, and contextual factors ranging from access to health services to housing, transport, information and communication technology (ICT), and the risk environment.
- Individual and contextual factors are likely to differ across sites in a multi-site study, so consultation and collaboration among the adherence specialists in each site should be programmed into the protocol and budget.
- Adherence assessment can be optimized by early consideration and as an ongoing dimension of trial implementation across the life cycle of the trial: 1) determining/establishing clarity of purpose *a priori* in both the overall design of the trial and as explicitly crafted elements of that design, 2) in trial implementation, beginning with recruitment, screening and enrollment, 3) during the trial in response to monitoring indicating that adjustments are required.
- There is no gold standard method for adherence assessment. All product adherence measurement approaches – including self-report, pill counts/applicator returns, electronic monitoring, pharmacy refills, therapeutic drug monitoring, and qualitative methods – have strengths and weaknesses, so multi-method approaches, and triangulation of findings, are recommended. These should be assessed in relation to the particular study population/s, site/s and resources.
- Where possible, it is advisable to use methods and instruments that have been validated in with the study population and that will yield results that can be compared with other relevant research.
- The challenges of using multiple measures are determining how best to combine measures, how many measures to combine, and how many time points for measurement should be included. Behavioral and social science research expertise along with intimate knowledge of the study setting will aid in answering these questions.

- The cost of adherence assessment should be built into trial protocols and budgets. These costs may be significant. However, the experience of several recent clinical trials has convincingly shown that the costs of measuring it poorly or too narrowly to interpret trial results, are far higher.

CONCLUSIONS

Adherence to treatment is more than simply remembering medications, but rather complex issue involving individual, social, cultural, economic, and ultimately, political factors. The background factors that influence the costs of adherence assessment (reach of the health care system, health, research, and rights literacy in host communities, as above) reflect political issues – from resource allocation decision to philosophies of community engagement and universal access to health. These factors concern participants and site staff as well. Behavioral and social science theory and evidence provide a framework for mapping and prioritizing the factors most relevant to a particular clinical trial.

There is no ‘Gold Standard’ for the assessment of adherence, and there is no single tool that will optimize measurement of adherence in all settings. Indeed, the motto in adherence assessment could be, ‘build trust, and verify.’ Nevertheless, there is a burgeoning literature and cadre of experts in biomedical product adherence who utilize behavioral and social science theory, resources and knowledge to design approaches that suit their study site and resources. Adherence assessment should draw upon and be aligned with behavioral and social science risk assessment, as many of the biomedical, behavioral and structural factors that influence risk can be expected also to influence adherence. Investigators planning clinical trials of HIV NPTs should consider mobilizing this expertise and knowledge as matter of priority and including it as an integral and integrated part of the study design and budget, as adherence assessment makes a critical difference to study quality and to the ability to interpret trial results.

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CHAPTER 6. INTERVENTIONS TO SUPPORT PRODUCT AND REGIMEN ADHERENCE

“Drugs don’t work in patients who don’t take them.”

- C. Everett Koop

INTRODUCTION

Sound strategies to support product adherence (consistent use of the investigational product, according to the prescribed dosing regimen, for the prescribed period) are essential for optimizing product adherence and for establishing the safety, efficacy, and effectiveness of biomedical HIV prevention strategies. Although strong product adherence is critical to the conduct, outcomes, and interpretation of HIV prevention trials, product adherence has been challenging to achieve in many biomedical prevention trials to date.

Yet behavioral and social science theory and a growing body of empirical evidence from HIV treatment and prevention studies demonstrate that product adherence can be improved through active support (see Box 6.1). A meta-analysis of 19 randomized controlled trials that tested antiretroviral adherence interventions found that intervention participants were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load compared with participants in comparison conditions (Simoni et al, 2006). Additional meta-analyses further indicate the effectiveness of ART adherence interventions for improving medication adherence (Amico et al, 2006) and reducing viral load (De Bruin et al, 2010). These studies provide “proof of concept” that interventions to support adherence do have an impact.

Chapter 5 presented evidence and strategies for assessing product adherence in HIV new prevention technologies (NPT) trials. This chapter reviews intervention strategies, and resources available to improve adherence in HIV prevention trials. As with risk assessment, risk reduction interventions and adherence assessment, there is no single approach that suits all study populations, sites and objectives. Design, implementation, monitoring and analysis of adherence support strategies must draw on existing knowledge of the populations and sites, and/or include formative research to document crucial behavioral and social factors affecting HIV risk, risk reduction, and adherence.

Thus, efforts to plan an adherence support strategy should occur early and collaboratively during the course of designing a prevention trial. The role of adherence and factors influencing it, should be included in the trial’s overall conceptual framework, guided by theory and the best available biomedical, behavioral and social science evidence, and by experts in adherence science.

Comment 6.1 Example: Enhanced Adherence Support

Partners PrEP was a PrEP efficacy trial conducted with 4700 serodiscordant couples in nine sites. The trial outcome showed PrEP to be highly efficacious for preventing HIV transmission (Mujugira, 2011).

An ancillary adherence sub-study was conducted in three of the nine study sites (Psaros et al, 2012). The ancillary study added several measures of medication adherence, including unannounced pill counts (Bangsberg, Hecht, Charlebois et al, 2001; Kalichman et al, 2007). Trial participants who showed adherence <80% of prescribed doses via an unannounced pill count received an enhanced set of cognitive-behavioral adherence counseling sessions. Among 1147 participants enrolled in the ancillary adherence study, approximately 11% triggered the enhanced intervention through low adherence. The majority of participants who received the targeted intervention (92.4%) showed improved adherence (>80%) during follow-up pill counts (Ware et al, 2012).

Outcomes from the Partners PrEP Adherence Sub-study found that adherence was nearly-perfect (~99%) under conditions where added adherence counseling was provided to individuals evidencing incomplete adherence. At this exceptionally high level of adherence, no HIV infections were observed among individuals receiving active drug and 14 infections were found among those receiving placebo (Haberer, 2013). **End of comment 6.1**

The importance of supporting product/regimen adherence in biomedical HIV prevention trials is clear, when we consider (1) the centrality of adherence to antiretroviral treatment outcomes; (2) the dose-response relationship observed to date between product adherence and product efficacy in biomedical HIV prevention trials; (3) the theoretical understanding that poor product adherence can dilute proof-of-concept HIV prevention trial outcomes; and (4) the practical recognition that poor product adherence has compromised the ability of some HIV prevention trials to provide an adequate proof-of-concept test.

HIV prevention clinical trial teams should therefore undertake every possible effort to strengthen product adherence among trial participants. In an authoritative review in 2008, an expert panel convened by the Institute of Medicine concluded that activities and resources to address adherence support should be commensurate with the efforts undertaken to support trial enrollment and retention, as product adherence is equally important to trial outcomes (Institute of Medicine (IOM), 2008).

These and other attendant points to consider are outlined below.

Identifying Product Adherence Support Strategies.

Adherence support strategies in HIV clinical trials have not been studied to the same level as behavioral risk assessment and risk reduction. Thus, the scientific evidence base on the feasibility, acceptability, and impact of adherence support strategies delivered in the context of clinical trials is thin (Amico et al, 2013).

One source of potential strategies to support clinical trial product adherence comes from HIV treatment adherence interventions. The CDC Prevention Research Synthesis (PRS) project's periodic search for rigorously-tested and efficacious HIV interventions has identified 74 evidence-based risk reduction interventions in the research literature, but only eight evidence-based antiretroviral adherence interventions

(<http://www.cdc.gov/hiv/prevention/research/compendium/rr/index.html>).

Comment 6.2 Practical Tip.

Although there are key contextual differences in HIV prevention compared to HIV treatment, strategies tested in the context of HIV treatment may hold relevance to HIV prevention strategies based on oral medications, such as oral PrEP, since they share a common route of delivery. Evidence from ART adherence studies also offer lessons learned for prevention regimens that involve a daily dosing schedule. **End of comment 6.2**

Most antiretroviral adherence intervention trials to date have been conducted with patients in the U.S. or other resourced settings, but adherence intervention research in resource-limited settings is advancing rapidly. Systematic reviews of the evidence based on antiretroviral treatment adherence interventions have identified interventions known to be effective within resource-poor settings. For example, patient-based counseling and educational interventions, such as individual adherence during ART initiation, reduced the risk of poor adherence and electronic dose monitoring (EDM) during counseling increased the mean adherence rate. (Scanlon & Vreeman 2013). This study and findings from other reviews have produced recommendations on the best adherence practices to HIV treatment in the context of clinical care (Thompson et al, 2012).

