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Combination HIV Prevention Interventions: The Potential of Integrated Behavioral and Biomedical Approaches

Jennifer L. Brown¹, Jessica M. Sales^{2,3}, and Ralph J. DiClemente^{2,3}

¹Department of Psychological Sciences, Texas Tech University

²Department of Behavioral Sciences & Health Education, Emory University

³Center for AIDS Research, Emory University

Abstract

Background—Combination HIV prevention interventions that integrate efficacious behavioral and biomedical strategies offer the potential to reduce new HIV infections.

Purpose—We overview the efficacy data for three biomedical HIV prevention approaches: microbicides, pre-exposure prophylaxis (PrEP), and an HIV vaccination, review factors associated with differential acceptability and uptake of these methods, and suggest strategies to optimize the effectiveness and dissemination of combination HIV prevention approaches.

Methods—A narrative review was conducted highlighting key efficacy data for microbicides, PrEP, and an HIV vaccination and summarizing acceptability data for each of the three biomedical HIV prevention approaches. Recommendations for the integration and dissemination of combined behavioral and biomedical HIV prevention approaches are provided.

Results—To date, microbicides and an HIV vaccination have demonstrated limited efficacy for the prevention of HIV. However, PrEP has demonstrated efficacy in reducing HIV incident infections. A diverse array of factors influences both hypothetical willingness and actual usage of each biomedical prevention method.

Conclusions—Strategies to effectively integrate and evaluate combination HIV prevention interventions are urgently needed.

Keywords

combination HIV prevention; microbicide; PrEP; HIV vaccine; biomedical HIV prevention; behavioral HIV prevention

Corresponding Author: Jennifer L. Brown, Ph.D., Department of Psychological Sciences, Texas Tech University, MS 2051, Lubbock, TX 79409-2051, jennifer.brown@ttu.edu.

Conflict of Interest

Jennifer L. Brown, Jessica M. Sales, Ralph J. DiClemente declare that they have no conflict of interest

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Rates of new HIV infections in the United States (U.S.) remain relatively stable with approximately 50,000 incident cases diagnosed annually [1]. Globally, there were 2.3 million incident HIV cases in 2012 [2]. HIV prevalence continues to rise with an estimated 35.3 million people now living with HIV worldwide [2]. To curb the tide of new HIV infections, the HIV prevention “toolkit” has increased its arsenal of available prevention methods through use of both behavioral and biomedical approaches. Combination HIV prevention interventions that integrate efficacious behavioral and biomedical strategies offer the potential to reduce new HIV infections and, as a consequence HIV prevalence worldwide [3–5], particularly when implemented in conjunction with broader structural interventions [6]. However, to enhance widespread dissemination and uptake of these methods, strategies to facilitate integration and acceptability of combined behavioral and biomedical HIV prevention strategies are essential.

Behavioral HIV prevention strategies focus on reducing high-risk practices including non-condom protected sexual encounters and sharing of contaminated needles, among others. A multitude of efficacious behavioral HIV prevention approaches have been developed. For example, the U.S. Centers for Disease Control and Prevention (CDC) have reviewed, evaluated and identified efficacious behavioral HIV prevention interventions [7, 8]. These approaches employ a variety of intervention modalities (e.g., one-on-one, small group) and typically target at-risk populations (e.g., men who have sex with men, African American adolescents) [7]. When behavioral interventions are used alone, they may reduce high-risk sexual practices, use of contaminated needs, and other behaviors that increase HIV risk.

In addition to behavioral strategies, the HIV prevention “toolkit” has expanded to include biomedical prevention approaches. Biomedical HIV prevention approaches encompass a diverse array of strategies at different stages of development, of varying efficacy, and at various states of approval including: (a) microbicides applied either to the vagina or to the rectum; (b) Pre-exposure prophylaxis (PrEP) antiretroviral (ARV) medication use, use of ARV medications as a preventive strategy among high-risk seronegative persons; (c) Post-exposure prophylaxis (PEP), use of ARV medications following HIV exposure; (d) HIV vaccination; (e) medical male circumcision; (f) HIV testing, linkage, and retention in HIV care (“test-and-treat”); and (g) enhanced ARV adherence among HIV seropositive individuals (treatment as prevention). While not all of these biomedical HIV prevention strategies have demonstrated efficacy or are approved for widespread use, they offer the possibility to further curtail the HIV epidemic. Combination HIV prevention approaches that integrate both behavioral and biomedical strategies may offer an even greater potential to reduce HIV transmission among high-risk populations.

To illustrate the potential of combination prevention approaches, we first briefly overview the efficacy data for three biomedical HIV prevention approaches: microbicides, PrEP, and an HIV vaccination. We then review factors associated with differential acceptability and uptake of each of these three methods. Lastly, we provide possible strategies to optimize the effectiveness and dissemination of combination HIV prevention approaches that integrate both behavioral and biomedical intervention strategies.

Overview of Literature Search Method

Database searches of PsycINFO, PsycARTICLES, Medline, and PubMed were conducted to identify published articles in peer-reviewed journals that either: (a) provided efficacy data or evaluated the acceptability of microbicides, PrEP, or an HIV vaccine; or (b) discussed strategies to optimize the implementation and dissemination of combination HIV prevention interventions. Combinations of the following search terms were used to identify relevant articles: *combination HIV prevention, microbicide, PrEP, pre-exposure prophylaxis, HIV vaccine, HIV vaccination, HIV, AIDS*. A search of references cited in relevant studies was conducted to identify additional articles. English language articles published in peer-reviewed journals were screened for inclusion in the review.

Microbicides

Unlike either male or female condoms that may require negotiation between sexual partners for their use, vaginal microbicides allow for greater control by women as an HIV prevention strategy [9]. Similarly, efficacious microbicides applied rectally may increase both men and women's protection from HIV via a method that allows for greater individual control [10]. Currently there are a number of microbicides in various stages of development and testing. However, in the U.S. there are no FDA-approved microbicides available.