Another source of possible clinical trial product support strategies comes from prevention research outside of the HIV/AIDS field. Marcus et al (2014) reviewed the existing evidence base for prevention medication adherence interventions, as drawn from fields (e.g. contraception, malaria prophylaxis, hypertension medications, and medications to prevent osteoporosis). Adherence support approaches that had the strongest evidence base included strategies utilizing multiple modalities, education-based methods, provision of feedback on adherence or clinical trial outcomes, and telephone-based counseling. A crucial source of potential strategies to support clinical trial product adherence can be derived from HIV prevention clinical trials themselves. Knowledge of the evidence-based product

adherence support schemes used successfully in prior HIV clinical trials provides essential background for the selection of adherence support models in future trials.

Several strategies have been documented and have shown clear evidence of acceptability, feasibility, or impact in HIV clinical trials (Amico et al. 2013). An analysis of the adherence support experiences from four HIV prevention trials and (CAPRISA 004, FEM-PrEP, iPrEx, and VOICE) “...provide key lessons for optimizing adherence in future research and programmatic scale-up of PrEP.

Recommendations from across these trials include participant centered approaches, separating measurement of adherence from adherence counseling, incorporating tailored strategies that go beyond education, fostering motivation, and addressing the specific context in which an individual incorporates and negotiates PrEP use.” (Amico et al, 2013).

The involvement of behavioral and social scientists who have knowledge of the study sites and expertise in adherence research at the start of protocol development can help to strengthen the identification and selection of an appropriate and effective product adherence support strategy. This multi-disciplinary approach should continue throughout the life cycle of the protocol, from concept to the end of the study.

Comment 6.3. Practical Tip

A panel of scientists (Thompson et al, 2012) made the following recommendations for adherence care in clinical practice:

1. Individual one-on-one ART education is recommended (II A).
2. Providing one-on-one adherence support to patients through one or more adherence counseling approaches is recommended (II A).
3. Reminder devices and use of communication technologies with an interactive component are recommended (I B).
4. Education and counseling using specific adherence-related tools is recommended (I A) **End of comment 6.3**

Basic Support for Clinical Trial Product Adherence

Efforts to support product adherence in HIV prevention trials should, at minimum, include provision of adherence counseling and adherence support tools (IOM, 2008). Brief one-on-one adherence counseling and adherence tools such as pillboxes represent essential ingredients for promoting ART adherence (Thompson et al 2012). Counseling interventions for antiretroviral treatment adherence have demonstrated proven impact on behavioral adherence and viral load outcomes (Simoni, 2006). Most antiretroviral adherence counseling interventions involve a combination of strategies, such as the provision of information and cognitive-behavioral counseling (Simoni et al, 2006).

Relevant individual adherence counseling and support strategies include:

Individual counseling approaches.

- Individualized information and education sessions (e.g., Thompson et al 2012)
- Cognitive-behavioral therapy (CBT) problem-solving adherence counseling (e.g., Gross et al 2013)
- Home-based education and nursing assessment (e.g., Williams et al 2006)
- Computer-delivered, individually-tailored education and counseling (e.g., Fisher et al 2011; Kurth et al, 2014).

Adherence support tools.

- Pillbox organizers (Petersen et al, 2007)
- Electronic pager reminders or alarms (Simoni et al, 2009)
- Interactive mobile phone SMS text-messages (Lester et al, 2010).

Comment 6.4 Practical Tip.

All other things being equal, investigators should consider prioritizing adherence support strategies that have been used in trials with successful endpoint outcomes.

End of comment 6.4

An example of an adherence counseling strategy previously used with success in an HIV prevention clinical trial context is “Next Step” counseling (NSC) (Amico, 2010; 2011; 2013). Next Step Counseling was originally developed for use in the iPrEx trial, which tested the efficacy of oral PrEP for HIV prevention among men-who-have-sex-with-men and transgender women. NSC has subsequently been utilized in the iPrEx open-label extension (iPrEx-OLE), as well as in the HPTN 067/ADAPT study, which is conducting an open-label comparison of non-daily PrEP dosing schedules to enhance regimen acceptability and adherence.

Next Step Counseling is a brief, discussion-based, and participant-centered strategy to support adherence to a study product. The counseling is grounded in the Information-Motivation-Behavioral Skills (IMB) theoretical model, as well as the tenets of motivational interviewing. NSC involves brief guided discussions to help participants identify their adherence-related facilitators, barriers, and needs, and the counselor subsequently strategizes with the participant on an appropriate “next step” that will help to make pill taking easier, and encourages participants to try the strategy before returning for the next clinical trial visit.

Most NSC counseling sessions can be delivered in less than 10 minutes, which represents a good match to busy clinical trial settings. In a qualitative evaluation study, iPrEx counselors positively evaluated NSC as appropriate for their participant populations and feasible to implement (Amico et al, 2010; 2011; 2013).

Strengthening Adherence Interventions in HIV Prevention Trials

Where possible, HIV prevention trials should consider use of additional product/regimen adherence support methods (beyond basic counseling and support tools) to incorporate their different and complementary strengths, inside and outside of setting of the clinical trials unit. Such an approach follows from the “combination prevention” concept, which is rooted in an analogy to combination antiretroviral treatment (Coates et al, 2008; Kurth et al, 2011). Just as combination therapy employs multiple drugs to intercept HIV at various junctures in its life cycle, HIV prevention protocol teams could consider developing a combination approach to adherence support to address the varied barriers and facilitators identified through formative research, risk assessment and adherence assessment (see Chapters 3 and 5).

Comment 6.5 Stakeholder Viewpoint

“Adherence must be measured prospectively in future trials. Under these conditions trial participants who do not adhere to treatment can be counseled, or the study analysis designed to incorporate these most rigorous measures of adherence.”

Kashuba et al, 2012. **End of comment 6.5**

Prospective adherence monitoring and feedback. A further important addition, particularly relevant in proof-of-concept tests of NPTs, is delivery of additive support to participants who fall below an adherence threshold, and who are identified through prospective monitoring of adherence behavior. As noted earlier, this requires a method for monitoring adherence behavior and/or adherence-related biomarkers prospectively. For example, study procedures and prospective monitoring of viral load contributed to high levels of ART adherence and viral suppression among HPTN 052 trial participants.

While HPTN 052 used a biomarker (viral load), the Partners PrEP sub-study used a behavioral measure of adherence (unannounced pill counts), one that is considered less vulnerable to tampering than counting product returned during clinic visits. The success of the prospective adherence monitoring on HPTN 052 led Kashuba et al (2012) to view investment in this approach as a necessity in future HIV clinical trials (see Box 6.5).

Novel biomarkers. Additional approaches could be considered, such as the use of novel biomarkers (e.g., dried blood spots to indicate presence of a detectable drug) or other relatively objective measures of behavioral adherence (e.g., electronically monitored adherence). It is important to note, however, that the success of focusing and delivering supplemental adherence support to individuals who do not adhere hinges upon valid measures of volunteers’ product use. The VOICE trial unsuccessfully attempted to target additional adherence support using an adherence measure based on product returns (<http://www.mtnstopshiv.org/node/2003>).

Feedback to volunteers. Research suggests that providing volunteers with feedback on their adherence behavior or adherence-related biomarkers can be feasible and acceptable. Sabin (2010) found that informing HIV patients about their adherence measured by electronic monitoring (MEMS) promoted high adherence. Amico et al. (2012) described a procedure used in a subset of the participants enrolled in the iPrEx-OLE trial, in which the study team carefully explained drug concentration data to participants, noting that the absence of drug could be due to factors beyond a lack of pill-taking. The information on biomarkers was generally well-received in this population; some but not all participants also reported in interviews that this feedback promoted more accurate self-reporting of their product use.

In evaluating adherence prospectively, it is important to recognize that ceasing to adhere to a PrEP regimen does not represent prevention failure, if the participant has switched to another effective means of prevention (WHO/UNAIDS 2013 - PrEP Demonstration Project Framework; Baeten, et al, 2013). Adherence support strategies should account changes in the individuals' risk environment and individual risks, which may make PrEP unnecessary and thus not medically advisable. Trials need to be powered and analytic methods put in place to deal with this issue.

Additional adherence enhancement strategies. To maximize adherence to biomedical HIV prevention strategies within the context of clinical trials, many additional and complementary adherence support strategies could be employed to strengthen trial procedures for supporting product adherence. Many of these addresses more “macro” levels of ecologic influences on adherence behavior. Examples include:

- Peer support (Simoni et al, 2009)
- Relationship partner support (Remien et al, 2005; 2006)
- Behavioral economic and contingency management incentives (Rosen et al, 2007; Sorensen et al, 2007)
- Modified directly observed therapy (Lucas et al, 2006; Altice et al, 2007; Goggin et al, 2007)
- Community-based efforts to address stigma, norms and beliefs regarding clinical trial participation (van der Straten, 2014).

Adapting Adherence Interventions to the Individuals, Populations, and Contexts

While protocol development teams and other stakeholders can learn from the evidence and experience of prior trials, this does not mean pulling a model “off the shelf” to apply in a new situation. For example, adherence interventions that were developed and tested in resource-rich settings may not have immediate relevance to resource-limited settings without significant adaptation (Chesney, 2006).

It is critical for teams involving behavioral and social scientists to study adherence challenges in the study area(s) proposed in the protocol and to develop socially and culturally relevant strategies for reducing the individual and structural barriers found. Such teams also need to explore translation of strategies that are effective in one setting to settings with different personal, economic, and sociocultural influences on adherence and risk behaviors. (IOM 2008, page 5-12). Cultural adaptation of adherence interventions should be grounded in a close understanding of local social-contextual issues that influence correct, consistent product use (Ware, Wyatt, and Bangsberg, 2006).

Comment 6.6 Practical Tip

PrEP efficacy trials such as iPrEx and Partners PrEP have identified age as a predictor of product adherence, where younger participants evidence lower adherence. Adherence challenges in youth populations are well documented, and may require tailoring adherence support in age- and culturally-appropriate ways.

End of comment 6.6

Behavioral and social scientists, including host country nationals, can assemble local knowledge on the study populations, community, and research context (see Chapter 1), and can organize the information in a framework that can be developed and refined by the whole protocol team. As noted earlier, an explicit model of the behavioral and social factors that influence participant engagement, adherence and retention in the trial helps to maintain focus and coherence of the various study procedures (Ware, Wyatt, and Bangsberg, 2006)

Comment 6.7. Stakeholder Viewpoint

“The cultural competence of adherence support interventions- or any behavioral intervention for that matter – is critical to their acceptability and impact. “

DAIDS SBS Points to Consider Working Group 4 member. **End of comment 6.7**

When designing adherence support strategies for a trial, protocol teams should prioritize strategies that (1) are grounded in behavioral and social theory and methods, (2) show research evidence for their acceptability, feasibility, and impact, (3) address the specific social, cultural, economic and political barriers that have been identified in the risk assessment and adherence assessment procedures, and (4) resonate with both potential participants and site staff (Ware, Idoko, et al, 2009; Binagwaho & Ratnayake, 2009).

Prioritizing and adapting an appropriate package of adherence support strategies for any given trial can be challenging. Protocol teams must contend with a number of concerns that may not necessarily align – such as competing needs to conserve time and get on with recruitment, and to take time for formative research and pre-testing that meet professional standards. Adaptation of approaches and instruments to the local setting need not be at the expense of external validity and

comparability. However, especially in large multi-site trials across multiple nations, many clinical trial sites, and different cultural settings, achieving local relevance while retaining construct validity and comparability across sites, requires expertise and several rounds of consultation.

Expanding the Evidence Base on Adherence Interventions in HIV Prevention Trials

Given the critical role of adherence in HIV prevention trials of NPTs, and the limitations of current evidence, research stakeholders should take every opportunity to test individual and combination approaches to improving adherence within clinical trials. The Institute of Medicine (2008) has recommended that biomedical HIV prevention trials should incorporate concurrent evaluations of adherence support approaches. For example, an adherence sub-study was conducted within the Partners PrEP trial regarding the potential use of prospective adherence monitoring as trigger for enhanced adherence support (see [comment 6.1](#)).

Comment 6.8. Stakeholder Point of View

“Donors should fund, and investigators should undertake empirical evaluations of strategies to increase adherence to biomedical HIV prevention products during and after a clinical trial. These evaluations should be adequately powered, methodologically rigorous, socially and culturally relevant, grounded in behavioral and social science theories, and conducted in the regions where the strategies will be utilized.” (IOM 2008, page 5-12). **End of comment 6.8**

Investigational products are typically tested in a superiority trial design that compares the active product with placebo. However, the IOM panel noted that the use of factorial designs would permit evaluating a prevention product (e.g., active drug vs. placebo or comparator) while simultaneously evaluating a behavioral intervention (e.g., intensive adherence support vs. standard adherence support) without substantially increasing the sample size (IOM 2008, page 10-6).

Incorporating evaluations of adherence support approaches within a clinical trial design provides benefits such as:

- Addressing the dearth of evidence-based strategies for providing product adherence support in clinical trials;
- Improving the ability of future clinical trials to identify and employ effective, evidence based adherence support strategies;
- Ascertaining if particular adherence support strategies can magnify the efficacy of biomedical prevention products; and
- Providing a model that can inform the provision of effective adherence support when proven products move into real-world demonstration projects or wider public use.

The need for evidence is not confined to experimental tests of adherence strategies with HIV infection endpoints. Building knowledge regarding the interacting individual, community, research and macro level factors that affect biomedical prevention trials will aid and expedite all future HIV prevention trials. As noted earlier, the evidence gap is greatest in low and middle-income countries where the need for HIV prevention products is greatest.

Comment 6.9. Example of Opportunities to Expand the Evidence for Adherence Support

Conduct a qualitative sub-study to assess the acceptability of an adherence support strategy and to identify process factors that helped or hindered the delivery of effective adherence support in the trial. A set of qualitative interviews and/or focus groups conducted with a sub-set of trial participants and/or staff could ascertain this information, to help improve the delivery of adherence support in future trials.

End of comment 6.9

RECOMMENDATIONS

Points to consider on adherence support in HIV prevention clinical trials are summarized below. These recommendations are also incorporated into Figure 6.1, arrayed across the life cycle of a clinical trial.

- Efforts to address adherence support should be commensurate with the efforts undertaken to support trial enrollment and retention, in terms of importance, procedures, and resources.
- Early in protocol development, protocol teams should incorporate or consult Behavioral and social scientists with adherence research expertise to help design an appropriate set of adherence support strategies.
- HIV research has developed and tested a number of adherence support strategies. Much of the evidence deals with antiretroviral treatment adherence, which differs in important ways from the needs of prevention trials. However, ART adherence interventions illustrate a range of methods available for supporting product adherence within HIV prevention clinical trials. Evidence-based adherence support strategies for prevention medications in areas other than HIV/AIDS may also inform the selection of adherence support strategies.
- Product adherence support strategies from prior HIV clinical trials provide options for the selection of adherence support strategies in future trials.
- When selecting adherence support strategies for a trial, protocol teams should prioritize strategies that (1) are grounded in behavioral and social science theory, (2) show research evidence for their acceptability, feasibility, and impact, (3) address the specific social, cultural, economic and political barriers that have been identified in the risk- and adherence assessment procedures, and (4) resonate with potential participants as well as research staff.