Overview of microbicide efficacy—A 2008 study reviewed 73 pre-clinical and 45 clinical trials of microbicides at various phases of development [10]. Generally, as of this 2008 review, completed Phase I and Phase II microbicide trials demonstrated microbicide safety and the products were well tolerated [10]. However, microbicide Phase III trials had not demonstrated HIV prevention efficacy [10].

A subsequent 2012 meta-analysis examined the effectiveness of vaginal microbicides relative to placebo or no intervention condition across 13 randomized controlled trials [11]. Across trials, tenofovir as a microbicide demonstrated initial efficacy in reducing HIV acquisition, but a subsequent large-scale trial was discontinued due to a decreased protective effect against HIV [11]. Further, there was no efficacy for reduced HIV acquisition from nonoxynol-9, cellulose sulfate, SAVVY, Carraguard, PRO 2000, or BufferGel [11]. Additionally, nonoxynol-9 demonstrated the potential to *increase* the probability of HIV acquisition via increased risk of genital lesions [11].

Should a safe and efficacious microbicide be developed, its acceptability by potential users will be important for its successful marketing, uptake, and widespread dissemination [12]. Further, factors associated with differential acceptability can be used to tailor intervention messaging related to microbicide use and to address potential adherence challenges [12]. Dimensions of microbicide acceptability have been assessed for both hypothetical future microbicide products and also for individual microbicides during pre-clinical and clinical trials.

Acceptability of future potential microbicides—Two studies examined factors associated with the acceptability of future potential microbicides among men who have sex with men (MSM) [13] and women in the U.S. [14]. A qualitative study conducted with

MSM examined the acceptability of microbicides, an HIV vaccine, PrEP, and PEP [13]. Participants endorsed enthusiasm for a future potential microbicide if the product acted like a lubricant and was also efficacious in preventing HIV [13]. However, participants noted some concerns about product characteristics (e.g., consistency, taste, form of use) [13]. In a second study, U.S. women provided feedback on the acceptability of future vaginal microbicides using a mixed-methods study design [14]. Women noted concerns about the physical characteristics of potential microbicide gels (e.g., messiness, chemical make-up) and fears about possible discomfort and embarrassment using the product [14]. However, women highlighted the importance of having a self-controlled HIV prevention method, particularly if the microbicide was effective, discreet, long-lasting, comfortable, and affordable [14]. Quantitative analyses also examined the role of personal, relational, and attitudinal dimensions of microbicide acceptability; microbicide acceptability was negatively associated with past experiences of physical or sexual violence or experiencing decreased power in their sexual relationships and positively associated with past vaginal contraceptive product use [14].

Acceptability of microbicides during pre-clinical or clinical trials—During pre-clinical or clinical trials, acceptability of the candidate microbicides of nonoxynol-9 [15, 16], cellulose sulfate [17], BufferGel [9, 18, 19], PRO 2000 Gel [18–20], a vaginal ring microbicide delivery modality [21], and tenofovir [22–24] were examined. In what follows, we briefly review acceptability data for each of the candidate microbicides.

In an early trial of nonoxynol-9 among sex workers in South Africa, there were no overall differences between the nonoxynol-9 and placebo groups for side effects; however, a minority of women noted adverse side effects including vaginal burning and pain during sex [16]. Participants noted no difficulties using the product and reported that the product was not detectable to their clients [16]. Subsequent to trial participation, a subset participated in qualitative focus groups regarding nonoxynol-9 acceptability [15]. Of note, this microbicide was found to be ineffective for STI/HIV prevention [15]. Despite being told of the microbicide's lack of efficacy, qualitative findings indicated that women believed the gel afforded STI/HIV prevention benefits and alleviated STI symptoms and reproductive tract pain [15]. For example, women stated that the gel reduced vaginal wetness and discharge, rashes, and uterine, bladder, abdominal, and menstrual pain, despite the lack of trial evidence to support these beliefs [15].

A Phase I trial of a Cellulose Sulfate (CS) gel assessed its acceptability relative to a placebo gel among HIV-infected women and their male partners [17]. Women reported less likelihood to use the CS gel relative to the placebo gel; 64% of the sexually active women reported leaking of either the CS or placebo gels during sex [17]. Male partners indicated high support for the product if it became available and was efficacious, with women indicating a preference for a product that would not be detectable by their male partners [17].

In a trial of the vaginal microbicide BufferGel, HIV seronegative women at low HIV risk in Malawi, Zimbabwe, India, and Thailand reported on the overall acceptability of the microbicide by themselves and their male partners [9]. Overall, 73% of respondents

indicated that if the microbicide was approved they would use the product [9]. With regards to preferred features, 93% liked the product's color, 92% liked the ease of insertion, 81% liked the product's smell, and 66% appreciated the reusable applicator [9]. However, 49% of participants indicated the microbicide "felt too wet or drippy," with 31% indicating the microbicide soiled their clothing [9]. Qualitative findings suggested that women with heightened concerns of HIV risk and/or partner fidelity found BufferGel to be more acceptable; however, male partners expressed concerns that microbicide use might encourage greater promiscuity [9]. Given product characteristics, both men and women did not believe it would be feasible to use the microbicide without partners' awareness of use [9].

A mixed-methods study examined the acceptability of PRO 2000 Gel, a topical microbicide in a Phase I trial among both sexually active HIV-uninfected and sexually abstinent HIV-infected women in the U.S. and South Africa [20]. Global acceptability ratings indicated participants would purchase the microbicide and recommend the product to other women if it were to be made available [20]. With regards to desired features, women indicated the ability to effectively to prevent STI/HIV was critical, with a majority also endorsing a desire to have the gel also prevent pregnancy [20]. Physical characteristics (i.e., color, smell) of the product were also favorably reviewed, with some indicating a preference for a colorless product [20]. Qualitative findings highlighted some dissatisfaction associated with the gel leaking, both throughout the day and during sex [20].