- Efforts to support product adherence in prevention trials should, at minimum, include provision of adherence counseling and adherence support tools. The use of additional product adherence support methods (beyond counseling and support tools) should be considered to incorporate their different/complementary strengths and maximize adherence. Prospective monitoring of adherence behavior and adherence biomarkers (drug levels) can further enhance adherence support to volunteers who need it.
- HIV prevention product adherence is contingent on a myriad of individual, community, research and macro-level psychosocial factors. Adherence support methods must be adapted to suit both the individual and the social and cultural context.
- Adaptation of support strategies is challenging, especially in multinational, multi-site studies. Special effort and expertise is required to ensure that adapting methods to be locally appropriate does not sacrifice construct validity, external validity, and comparability of data across sites.
- Investigators should design and donors should fund more research on adherence support strategies, especially in low and middle-income countries and low resource settings where the evidence gaps are largest.
- To help expand the available toolbox of evidence-based adherence support strategies, investigators should consider testing product adherence support interventions in the context of the trial.

CONCLUSIONS

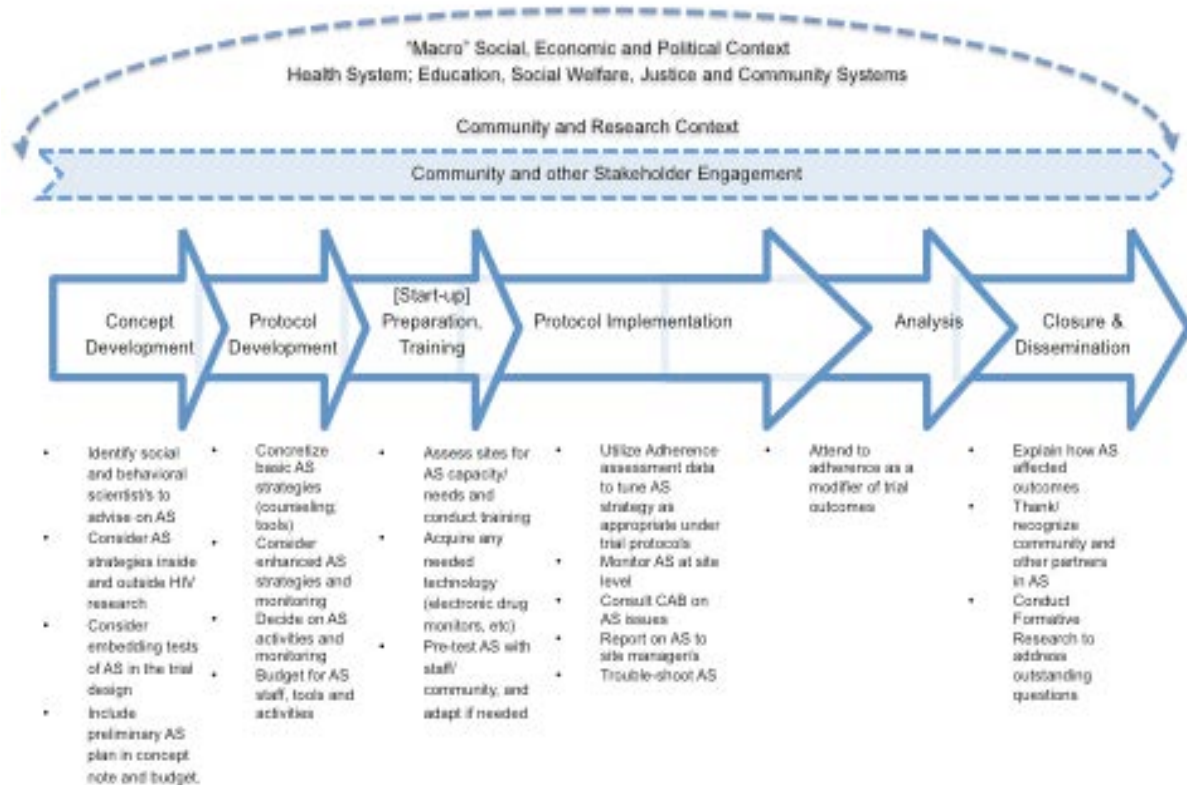
Every possible effort should be made to strengthen product adherence in biomedical HIV prevention clinical trials. Sound strategies to support adherence are essential for optimizing product adherence and soundly establishing the safety and efficacy of biomedical HIV prevention strategies.

Efforts to plan an adherence support strategy should occur early in the design of a prevention trial, and these efforts should be guided by the best available science regarding the biomedical, Behavioral and social dimensions of adherence, and by experts in adherence science.

Many factors could impact adherence support activities in any given clinical trial. Potential constraints include funding limitations, staffing limitations at clinical research sites, and the need to manage the burden on trial volunteers. However, sophisticated efforts to achieve enrollment and retention goals may be fruitless if study participants do not use the investigational product, follow a regimen or service. Investment in and planning of adherence support strategies, using and building on the array of proven approaches and tools, will help to ensure that proof-of-concept biomedical HIV prevention clinical trials are successful in evaluating new prevention technologies (NPTs). By lodging investigation of adherence behavior in

a broader, socio-ecological framework, the research will go further to building understanding of what to improve and what to do next.

Figure 6.1. Behavioral and Social Issues in Adherence Support across the Life Cycle of a Clinical Trial.



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ANNEXES

Pont to consider 4.

"Stigma remains the single most important barrier to public action. It is a main reason why too many people are afraid to see a doctor to determine whether they have the disease, or to seek treatment if so. It helps make AIDS the silent killer, because people fear the social disgrace of speaking about it, or taking easily available precautions. Stigma is a chief reason why the AIDS epidemic continues to devastate societies around the world."

UN Secretary-General Ban Ki Moon

Ban Ki-moon op-ed (2008, 6th August), 'The stigma factor', The Washington Times

ANNEX I: HISTORY OF THE BSS POINTS TO CONSIDER PROJECT

More than three decades of HIV and AIDS has wrought suffering on millions worldwide and remains one of today's most urgent health crises to solve. It is clear that the acquisition of HIV and AIDS is heavily influenced by individual behavior and the socio-political context in which people live. The breadth of connections between behavior and health is formidable and behavioral, social, environmental as well as genetic influences all moderate one another. Behavior is central to the prevention, treatment/management of diseases-particularly HIV/AIDS, and to decrease mortality (Fisher et al, 2011; Kippax et al, 2011). To eventually reach the globally sanctioned goal of ending AIDS, new tools for HIV prevention are needed. The 2010 Annual Status Report of the National Prevention, Health Promotion and Public Health Council (June 2011) notes that "the most effective approach to address the leading causes of disease and death is to address, reduce and/or prevent underlying risk factors"

(<https://www.surgeongeneral.gov/priorities/prevention/strategy/report.pdf>)

Clinical trials to discover and test a variety of safe and effective biomedical technologies to prevent HIV infection are critical components of a broad approach to control the AIDS pandemic, and understanding the social context and individual behavior that enable transmission events is essential. The same holds true regarding a full appreciation of influences on acceptability of, and adherence to, effective products that may prevent HIV acquisition. Given the severity of the HIV pandemic, waning in some areas while waxing still in others, we cannot afford further missed opportunities that may be addressed by more rigorous integration of socio-behavioral science.

This document was born out of broad-based concern that priority be placed on optimizing the collection, characterization and measurement of risk behaviors, risk reporting and adherence to (study) product. The Division of AIDS (DAIDS) at the National Institutes of Health (NIH) has recognized the need for heightened attention to behavioral components of HIV prevention research and in recent years has convened pivotal meetings to address these issues. The first was held in May of 2009, in conjunction with the HVTN meeting and addressed multiple aspects that were critical to consider in the development and implementation of HIV Vaccine trials. These important aspects for consideration included: risk assessment, risk-reduction counseling, adherence, social impact, community engagement, and informed consent matters.

The previous meetings, and further discussions within DAIDS, spawned the decision to further address two important aspects: 'Risk Assessment' and 'Adherence' (specifically as it relates to risk). A multi-disciplinary meeting was held in June of 2011, which was a large, collaborative effort to further characterize and conceptualize risk assessment-particularly after the results of the Thai trial (RV 144) were announced in October 2010. This meeting also addressed Adherence, to a lesser degree, and its impact on Prevention trials. From the 2011 meeting, DAIDS proposed the creation of a guidance/resource document that could serve as a practical guide for a wide audience and that would include Behavioral and social scientists, clinical trialists, clinicians, community agencies, communicators and funding agencies.

At the Bangkok AIDS Vaccine Conference in 2011, a satellite meeting was organized by several partners to explore best practices in *gathering sexual risk information in HIV biomedical prevention trials*. Clinicians, researchers, statisticians and regulators from around the world came together to discuss the shared struggle to improve methods of gathering sexual risk activity assessments for the sake of being more confident in study findings. The satellite reiterated the successes and continued struggle researchers face in accurately assessing critical dimensions of behavior that have significant impact on clinical research outcomes. More importantly, the discussions and attendance underscored the valuable contribution of social behavioral research to the success of HIV AIDS prevention clinical research, and ultimately achieving better health outcomes for all.

The "Guide to Behavioral and Social Sciences in HIV Prevention Clinical Trials: Points to Consider when Undertaking Research" has emerged from these efforts to provide the field with a working document capable of moving the field forward in this regard. The '***Points to Consider***' document is the product of large and ongoing collaborations with clinicians, basic and social scientists, anthropologists, psychologists, epidemiologists, academic institutions, major funders, administrators, community activists, former trial participants and others who are committed to the discovery of effective, acceptable and accessible products capable of preventing HIV. The contributors of this document represent numerous agencies

and organizations promoting and advocating for better collaboration with behavioral and social scientists throughout the lifecycle of protocol development from the generation of research questions, community engagement, to protocol trial design, implementation and interpretation of protocol results and the planning for future research.

ANNEX II: ADDITIONAL RESOURCES

Sources	Type of Tool/Resource	Areas of Focus/Populations	Regions/Countries	Source & Year	Comments	Links
<i>Stakeholder Engagement</i>						
<i>CAB Handbook</i>						
<i>GPP Blueprint for Stakeholder Involvement</i>	Practical tool with overview of issues, followed by tools to aid planning and action for stakeholder engagement	Adults, advocacy groups, communities	Global	AVAC (2014)		http://www.avac.org/gpp
Community Tool Box- University of Kansas	Toolkit provides guidance and a quick start on key activities in community work and examples.	Communities	USA		Addresses Partnerships, assessing community needs/resources, analyzing problems, developing action plans and building leaderships	http://ctb.dept.ku.edu/en/toolkits
Alameda AIDS Research Coalition (AARC)	AARC Resources include guidance and examples that promote research collaboration	Communities & researchers	USA			https://caps.ucsf.edu/research/alameda-aids-research-coalition/

	between researchers and community-based organizations.					
<i>Positive Health, Dignity and Prevention guidelines</i>				GNP+ and UNAIDS, 2012		
<i>Risk Assessment and Prevention Planning</i>						
Cochrane HIV/AIDS Group/Cochrane Collaboration (USCF Global Health Sciences, AIDS Research Institute at UCSF)	Review of health care interventions by medical specialty	Varying populations including Women, MSM, sex workers, homeless youth, etc.	Several HIV related prevention topics for high, middle and low-income countries.		NA	http://www.thecochranelibrary.com
Condom Use Self Efficacy Scale (CUSES)	Assess condom use, self-efficacy, knowledge, and an individual's perception of their ability to use condoms.	Adults	USA	Brien et al., (1994)	Health Belief Model-	http://chipts.ucla.edu/resources
Sexual Risks Scale-Attitudes toward Condom Use (SRSA)	Assess attitudes toward condom use among college students.	College Students/young Adults	USA	DeHart & Birkimer (1997)		http://chipts.ucla.edu/resources

AIDS Risk Behavior Assessment (ARBA)	Assess self-report sexual behavior, drug/alcohol and needle use associated with HIV infection	Adolescents	USA	Donenberg, Emerson, Bryant, Wilson, Weber-Shifrin (2001)		http://chipts.ucla.edu/resources
Risk Behavior for Gay Men	Used with EXPLORE Project to assess social activity, attitude, PEP, drug use and sexual behavior	Adult, MSM	USA	2002		http://caps.ucsf.edu/resources/survey-instruments
Sexual Behavior for Students in Public Middle Schools	Developed at the Center for AIDS Prevention Studies at UCSF. Designed to evaluate the impact of middle school pregnancy/STD/HIV prevention programs. Also available in Spanish	Middle School grades 6 th -8 th	USA	Marin & Gomez (2000)		http://caps.ucsf.edu/resources/survey-instruments
HIV Risk taking behaviors	Asses HIV risk among IV drug users- subscales include measuring injection drugs and sexual behavior.	Adults, People who inject drugs	Australia	Darke, Hall, Heather, Ward & Wodak (1991)		http://chipts.ucla.edu/resources
HIV/AIDS Risk Assessment0TC U Scale	Assess injecting drug use, and condom use.	Adults, People who inject drugs	USA	Joe, Menon, Copher & Simpson (1990)		http://chipts.ucla.edu/resources
HIV prevention for MSM and			Asia and Pacific	Developing a Comprehensive Package of		

transgender people				Services to Reduce HIV among Men Who Have Sex with Men (MSM) and Transgender (TG) Populations in Asia and the Pacific, Regional Consensus Meeting, 29 June - 1 July 2009, Bangkok, Thailand http://apcom.org/2009/09/01/developing-a-package-of-services-to-reduce-hiv-among-msm-and-tg-populations-in-ap/		
Toolkit to reduce HIV related Stigma	Conceptual overview on stigma (what is it, how is it created and changed), followed by practical exercises on stigma, sexuality, and rights.	Adults, MSM, service providers	Middle East and North Africa	International HIV/AIDS Alliance (2009) http://www.aidsalliance.org/resources/305-toolkit-		

				understanding -and- challenging- hiv-stigma-in- the-mena- region		
Adherence Assessment						
Self-report Adherence to Medications	Developed by Adult Clinical Trials Group (ACTG) to assess self- reported adherence to ARV's	Adult	USA	Chesney & Ickovics (2000)		https://actgnetwork.org http://www.ghdonline.org/adherence/discussion/actg-adherence-baseline-and-follow-up-questionna-3 http://caps.ucsf.edu/resources/survey-instruments
HIV Treatment Adherence Self- Efficacy Scale	Measure self-efficacy for adherence to HIV treatment plans, including medication	Adult	USA	Johnson, Neilands, Dilworth, Morin, Remien, Chesney (2007)		http://caps.ucsf.edu/resources/survey-instruments

Center for Community Health Medication Adherence Scale (UCLA)	Medication adherence, medical history, assess living with HIV.	Adult	USA			http://chipts.ucla.edu/resources
Adherence Intervention						
<i>Overall Prevention</i>						
National Sexual Health Survey (NSHS)	Telephone survey to assess HIV and sexuality related topics including condom attitudes, HIV testing, STD, perceptions of HIV risk etc.	Adult (18 yrs and older)	USA			http://caps.ucsf.edu/resources/survey-instruments
CDC HIV Testing Questions	Core measures: sexual behavior, drug-related HIV risk, HIV testing.	Adults	USA	CDC (2001)		http://chipts.ucla.edu/resources
Intentions for Safer Sex	Assess safer sex intentions among adolescents-self-efficacy, condom use.	Adolescents	USA (??)	Lux & Petosa (1994)	Health Belief Model-	http://chipts.ucla.edu/resources

Perceived Susceptibility (HMBP)	Asses perceived susceptibility of HIV infection among adolescents. (AA/Caucasian Incarcerated youth).	Adolescents	USA	Lux & Petosa (1994)	Health Belief Model-	http://chipts.ucla.edu/resources
China MSM Stigma Scale		Adults, Men who have sex with men				
<i>Capacity Building</i>						
Center for AIDS Prevention Studies (CAPS) (Univ. of Calif.- San Francisco	Capacity Building Assistance. Provides guidance for Culturally and linguistically competent approach to capacity building assistance services.		USA			http://caps.ucsf.edu/resources/capacity-building-assistance-cba

RESOURCES on RISK ASSESSMENT:

1. Condom Use Among Hispanics

Instruments:

- [Condom use for Females in English](#)
- [Condom use for males in English](#)
- [Uso de condones paramujeres en Español](#)
- [Uso de condones para hombres en Español](#)
[detailed description of the instruments.](#)

2. Latino Gay/Bisexual Men

The following Spanish survey has been used to assess risk behavior. It was developed through the [Hermanos de Luna y Sol](#) program, a culturally-appropriate HIV risk-reduction intervention that targets immigrant, Spanish-speaking gay/bisexual men in San Francisco, CA. See the [latest report](#) of the program evaluation for HLS that includes a comparative of behavioral change pre- and post-intervention as well as barriers and limitations for this instrument.