A third study examined the acceptability of both BufferGel and PRO 2000 Gel relative to a placebo K-Y jelly condition for sexually abstinent HIV-uninfected and HIV-infected men used by direct application to the penis [19]. Men rated both BufferGel and PRO 2000 gel to be acceptable, with few noting that they would object to a potential partner using the product [19]. Further, men using both gels indicated high likelihood to use the product in the future [19]. A second trial of BufferGel and PRO 2000 Gel microbicides was conducted with women and their male partners from Malawi, South Africa, the U.S., Zambia, and Zimbabwe [18]. Overall acceptability was high among both women and their male partners [18]. The ability for women to use a microbicide without her male partner's knowledge was perceived to be an important characteristic by women [18]. However, some men expressed less favorable attitudes regarding microbicides being a woman-initiated product [18].

An additional study examined the acceptability of a vaginal ring to continuously deliver microbicides via a mixed-methods design among HIV-negative, sexually active women and their male partners [21]. The majority of women (69%) reported high levels of interest in trying the vaginal ring and liked the possibility that the ring could prevent HIV and not interfere with sexual activity [21]. However, some (20%) noted concerns that the ring would get lost inside the body, and 10% endorsed concerns that the ring would come out [21].

Lastly, three papers reported on the acceptability of a tenofovir gel microbicide [22–24]. In a study comparing tenofovir gel versus a placebo microbicide, 97.4% of the female South African participants found tenofovir gel to be acceptable, with 97.9% indicating that they would use the gel if it prevented HIV [22]. Similarly, in a Phase I trial of tenofovir gel with HIV-negative U.S. women, 94% reported they would either "definitely" or "probably" use

the gel if found to be effective [23]. Additionally, 81% of participants' male partners indicated they would use the gel if found to be efficacious [23]. The majority of women (79%) and men (76%) also endorsed liking the gel [23]. Lastly, in a Phase I trial of tenofovir gel, a mixed-methods study examined the microbicide's acceptability among both HIV-uninfected and HIV-infected women [24]. Overall, quantitative acceptability ratings were high, with 94% of participants indicating they would either definitely or probably use the gel [24]. During qualitative interviews, the physical characteristics of the product were found to be acceptable (e.g., color, odor), but participants noted dissatisfaction with gel leakage [24]. Most participants (90%) reported that the gel increased her sexual pleasure, with 86% noting that the gel increased her male partner's sexual pleasure; a majority of participants reported a desire to use the gel in combination with condoms [24]. Additionally, most participants preferred a gel that would not be noticeable to their male sexual partners [24].

Microbicide acceptability: Measurement and study design issues—As noted in our review and reviews conducted by Mantell and colleagues [12] and Morrow and Ruiz [25], the bulk of studies investigating microbicide acceptability have focused on product formulation features or physical characteristics (e.g., texture, viscosity). Across studies there is a lack of consensus regarding the definition and operationalization of microbicide acceptability [12]. Acceptability has often been conceptualized as either hypothetical intention to use a future product or actual product usage [18, 25]. However, studies investigating broader, theoretically-driven constructs of relevance to microbicide acceptability (e.g., social and cultural norms relevant to microbicide use, partner acceptability) have been less common throughout all phases of microbicide development and testing [12, 25]. Further, as suggested by Morrow and Ruiz, there is a need for well-designed mixed methods' studies of microbicide acceptability [25]. Such studies should also account for study conditions when assessing the acceptability of microbicides; for example, in trials where condoms in conjunction with microbicide use is the recommended practice, acceptability should be assessed in light of these relevant study design features [25].

PrEP

Pre-exposure prophylaxis (PrEP) is the use of ARV medications by HIV-uninfected individuals before HIV exposure [26]. The U.S. Food and Drug Administration approved Truvada® (emtricitabine/tenofovir disoproxil fumarate) in 2012 as an HIV prevention method to be used in combination with safer sexual practices [27]. PrEP treatments using tenofovir disoproxil fumarate and emtricitabine/tenofovir disoproxil fumarate have demonstrated efficacy to prevent HIV among high-risk groups including serodiscordant heterosexual couples [28], heterosexual men and women [29], and MSM and transgender women [30]. However, in the FEM-PrEP trial of oral PrEP (emtricitabine/tenofovir disoproxil fumarate) with HIV-uninfected at-risk women in Kenya, South Africa, and Tanzania the trial was halted before completion due to equivalent HIV incidence between study arms [31]. Furthermore, in the FEM-PrEP trial, adherence was poor with less than 40% of the sample demonstrating recent PrEP use [31]. Despite the promise of PrEP, poor adherence underscores the need to better understand factors affecting the acceptability, uptake, and adherence to PrEP. Thus, in the following sections, we highlight studies exploring factors associated with oral PrEP acceptability.

PrEP acceptability: Review of measurement issues—A recent review examined the way in which acceptability was measured in both PrEP and treatment-as-prevention studies [26]. Within PrEP trials, acceptability was typically measured via individual adherence rates [26]. Additionally, four studies operationalized acceptability as willingness to take PrEP [26]. Eight studies focused on a multi-dimensional assessment of PrEP acceptability including factors such as access, perceptions of HIV risk, stigma, and willingness to use PrEP, among others [26]. Qualitative acceptability studies assessed an even broader array of constructs including perceived HIV transmission risk, safer sex beliefs, cost concerns, access concerns, potential side-effects, desired PrEP information, and the role of regular HIV testing [26]. This review highlights the diversity by which PrEP acceptability has been measured. In what follows we briefly review studies examining PrEP acceptability for both future potential products and also during randomized controlled PrEP trials.