Instrument:

- [Behavioral Risk Assessment Survey](#) (The survey is only available in Spanish--PDF document)

3. Measures of Sexual Attitudes and Behavior of Latino Adults

Instruments:

- [Questionnaire for Unmarried Latina Women](#)
- [Questionnaire for Unmarried Latino Men](#)
- [Cuestionarioparamujereslatinassolteras](#)
- [Cuestionariopara hombres latinossolteros](#)

4. United States National Sexual Health Survey (NSHS)

The US NSHS is national telephone survey of adults 18 years and older residing in the 48 contiguous states. Measures were developed to assess a wide range of HIV-related and human sexuality topics, including, but not limited to: condom attitudes, condom slips and breaks, HIV-related caregiving, HIV-testing and home testing use, STD histories, perceived risk for HIV and other STDs and optimistic bias assessments, extramarital sex, sexual development, sexual abuse and rape, sexual dysfunctions, various psychological scales (sensation-seeking, machismo), family assessments and history, health and demographics, and a detailed assessment was conducted of sexual activities with each of the respondent's

sexual partners in the past year up to a total of 10 partners, and, in addition, demographic, geographic, and HIV/STD risk characteristics of their sexual partners were determined.

Instruments:

- [Screening questionnaire](#)
- [Questionnaire guidelines](#)
- [Questionnaire map](#)
- [National Sexual Health Survey \(NSHS\)](#)
- [Cuestionario de selección](#)
- [Información sobre el cuestionario de NSHS](#)
- [Cuestionario NSHS](#)

Supporting documentation:

- [Table of contents](#)
- [Introduction](#)
- [Sample design & procedures](#)
- [Disposition codes](#)
- [Variables & univariate statistics](#)
- [Derived variables](#)
- [Contact information](#)

5. Teen Peer Educators

The following surveys are used with the [Healthy Oakland Teens](#) project, at an urban, ethnically diverse junior high school. The project's goal is to reduce adolescents' risk for HIV infection by using peer role models to advocate for responsible decision making, healthy values and norms, and improved communication skills.

Instruments:

- [Teen knowledge, attitude, behavior, belief \(KABB\) questionnaire](#)
- [Student evaluation of peer educators](#)
[detailed description of the instruments](#)

6. HIV Counseling and Testing in Developing Countries

The following surveys are used with the [Voluntary HIV Counseling and Testing Efficacy study](#), a randomized clinical trial of the effectiveness of HIV counseling and testing for the prevention of new HIV infections. The study was conducted at three sites: Nairobi, Kenya; Dar es Salaam, Tanzania and Port-of-Spain, Trinidad.

Instruments:

- [Baseline survey](#)
- [Six-month follow-up survey](#)
 - [Six-month counselor questionnaire](#)

- Six-month STD test
- Twelve-month follow-up survey
 - Twelve-month counselor questionnaire

7. Qualitative Survey -- HIV Testing and Counseling Among Injection Drug Users

The following qualitative survey was used with Project Access, a qualitative needs assessment commissioned by the California State Office of AIDS and the Centers for Disease Control and Prevention to examine counseling and testing utilization and prevention programs through the perspective of drug-using clients. The instrument is designed to assess: 1) the behavioral, psychosocial and social risk factors that influence high-risk drug users' decisions to test for HIV; 2) the service delivery factors that influence high-risk drug users' decision to test for HIV; 3) how high-risk drug users employ HIV testing in personal prevention strategies; 4) and how knowledge of HIV test results affects risk behavior.

Instrument:

- Qualitative Interview Instrument.

8. Self-Report Adherence to Medications

This questionnaire was developed by the AIDS Clinical Trials Group (ACTG) Recruitment, Adherence and Retention Subcommittee, Margaret A. Chesney, Ph.D., and Jeannette Ickovics, Ph.D., Co-Chairs. Please read the two abstracts on adherence in clinical trials and practice. Note that recent results of the VOICE study showed a high correlation of self-reported adherence to pill and applicator counts but poor correlation of self-reported adherence and counts to biological measures, e.g., pharmacokinetics (PK) [Marrazzo J et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003). 20th CROI, 3-6 March 2013, Atlanta. Oral abstract 26LB; Smith J et al. A tenofovir disoproxil fumarate intravaginal ring completely protects against repeated SHIV vaginal challenge in nonhuman primates. 20th CROI, 3-6 March 2013, Atlanta. Oral abstract 25LB. Webcast (third presentation)]

Instruments:

- ACTG Adherence Baseline Questionnaire (PDF)
- ACTG Adherence Follow Up Questionnaire (PDF)

9. Focus Group Questions for Sexual Negotiations

The following two outlines of focus group questions are taken from the following research study: "Sexual Negotiations Among Young Adults in the Era of AIDS." Prepared by Diane Binson, PI. Funded by the Universitywide AIDS Research Program, R94-SF-050.

Instruments:

- [Focus Group Questions for Young Women who Have Sex with Men](#)
- [Focus Group Questions for Young Gay/Bisexual Men](#)

10. Sexual Behavior for Students at Public Middle Schools

Barbara Marín and Cynthia Gomez at the Center for AIDS Prevention Studies at UCSF and Karin Coyle and Doug Kirby at ETR Associates developed this questionnaire as part of an evaluation study. These questionnaires are available as PDF files both in English and Spanish. [Please read a description of the questionnaires.](#)

Instruments:

- [Student Health Questionnaire](#) (PDF file 54K)
- [Encuesta de SaludEstudiantil](#) (PDF file 51K)

11. Prevention Services for HIV+ Patients

The following instruments were developed to assess frequency and variation of prevention services as reported by HIV positive patients across the US.

- <http://www.jhsph.edu/research/centers-and-institutes/research-to-prevention/publications/positiveprevention.pdf>

12. Risk behavior for gay men

These questionnaires were used with the [Explore project](#) and cover social activity, attitude, PEP, drug use and sexual behavior.

Instruments: See the following for additional information

- <https://www.cdc.gov/hiv/research/interventionresearch/compendium/rr/explore.html>

13. Risk behavior and health care for HIV+ injection drug users

These instruments were used to measure the effectiveness of the multi-site INSPIRE Study ([VOICE](#) in San Francisco) and cover medication use and adherence, health care utilization, substance abuse, injection behavior, sexual behavior, partner relationships and more.

Instruments:

- [Screening questionnaire](#) (PDF)
- [Baseline survey](#) (NOTE: This is a 7.4 MB PDF file)

14. Risk behavior and health care for HIV+ injection drug users

These instruments were used with the SUDIS Study and cover medication use and adherence, health care utilization, disclosure, alcohol and drug use, sexual behavior, partner relationships, social support and more.

Instruments:

- [Screening questionnaire](#) (PDF)
- [Female questionnaire](#) (NOTE: This is a 7.9MB PDF file)
- [Male questionnaire](#) (NOTE: This is a 5.9MB PDF file)

15. Women with incarcerated male partners

These instruments were used with the [HOME Study](#).

- [Longitudinal survey - baseline](#) (We administered these to women visiting their incarcerated partners at the prison under study. Women completed the baseline while their partner was incarcerated and they completed the follow-up 30 days after their partner was released from custody.)
- [Longitudinal survey - follow-up](#)
- [Cross-sectional survey](#) (We administered this survey to women visiting incarcerated men at the prison under study before our intervention began and after our intervention ended to measure community impact.)

16. Attitudes and risk behavior for healthcare providers and their HIV+ patients

These instruments were used with the [EPPEC Project](#).

- [Patient Assessment](#)
 - [Encuesta en español](#)
- [Provider Assessment](#)
- [Patient program evaluation](#) - qualitative
- [PI and Project Director implementation](#) - qualitative

17. Risk behavior for jail inmates and jail staff

These instruments were used with the [Innovative Condom Distribution](#) study and attitudes towards and awareness of condoms and sexual activity in jail.

Instruments:

- [Pre-intervention prisoner survey](#) (PDF)
- [Follow-up prisoner survey](#) (PDF)
- [Prison staff interview guide](#) (PDF)

18. Ways of Coping

Ways of Coping Questionnaire by Susan Folkman and Richard S Lazarus is used to identify the thoughts and actions an individual has used to cope with a specific stressful encounter.

Instruments:

- [Ways of Coping](#) (PDF)

19. Female Condom Attitudes Scale (FCAS)

Instrument:

- [Attitudes Toward the Female Condom](#) (PDF)

20. Coping Self-Efficacy Scale

Instrument:

- [Coping Self-Efficacy Scale](#) (PDF)

21. SECOPE - Coping with HIV treatment side effects

Instrument:

- [SECOPE](#) (PDF)

22. HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES)

Instrument:

- [HIV-ASES](#) (PDF)

23. Modified Schedule of Sexist Events (SSE-LM) - The Schedule of Sexist Events (SSE) (Klonoff & Landrine, 1995) composed of 20 items that evaluate perceived frequency of sexist discrimination. Items are rated along a 6-point scale ranging from 1 (the event never happened) to 6 (the event happened almost all the time).

Instrument:

- [SSE-LM](#) (PDF)

24. China MSM Stigma Scale -The China MSM Stigma Scale assesses both impressions of the degree of societal stigmatization of homosexuals and enacted stigma, which is direct personal experiences of stigmatizing behaviors.

Instrument:

- [China MSM Stigma Scale](#) (PDF)

25. India HIV-related Stigma Scales -The India HIV-Related Stigma Scale was developed from a HIV-related stigma theoretical framework for use in India.

Instrument:

- [India HIV-related Stigma Scales \(PDF\)](#)

26. Outside of Center for AIDS Prevention Studies (CAPS); University of California, San Francisco

- **An excellent resource for scales can be found at the Center for Identification, Prevention and Treatment Services (CHIPTS), UCLA, Drew University.**
Assessment Instruments
- **Population Council**
- **The Measurement Group**

Related

- [Evaluation manuals](#)

RESOURCES: -from Chapter 4, Interventions to Reduce HIV Risk

<https://effectiveinterventions.cdc.gov/en>

<https://effectiveinterventions.cdc.gov/en/HighImpactPrevention.aspx>

The Cochrane Collaboration has a collection of Behavioral Interventions by population that may be of interest as examples:

1. The Cochrane Collaboration (2011). Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries (Review). Retrieved from: <http://www.thecochranelibrary.com>
2. The Cochrane Collaboration (2008). Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men (Review). Retrieved from: <http://www.thecochranelibrary.com>
3. The Cochrane Collaboration (2011). Male Circumcision for prevention of heterosexual acquisition of HIV in men (Review). Retrieved from: <http://www.thecochranelibrary.com>
4. The Cochrane Collaboration (2009). Interventions for educating traditional healers about STD and HIV medicine (Review). Retrieved from: <http://www.thecochranelibrary.com>

US Center for Disease Control and Prevention (CDC) Compendium of Evidence-Based HIV Behavioral Interventions (EBIs)

The CDC's Prevention Research Synthesis (PRS) Project undertakes a series of ongoing systematic reviews to produce the Compendium of Evidence-based Interventions and Best Practices for HIV Prevention. The Compendium is divided into three chapters, each

containing “best practices” (BP) and “evidence-based interventions” (EBI) that meet or exceed a series of criteria for each type of intervention, and have shown to be sufficient to prove that the intervention works. The criteria for each intervention type are also available at the links provided in Annex III.

<https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html>

The three Compendium chapters and some example BPs/EBIs are:

1. ***Linkage to, Retention in, and Re-engagement in HIV Care (LRC)***, 14 best practices

- a. [2010 New York State HIV Testing Law](#) **NEW 2016**
Target population: Persons newly diagnosed with HIV and medical providers who diagnose HIV
Year published: 2015
Author: Daniel E. Gordon
Study years: 2007 – 2012
- b. [Bilingual/Bicultural Care Team](#)
Target population: Hispanic/Latino HIV clinic patients
Year published: 2008
Author: Maithe Enriquez
Study years: 2006 – 2007
- c. [Centralized HIV Services](#)
Target population: Young black or African American, Hispanic/Latino HIV clinic patients
Year published: 2013
Author: Jessica Davila
Study years: 2004 – 2007
- d. [Clinic-Based Surveillance-Informed Patient Retracing](#) **NEW 2016**
Target population: Out-of-care HIV-clinic patients
Year published: 2015
Author: Joanna Bove
Study years: 2011 – 2012
- e. [HIV Care Coordination Program](#)
Target population: Recently diagnosed HIV clinic patients
Year published: 2015
Author: Mary Irvine
Study years: 2009 – 2011
- f. [Project CONNECT](#)
Target population: Recently diagnosed HIV clinic patients
Year published: 2008
Author: Michael J. Mugavero
Study years: 2007 – 2008
- g. [Routine Universal Screening for HIV \(RUSH\) Program](#) **NEW 2016**
Target population: Previously-diagnosed HIV patients
Year published: 2015
Author: Charlene A. Flash
Study years: 2009 – 2012
- h. [Stay Connected](#)
Target population: HIV clinic patients
Year published: 2012

Author: Lytt I. Gardner
Study years: 2008 – 2009

i. [STYLE](#)

Target population: Recently diagnosed or lost-to-care young HIV-positive black or African American, Hispanic/Latino men who have sex with men (MSM)

Year published: 2011

Author: Lisa Hightow-Weidman

Study years: 2006 – 2009

2. **Medication Adherence (MA)**, containing 13 Evidence-based Interventions

a. [Adherence Through Home Education and Nursing Assessment \(ATHENA\)](#)

Good

ART experience: Treatment-experienced

Target population: HIV-positive clinic patients who are antiretroviral treatment-experienced

Intervention level: Individual-level (ILI)

Year published: 2006

First author: Ann B. Williams

Study years: 1999 – 2002

b. [CARE+](#)

Good

ART experience: Treatment-experienced

Target population: HIV clinic patients who are antiretroviral treatment-experienced

Intervention level: Individual-level (ILI)

Year published: 2014

First author: Ann E. Kurth

Study years: 2006 – 2008

c. [Text Messaging Intervention to Improve Antiretroviral Adherence among HIV-Positive Youth \(TXTXT\)](#) **NEW 2016**

Good

ART experience: Treatment-experienced

Target population: HIV-positive adolescents and young adults with poor medication adherence

Intervention level: Individual-level (ILI)

Year published: 2016

First author: Robert Garofalo

Study years: 2010 – 2014

3. **Risk Reduction (RR)**, containing 59 behavioral Evidence-based Interventions

a. [AMIGAS](#)

Best

Target Population: Latina women

Intervention level: Group-level

Year published: 2011

First author: Gina M. Wingood

Study years: 2007 – 2010

b. [Adapted-Stage Enhanced Motivational Interviewing \(A-SEMI\)](#)

Good

Target Population: High-risk Hispanic/Latino migrant workers

Intervention level: Group-level

Year published: 2013
First author: Jesús Sánchez
Study years: 2008 – 2010

c. [CARE+](#)

Best

Target Population: HIV clinic patients who are antiretroviral treatment-experienced
Intervention level: Individual-level
Year published: 2014
First author: Ann E. Kurth
Study years: 2006 – 2008

d. [Centering Pregnancy Plus \(CPP\)](#)

Best

Target Population: Young pregnant women receiving prenatal care
Intervention level: Group-level
Year published: 2009
First author: Trace S. Kershaw
Study years: 2001 – 2004

e. [CHAT](#)