Acceptability of future potential PrEP use—The acceptability of oral PrEP for future potential use has been assessed predominantly among MSM [13, 32–36] or gay or bisexual men in serodiscordant couples [37, 38]. Additional studies have explored the acceptability of potential future PrEP use among other at-risk populations [39–41] or among African-American adults [42] and adolescents [43]. Two studies assessed PrEP acceptability among HIV healthcare providers [44, 45].

Among MSM in Seattle PrEP acceptability was assessed among men attending either a Gay Pride event or an STI clinic [32]. Only 2% endorsed current PrEP use, with 22% stating that they knew of other MSM taking PrEP [32]. 44% reported that they would take PrEP daily if it would prevent HIV, 31% stated they would not take PrEP, and 20% were undecided [32]. Correlates of willingness to take PrEP included an income below \$15,000, younger than 40 years of age, and being recruited via the STI clinic [32]. A second study of U.S. MSM examined PrEP use intentions [33]. Almost three-quarters (74%) of participants endorsed PrEP use intentions; factors associated with PrEP use intentions included less education, moderate income, no perceived side effects, and PrEP being made available for free [33].

A sample of HIV-uninfected U.S. MSM assessed their likelihood for using PrEP and potential risk compensation behaviors [34]. Overall, 70% of participants reported willingness to use PrEP if it was at least 80% effective [34]. Correlates of increased likelihood of use included being Black, increased engagement in HIV risk behaviors, and substance-related sexual risk behavior [34]. Among those indicating a desire to use PrEP, 35% reported that they would decrease their condom use [34].

A qualitative study of MSM who engage in unprotected anal sex was conducted to examine knowledge and acceptability of PrEP and other biomedical HIV prevention approaches [13]. Overall, participants had little PrEP knowledge and acceptability of PrEP was mixed [13]. Participants identified potential PrEP benefits as providing HIV protection in serodiscordant relationships; however, participants identified a number of possible negative attitudes including concerns about side effects and efficacy [13].

Among a sample of MSM and male sex workers, a qualitative study explored the acceptability of PrEP in light of FDA approval [35]. While participants endorsed having

little prior knowledge of PrEP, a majority endorsed willingness to use PrEP, citing potential barriers to use as cost and access to prescribing clinicians [35]. FDA approval was perceived as an important endorsement for PrEP's use and enhanced PrEP's acceptability [35]. However, other participants noted that other sources of information (e.g., physician recommendation, medical publications) were more critical than FDA approval to enhance PrEP acceptability [35].

Another study with MSM in France examined factors associated with willingness to participate in a future trial of PrEP usage "on-demand" (i.e., taking PrEP a few hours before potential HIV sexual exposure and a second dose a few hours later) [36]. Overall, 40% of participants were interested in participating in a potential future trial [36]. Factors associated with willingness to participate included lower educational level, self-reporting a greater number of casual sexual partners, endorsing greater frequency of unprotected sexual encounters, and providing PrEP in a convenient geographic location [36].

Two studies examined PrEP acceptability among gay and bisexual men in serodiscordant relationships [37, 38]. Motivating factors for PrEP usage included a desire to prevent HIV, lower concerns and fears related to HIV transmission, the ability to engage in unprotected sex, and belief in PrEP's effectiveness [37]. Barriers to PrEP use included cost, short- and long-term side effects, potential adverse effects for incomplete adherence, and limited accessibility [37]. In a second study, participants noted high overall acceptability and willingness to use PrEP [38]. Factors associated with PrEP acceptability included the ability to engage in unprotected sex with an HIV-infected partner, protection from HIV, and decreased anxiety when engaging in sex with an HIV-infected partner [38]. Additionally, 64% indicated that they would increase their HIV risk behaviors and 60% reported they would decrease their condom use if using PrEP [38].

Another study examined willingness to use PrEP and PrEP acceptability among individuals at elevated HIV risk in seven countries (Peru, Ukraine, India, Kenya, Botswana, Uganda, South Africa) [39]. Overall willingness to use PrEP was high with 61% indicating they "definitely" would use PrEP and 31% indicating they "probably" would use PrEP; a slight majority (52%) indicated they would disclose PrEP use to a partner [39]. Participants reported willingness to use PrEP even if there were associated side effects, costs and would require combined condom use or being regularly tested for HIV [39]. Correlates of increased likelihood to use PrEP included: past medication adherence, being female, being younger, having fewer children, condom use in the past month, past HIV testing experience, and no current injection drug use [39].

In a sample of MSM, female sex workers, and male-to-female transgendered individuals in Peru, focus groups examined factors that would influence PrEP acceptability [40]. While there was general support for PrEP use, potential barriers to PrEP use included costs, PrEP efficacy, possible side effects, sexual risk disinhibition, potential experiences of stigma and discrimination, and mistrust of healthcare professionals [40].

A study of young truck driving males in India assessed the acceptability of three biomedical HIV prevention approaches: HIV testing, circumcision, and PrEP [41]. PrEP was found to

be acceptable to 85.9% of the sample [41]. In multivariate analyses, correlates of PrEP acceptability included having a social network supportive of PrEP and having a history of prior sex with female sex workers [41].

One study examined the association between HIV risk behavior engagement, perceived HIV risk, and PrEP interest among a sample of African Americans attending an STI clinic [42]. Taking a single dose before sex was the most acceptable form of PrEP (77%), followed by a weekly PrEP dosage (76%) and taking a single dose 1 day before sex (75%); a daily PrEP dosage was least acceptable (63%) [42]. Further, participants indicated decreased PrEP interest due to current safer sex practices, concerns about side effects, and likelihood for low adherence [42]. 20% also indicated they would use condoms less frequently if taking PrEP and 7% reported they would not use condoms at all if taking PrEP [42].