Best

Target Population: High-risk heterosexual women and their social network
Intervention level: Group-level
Year published: 2011
First author: Melissa A. Davey-Rothwell
Study years: 2005 – 2010

f. [Choosing Life: Empowerment, Actions, Results \(CLEAR\)](#)

Best

Target Population: Young HIV-positive substance abusers
Intervention level: Individual-level
Year published: 2004
First author: Mary Jane Rotheram-Borus
Study years: 1999 – 2003

g. [Community Promise](#)

Good

Target Population: Underserved populations at risk for HIV infection
Intervention level: Community-level
Year published: 1999
First author: CDC ACDP Research Group
Study years: 1991 – 1994

h. [Connect: Couples](#)

Best

Target Population: Minority, inner-city heterosexual couples
Intervention level: Group-level
Year published: 2003
First author: Nabila El-Bassel
Study years: 1997 – 2001

i. [Connect: Woman Alone](#)

Best

Target Population: Minority, inner-city heterosexual couples
Intervention level: Individual-level
Year published: 2003
First author: Nabila El-Bassel
Study years: 1997 – 2001

- j. [Connect 2](#)
Best
Target Population: Drug-involved, HIV-negative concordant, high-risk heterosexual couples
Intervention level: Couple-level
Year published: 2011
First author: Nabila El-Bassel
Study years: 2005 – 2010
- k. [¡Cúdate!](#)
Best
Target Population: Latino youth
Intervention level: Group-level
Year published: 2006
First author: Antonia M. Villarruel
Study years: 2000 – 2003
- l. [Drug Users Intervention Trial \(DUIT\)](#)
Good
Target Population: Young HIV-negative and Hepatitis C-negative injection drug users (IDUs)
Intervention level: Group-level
Year published: 2007
First author: Richard S. Garfein
Study years: 2002 – 2004
- m. [Eban](#)
Best
Target Population: African American HIV serodiscordant heterosexual couples
Intervention level: Couple-level
Year published: 2010
First author: Nabila El-Bassel
Study years: 2003 – 2007
- n. [ECHO NEW 2016](#)
Best
Target Population: High-risk HIV-negative episodic substance using MSM
Intervention level: Individual-level
Year published: 2014
First author: Phillip O. Coffin
Study years: 2010 – 2012
- o. [Familias Unidas](#)
Best
Target Population: Hispanic or Latino delinquent youth and their primary caregivers
Intervention level: Group-level
Year published: 2012
First author: Guillermo Prado
Study years: 2009 – 2010
- p. [Female Condom Skills Training](#)
Best
Target Population: HIV-negative heterosexual women attending family planning clinics
Intervention level: Group-level
Year published: 2008
First author: Kyung-Hee Choi
Study years: 2003 – 2005

- q. [Focus on the Future](#)
Best
Target Population: Young African American heterosexual men newly diagnosed with an STD
Intervention level: Individual-level
Year published: 2009
First author: Richard A. Crosby
Study years: 2004 – 2006
- r. [Focus on the Future \(FoF\) for Black Male Youths](#) **NEW 2016**
Best
Target Population: Sexually active black males aged 15-23 years
Intervention level: Individual-level
Year published: 2014
First author: Richard A. Crosby
Study years: 2010 – 2012

Resources – Chapter 5: Adherence Assessment

- Behavioral and social scientists working in the HPTN and HVTN networks
- HANC Inventory of Network Studies with Adherence Measures and Objectives
- IAPAC/NIMH “International Conference on HIV Treatment and Prevention Adherence”
- “HAART Adherence_ Research Listserv”
- Adherence Tools:
 - ACTG Medication Adherence Questionnaire
 - [ACTG Adherence Baseline Questionnaire](#) (PDF)
 - [ACTG Adherence Follow Up Questionnaire](#) (PDF)
 - Patient Medication Adherence Questionnaire (PMAQ)
 - <https://www.effectiveinterventions.org/en/Home.aspx>
 - e-pill.com
 - [iHealth Patient Compliance Portal](#)
 - [West Portal](#)
 - <http://www.ihl.org/resources/Pages/Changes/HIVSelfManagementandAdherence.aspx>
 - <http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/30/adherence-to-art>

Resources – Chapter 6: Adherence Support Intervention

- <https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence.aspx>
- <https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/index.html>
- [http://www.iapac.org/uploads/IAPAC_Entry_Retention_Adherence_Guidelines_Summary Table 05JUN12.pdf](http://www.iapac.org/uploads/IAPAC_Entry_Retention_Adherence_Guidelines_Summary_Table_05JUN12.pdf)

ANNEX III: EVALUATING THE EVIDENCE FOR EFFECTIVE PREVENTION INTERVENTIONS.

1. HIV Risk Reduction Efficacy Criteria

<https://www.cdc.gov/hiv/dhap/prb/prs/efficacy/rr/criteria/index.html>

The [Prevention Research Synthesis \(PRS\) Project](#) risk reduction efficacy criteria are used to determine if an HIV behavioral intervention is evidence-based, that is, if there is sufficient evidence that the intervention reduced HIV-related risk behaviors. Based on the overall quality of the study, evidence-based risk reduction behavioral interventions are classified as either **best-evidence** or **good-evidence**.

a. Best-evidence Risk Reduction Interventions

Best-evidence interventions are HIV behavioral interventions that have been rigorously evaluated and have been shown to have significant and positive evidence of efficacy (i.e., eliminate or reduce sex- or drug-risk behaviors, reduce the rate of new HIV/STD infections, or increase HIV-protective behaviors). These interventions are considered to be scientifically rigorous and provide the strongest evidence of efficacy.

b. Good-evidence Risk Reduction Interventions

Good-evidence interventions are HIV behavioral interventions that have been sufficiently evaluated and have been shown to have significant and positive evidence of efficacy (i.e., eliminate or reduce sex- or drug-risk behaviors, reduce the rate of new HIV/STD infections, or increase HIV-protective behaviors). While the evaluations of these interventions do not meet the same level of rigor as best-evidence interventions, they are considered to be scientifically sound, provide sufficient evidence of efficacy, and address the HIV prevention needs of many communities by targeting high-risk populations.

2. HIV Medication Adherence Efficacy Criteria

<https://www.cdc.gov/hiv/dhap/prb/prs/efficacy/ma/criteria/index.html>

The [Prevention Research Synthesis \(PRS\) Project](#) efficacy criteria are used to determine if an HIV Medication Adherence (MA) intervention is evidence-based, that is, if there is strong or sufficient evidence that the intervention improves adherence to HIV antiretroviral medication or reduces HIV viral load. Each eligible study is evaluated against the efficacy criteria that focus on quality of study design, quality of study implementation and analysis, and strength of evidence of efficacy. Based on the overall quality of the study, evidence-based interventions (EBIs) are classified as either **best-evidence** or **good-evidence**.

a. Best-evidence Medication Adherence Interventions

Best-evidence MA interventions are HIV interventions that focus on medication adherence behaviors among persons living with HIV (PLWH), have been rigorously evaluated, and have shown significant effects in both improving medication adherence behaviors and reducing HIV viral load. These interventions are considered to be scientifically rigorous and provide the strongest evidence of efficacy.

b. Good-evidence Medication Adherence Interventions

Good-evidence MA interventions are HIV interventions that focus on medication adherence behaviors among PLWH, have been sufficiently evaluated, and have shown significant effects in reducing HIV viral load or improving medication adherence behaviors. While the evaluations of these interventions do not meet the same level of rigor as the best-evidence interventions, they are considered to be scientifically sound and provide sufficient evidence of efficacy.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system has been widely endorsed as the most effective method with which to grade the current state of evidence for a variety of clinical interventions (Baral, Wirtz et al, 2012;

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001469>).

The grade system presents a systematic and transparent framework for clarifying questions, determining the outcomes of interest, summarizing the evidence that addresses a question and moving from the evidence to a recommendation or decision (Akl, Kennedy, Korda, et al, 2012; <http://www.gradeworkinggroup.org>). The GRADE system integrates the potential for a separation between quality of evidence and strength of recommendations based on estimating circumstances such as cost-efficacy, risk benefit and contextual factors (Baral, Wirtz, et al. 2012).