PrEP attitudes were examined among a sample of African-American, urban dwelling adolescents [43]. Overall acceptability of PrEP was high, particularly if it was made available at no or little cost and was highly effective [43]. Participants also found the need for routine HIV testing on a regular basis to be an acceptable practice [43]. Factors that would enhance uptake and use of PrEP included convenient access through health department clinics, pharmacies, or other venues that were easily accessible via public transportation [43]. Barriers to PrEP usage included potential side effects, high medication cost, partial effectiveness, low perceived HIV risk, potential negative peer reactions, burden associated with a daily medication, beliefs that PrEP would be for MSM only, and concerns about potential increases in HIV risk behaviors as a form of risk compensation [43].

Two studies examined PrEP acceptability among HIV healthcare providers [44, 45]. Only 19% of those surveyed had prescribed PrEP, with the majority prescribing PrEP to MSM and individuals in serodiscordant relationships [44]. Providers noted concerns associated with ARV resistance and poor adherence along with the potential for increased engagement in HIV risk behaviors [44]. In a second mixed-methods study of Italian HIV healthcare specialists, providers noted a number of concerns including duration of PrEP use, potential side effects and toxicity, ARV resistance, difficulties monitoring adherence, and the possibility of increased prevalence of other STIs [45]. In addition, providers noted concerns that funding for PrEP could adversely affect the availability of funds for HIV-infected individuals using ARVs [45]. Providers disagreed about the optimal population for PrEP, but suggested that HIV-uninfected individuals in serodiscordant couples would be a key target population rather than individuals reporting high rates of sexual risk behavior because of fears of increased risk compensation [45]. Quantitative findings indicated that 30% would not prescribe PrEP; among those expressing a willingness to consider prescribing PrEP, 81% would provide PrEP to at-risk individuals under some circumstances and 93% would prescribe to serodiscordant partners [45]. Providers also endorsed greater acceptability for HIV prevention methods other than PrEP including greater HIV testing access, HIV care, and behavioral HIV prevention interventions [45].

PrEP acceptability in randomized clinical trials—As part of actual PrEP trials, several studies report on PrEP acceptability. In the PrEP trial of tenofovir disoproxil fumarate among women in Ghana, adherence and PrEP acceptability were examined using a

mixed-methods design [46]. Across the 12-month trial, the average self-reported adherence level was approximately 82% or greater [46]. In qualitative interviews with a subset of participants, acceptability was adversely affected by the experience of physical symptoms and challenges associated with consistent PrEP adherence [46]. For some of the women, a desire for privacy when taking PrEP was also identified as being important [46].

PrEP acceptability was qualitatively assessed in a Phase I trial among MSM and female sex workers in Kenya [47, 48]. Overall, PrEP acceptability was high, particularly if shown to be highly efficacious, safe, and available at little or no cost [47, 48]. Further, participants identified the self-controlled nature of PrEP as appealing, particularly for individuals whose partners did not want to use condoms [47]. Additionally, some noted that PrEP may be more acceptable among certain cultures or religious faiths relative to other HIV prevention methods [47]. In contrast, participants reported dissatisfaction with physical characteristics of the PrEP pill including its large size, irregular shape, and blue color which at times discolored one's mouth [47]. Participants also noted experiencing a variety of side effects, especially during the early phases of use, that dampened their overall enthusiasm for PrEP and in some instances decreased their adherence [47].

Among serodiscordant heterosexual couples enrolled in a PrEP clinical trial, the study investigated couples' preferences for either early ARV initiation by the HIV-infected partner relative to PrEP usage by the HIV-uninfected partner [49]. A majority of uninfected men and women indicated willingness to use PrEP [49]. Among the subset of participants unwilling to use PrEP, concerns included the need for 5 years of medication, potential side effects, a desire to use medication only when sick, and drug fatigue [49].

A qualitative study during a PrEP Phase III trial with African serodiscordant couples examined factors associated with PrEP adherence and acceptability [50]. Participants identified PrEP as a valuable resource providing a source of hope to prevent HIV, particularly given the heightened transmission risks posed by HIV-infected partners [50]. Participants cited their motivation to adhere to the PrEP regimen, despite often experiencing logistical challenges (e.g., traveling long distances for PrEP) [50]. Participants also cited social support provided by family, partners, and research study staff to be particularly important to enhance PrEP adherence [50].

Among a sample of Ugandan, HIV-uninfected individuals in serodiscordant relationships, 99% of participants stated that they would use PrEP if shown to be safe, effective, and available at little or no cost [51]. There were no differences in acceptability levels between the study conditions of daily versus intermittent PrEP usage [51].

In a PrEP trial with sexually active, HIV-infected individuals in South Africa, Uganda, and the U.S., the acceptability of oral PrEP tablets, vaginal PrEP gels, or both were examined [52]. Across sites, oral PrEP, if found to be effective, was the most acceptable mode of administration [52]. Differences by study site emerged in the acceptability of PrEP formulations with greater acceptability of multiple PrEP formulations in South Africa and Uganda and greatest oral PrEP acceptability among the U.S. participants [52].

HIV Vaccination

Since the early years of the HIV epidemic, research devoted to the development of a safe and efficacious vaccination to prevent HIV has been underway. Unfortunately, there has been limited evidence for an efficacious HIV vaccine [53]. Further, the development of a safe and efficacious HIV vaccine does not guarantee that it will be acceptable by individuals at elevated HIV risk and also by the broader population. As observed with other available vaccines, availability of an efficacious vaccine does not guarantee high uptake. Thus, an examination of factors associated with HIV vaccine acceptability is essential for future intervention efforts should a safe and efficacious vaccine become available. Assessment of HIV vaccine acceptability has typically focused on factors related to either participation in a future potential HIV vaccine trial or actual trial participation as illustrated by the following review.

Summary of previous reviews of HIV vaccination acceptability—A review conducted by Dhalla and colleagues examined motivating factors associated with participation in a HIV vaccination preparedness study in both developed and underdeveloped nations [54]. Social benefits of participation, particularly altruism, a desire to help one's community or others, or assist with efforts to find an efficacious vaccine were cited as key factors motivating study participation [54]. In addition, personal benefits including potential HIV protection, a desire to reduce personal HIV risk behaviors, and a desire for the study's monetary incentives were also cited as factors associated with participation in HIV vaccine preparedness studies [54].

A second review examined core themes of willingness to participate in an HIV vaccine trial [55]. The authors identified six key themes across the reviewed studies: (a) safety concerns (e.g., vaccine-induced seropositivity, insufficient efficacy); (b) fear or mistrust of the government, researchers, and/or pharmaceutical companies; (c) concerns or misunderstandings about the study's methodology (e.g., not fully understanding randomization and/or placebo conditions); (d) concerns about discrimination or stigmatization; (e) practical obstacles (e.g., insurance concerns, busy daily schedules); and (f) other concerns (e.g., dislike of needles) [55]. Additionally, in the quantitative studies reviewed, key barriers included concerns about vaccine safety and discrimination and stigmatization [55].

Lastly, a meta-analysis of HIV vaccine acceptability was conducted across 20 studies [56]. On an acceptability scale from 0 to 100%, the average acceptability rating was 65.6% [56]. The meta-analysis also compared the acceptability of potential vaccines varying possible vaccine efficacy, high versus moderate efficacy; high vaccine efficacy and belonging to a group at low HIV risk were associated with medium acceptability effect sizes [56]. Small effect sizes for HIV vaccine acceptability were identified for cost, perceived HIV susceptibility, side effects and safety concerns, vaccine fears, perceived vaccine benefits, duration of vaccine protection, and individuals' ethnicity, with African American ethnicity associated with lower vaccine acceptability [56].

HIV vaccine acceptability assessed via willingness to participate in future potential HIV vaccine trials—

HIV vaccine acceptability has been assessed via willingness to participate in future potential HIV vaccine trials among samples of South African [57, 58] and U.S. [59] adolescents, U.S. undergraduate students [60–62], Canadian Aboriginal individuals [63], Thai immigrants to the U.S. [64], MSM in China [65], and MSM and transgendered individuals in Thailand [66]. Additional studies have examined HIV vaccine acceptability among other at-risk, ethnically diverse samples of U.S. men and women [67–71].

A study of South African adolescents assessed motivating factors and barriers to participation in a potential HIV vaccine trial [57]. Motivating factors included a desire to protect oneself and their loved ones, community, and the broader global community from HIV [57]. Barriers included concerns about potential vaccine side effects and worries that vaccination might increase HIV acquisition [57]. Overall, 42% of adolescents reported they would accept an HIV vaccine if one was available and efficacious, while 8% said they would not accept a vaccine, and 50% were unsure [57].

A second qualitative study of South African adolescents assessed barriers and motivators to future HIV vaccine uptake [58]. Barriers included cost, possible adverse side effects, lack of perceived HIV vulnerability, HIV testing fears and associated stigma, negative community HIV attitudes, mistrust of government and science, potential HIV vaccination stigma, and a preference for traditional African healing practices rather than vaccination [58]. In contrast, a core motivating factor was a desire for HIV protection, particularly when transmission risk was outside an individual's personal control (e.g., partner infidelity) [58]. Motivating factors noted by women included a desire to raise a family, while young men wanted to engage in unprotected sexual encounters with multiple partners [58]. Additionally, youth identified that support from the broader community, media, and government would enhance motivation and uptake of a future HIV vaccine [58].

A third study examined the acceptability of a future HIV vaccine among a sample of U.S. adolescents [59]. Adolescents were asked to compare two hypothetical vaccines, one with 50% efficacy and another with 90% efficacy [59]. The lower efficacy vaccine was deemed to be unacceptable; however, adolescents reported that the higher efficacy vaccine could result in increased HIV risk behavior engagement [59].

Among a sample of U.S. undergraduate students, the association between Health Belief Model constructs and HIV vaccine acceptability was examined [61]. Approximately 65% endorsed high levels of overall HIV vaccine acceptability [61]. Correlates of HIV vaccine acceptability included younger age, greater perceived HIV vulnerability, greater perceived HIV vaccination benefits, fewer perceived barriers to HIV vaccination, lower HIV vaccine fears, lower perceived HIV vaccine stigma, and non-membership in an HIV high-risk group [61]. Additionally, this study examined vaccination characteristics of efficacy, cost, and the percentage of the population vaccinated as potential factors that would affect acceptability [60]. Overall, a vaccine with 80% efficacy, that was free, and had been received by 90% of the population was deemed to be most acceptable, while more expensive, less efficacious

vaccines that had been received by a small minority of the population were least acceptable [60].

A second study of U.S. undergraduates examined factors associated with acceptability for a hypothetical HIV vaccine [62]. On a scale from 0 to 100%, the mean acceptability for a hypothetical vaccine was 70.2% [62]. In a multivariate analysis, younger age, lower cost, greater HIV-related concerns, and a higher number of lifetime sexual partners were associated with greater acceptability [62]. However, perceived HIV invulnerability was associated with decreased vaccine acceptability [62].

Another qualitative study examined motivating factors and barriers to HIV vaccination among a sample of Canadian Aboriginal individuals [63]. A motivating factor was the desire to reduce HIV incidence and morbidity among the community [63]. However, HIV vaccine stigma, sexual orientation stigma, cost, lack of HIV vaccine information, pessimism regarding successful HIV vaccine development, mistrust of pharmaceutical companies, government, and the healthcare establishment and concerns about HIV acquisition via the vaccine were core factors associated with decreased acceptability [63]. Additionally, a general mistrust of western medical practices versus traditional medical practices was identified as a potential barrier to HIV vaccine acceptability [63]. Moreover, a vaccine that did not have 100% efficacy was perceived as less desirable and the overall efficacy level would affect acceptability [63].

A mixed methods study examined HIV vaccine acceptability among a sample of immigrant Thai residents in the U.S. for eight different possible vaccine profiles [64]. Participants identified that efficacy, physical side effects, and costs were the key factors that influenced vaccine acceptability [64]. Specifically, participants reported the need for a vaccine with high level of effectiveness (> 70%), general optimism about a potential vaccination, and trust in the government and research community as key motivating factors to enhance acceptability [64]. However, significant physical side-effects, high vaccine cost, and general fears about biomedical products and vaccinations were prominent barriers to acceptability [64]. Participants also noted some potential negative consequences should a vaccine become available; for example, some participants noted concerns that individuals would increase their engagement in HIV risk behaviors [64].

Another mixed-methods study with Chinese MSM investigated factors associated with willingness to participate in a potential future HIV vaccine trial [65]. The majority (71%) reported willingness to participate in a future trial and identified several potential benefits including receipt of HIV-related information, study-related incentives, free HIV testing and counseling, and enhanced motivation to reduce HIV risk behaviors [65]. However, participants voiced potential concerns including fears of contracting HIV and worries about how others would perceive them [65]. Multivariate analyses indicated that enhanced family support, HIV protection, and decreased stigma concerns increased willingness to participate in a potential future HIV vaccine trial [65].

A mixed-methods study examined HIV vaccine acceptability among a sample of Thai MSM and transgendered individuals [66]. Overall mean acceptability (rated from 0 to 100) was

73.8 [66]. Factors associated with lower acceptability included vaccine-induced HIV seropositivity, efficacy concerns, potential side effects, limited duration of vaccine protection, cost, and limited social and community support for the vaccine [66]. Participants indicated that they would engage in risk compensation behaviors (i.e., increasing HIV risk behaviors as a result of receiving the vaccine) if a highly efficacious vaccine were to become available [66].

Another study examined potential gender differences and vaccine characteristics that may affect HIV vaccine acceptability among an ethnically diverse, at-risk U.S. sample [67]. Overall mean acceptability (rated from 0 to 100) was 61 for men and 56 for women, with no difference by gender [67]. Efficacy of the proposed vaccine, protection against multiple HIV strains, and experiencing few side effects had the greatest impact on acceptability [68]. Gender-stratified analyses examined potential barriers to HIV vaccine acceptability [68]. Women noted concerns about their ability to secure health insurance due to possible vaccine-induced seropositivity, feared male partner reactions, and previous discrimination by health care workers as core barriers [67]. For men, core barriers to HIV vaccine acceptability included concerns that a vaccine would adversely impact their immune system or affect HIV test results [67]. In contrast, motivating factors for both men and women included family support of the vaccine and feeling safe with their sexual partners [67]. Men also endorsed that having friends supportive of the vaccine would increase HIV vaccine acceptability [67].

A qualitative study with women at increased HIV risk in Los Angeles examined barriers and motivating factors for a future HIV vaccination [69]. For barriers, women expressed concerns that a vaccine could result in HIV acquisition, would adversely affect future reproductive health, and that the use of syringes or injections could be a potential trigger for former injection drug users [69]. In addition, women noted that gender roles (e.g., caretaking for children) and concerns about partner reactions could also serve as barriers to HIV vaccine acceptability [69]. Furthermore, vaccination cost, mistrust of the government and scientific community, HIV stigma and the potential for experiencing discrimination based on vaccination were also barriers [69]. In contrast, a desire for HIV protection and the ability to normalize HIV vaccination as part of routine medical care were seen as factors that would increase vaccine acceptability [69].

One innovative qualitative study examined the association between willingness to participate in an HIV vaccine trial and HIV vaccine acceptability among an ethnically diverse U.S. urban sample [70]. Barriers that were common to both willingness to participate in an HIV vaccine trial and HIV vaccine acceptability included fear of vaccine-induced HIV acquisition, false-positive HIV tests, potential side effects, partial vaccine efficacy, general mistrust of the government and pharmaceutical companies, low perceived HIV risk, HIV stigma, and relationship concerns [70]. A common motivating factor was a desire for HIV protection [70]. Unique barriers for willingness to participate included uncertain vaccine properties and overall study demands; motivators included altruistic attitudes, free medical care/insurance, and monetary incentives [70]. For vaccine acceptability, barriers included short duration of vaccine effectiveness, cost, access, and inability to protect against multiple HIV strains; motivators for HIV vaccine acceptability

included a desire to engage in unprotected sex, endorsement of the vaccine by reputable sources, and the potential to improve overall health [70].

A qualitative study examined willingness to participate in an HIV vaccine trial by MSM in San Francisco, injection drug users in Philadelphia, and African Americans in Durham, NC [71]. Approximately 46% of participants indicated they would volunteer for such a trial, 41% would not volunteer, and 13% were undecided [71]. Participants identified a number of potential risks associated with participating in such a study including adverse side effects, concerns about vaccine safety, vaccine-induced seropositivity, and experiencing social stigma [71]. However, participants also identified a number of potential benefits from participation including potential health improvements, financial compensation, a desire to curb the HIV epidemic, and altruistic beliefs regarding the potential impact on the broader community or society at large [71].

In a sample of U.S. ethnic minority individuals in Los Angeles, focus groups were conducted to assess barriers and motivating factors of willingness to participate in an HIV vaccine trial [72]. Barriers to participation included: (a) concerns of vaccine induced HIV infection; (b) physical side effects; (c) uncertain vaccine efficacy; (d) unknown vaccine characteristics; (e) mistrust; (f) low perceived HIV risk; (g) study demands; (h) stigma; and (i) vaccine-induced HIV seropositivity [72]. Factors motivating participation included: (a) desire for protection against HIV; (b) potential free health insurance or medical care; (c) altruistic beliefs related to participation; and (d) provision of monetary incentives [72].

HIV vaccine acceptability via willingness to participate in a Phase 2 or Phase 3 vaccine trials—Two studies examined HIV vaccine acceptability among participants in either a Phase 2 [73] or Phase 3 [74] vaccine trial. In one study, individuals previously enrolled in an HIV preparedness study were contacted regarding their willingness to participate in a Phase 2 vaccine trial [73]. Thus, the study examined the relationship between hypothetical and actual willingness to enroll in an HIV vaccination trial [73]. Of those who stated their hypothetical willingness to participate in a subsequent HIV vaccination trial, only a small minority actually enrolled in the Phase 2 trial [73]. Correlates of Phase 2 study participation refusal included being African American, being less than 40 years of age, not attending college, and having fewer than 5 sexual partners in the past 6 months [73]. Additionally, concerns about vaccine-induced seropositivity were noted along with specific concerns voiced by African American individuals related to government mistrust and vaccine safety [73].

A second study assessed HIV vaccine acceptability via the reasons provided for enrolling in a Phase 3 HIV vaccine trial [74]. Participants cited altruistic reasons as their primary motivator for joining the study [74]. Additionally, approximately half noted desires for HIV protection and reductions in their HIV risk behaviors as motivating factors for joining the study [74].

Optimization of Combination HIV Prevention Approaches

With the advent of efficacious biomedical prevention strategies such as PrEP, there is now a growing array of HIV prevention approaches available. However, as described in the

preceding review, not all biomedical HIV prevention approaches have demonstrated efficacy and myriad factors may affect their acceptability, uptake, and dissemination among at-risk populations. Additionally, strategies to effectively integrate biomedical modalities with behavioral interventions are lacking. Thus, future HIV prevention approaches need to address both behavioral HIV risk behaviors and incorporate efficacious biomedical modalities.

A concern raised through the development of biomedical HIV prevention methods is the potential negative impact on behavioral HIV prevention methods including condom use [75]. Thus, risk compensation is a concern for the future of combination behavioral and biomedical HIV prevention approaches. For example, in a study with gay and bisexual men in serodiscordant couples, the majority indicated they would increase their sexual risk practices and decrease condom use if taking PrEP [38]. Further, in the case of microbicide trials, there has been debate regarding inclusion of a trial arm where participants only use condoms [10, 75]. However, since consistent condom use among high HIV prevalence regions is often low (e.g., 29.1% consistent condom use at baseline among South African women in the CAPRISA-004 trial [76]), combining biomedical and behavioral HIV prevention strategies may be the optimal strategy to reduce incident HIV infections. Thus, future intervention efforts should consider strategies to aid individuals' selection from the menu of available HIV prevention options [12] with consideration of a variety of factors including the overall efficacy of the method to prevent HIV, acceptability of the method, relevant relationship characteristics, and sexual practices, among others. Biomedical HIV prevention approaches should ideally be part of a comprehensive HIV prevention approach including HIV testing, monitoring of biomedical product safety, behavioral strategies to reduce HIV risk behaviors and potential risk compensation behaviors, monitoring and treatment of side effects, and structural interventions to increase widespread dissemination and scale-up of interventions [77]. However, the implementation science for combination HIV prevention approaches is lacking [77].

Use of CDC identified efficacious behavioral HIV prevention interventions [7], particularly those designed for use with clinic populations may be optimal behavioral strategies that can be integrated with the provision of biomedical HIV prevention approaches [78]. Such behavioral approaches will likely be essential to reduce risk compensation practices that may increase HIV risk [78]. Further, as suggested by Curran and Crosby, use of booster behavioral sessions or intervention approaches to bolster HIV preventive behaviors will be important to incorporate and evaluate in combination HIV prevention intervention approaches [78]. Further, application of strategies for the implementation, dissemination, and widespread uptake of efficacious combination prevention approaches will be critical to increase public health impact [77, 79]. As identified in the above reviewed literature, there are a number of potential challenges associated with the widespread dissemination of biomedical HIV prevention approaches including cost, optimal HIV/STI testing frequency, monitoring strategies, and the potential for behavioral risk compensation [79]. Moreover, there is a need to optimize adherence to biomedical HIV prevention options as they become available. For example, inconsistent adherence to an ARV-based vaginal microbicide product could potentially result in ARV resistance on the part of the user and increased HIV

transmission risk to one's partner [80, 81]. Furthermore, in the PrEP efficacy trials, adherence was correlated with PrEP efficacy [78, 82].

In addition, targeting populations at highest risk for HIV will be important for combination HIV prevention approaches. However, some biomedical HIV prevention approaches have encountered challenges enrolling populations experiencing increased HIV prevalence. For example, Mills and colleagues [83] identified potential barriers that could adversely impact enrolling women into HIV vaccination trials including concerns about subsequent pregnancy, negative consequences within one's relationship, and other forms of discrimination. Thus, there is a need for use of optimal behavioral strategies in the design and implementation of biomedical trials to ensure individuals at particular risk are included in the evaluation of biomedical prevention approaches that can subsequently be integrated with efficacious behavioral prevention strategies.

Despite the promise of combination prevention approaches, a limited number of randomized controlled trials have been conducted. In one such trial, a small cohort of young MSM (N=68) were randomized to one of three conditions: (a) a behavioral HIV prevention alone condition (Many Men, Many Voices: 3 MV); (b) 3 MV + tenofovir/emtricitabine; or (c) 3 MV + placebo medication [84]. Across the 24 weeks of follow-up assessment, there was no difference between the three groups in the frequency of unprotected anal sex with all three groups decreasing their frequency of unprotected anal sex [84]. Additionally, plasma detectable tenofovir levels steadily declined across the course of the trial suggesting concomitant declining adherence over time [84]. To evaluate the efficacy of combination prevention approaches, additional randomized controlled trials are urgently needed. Additionally, for combination approaches with demonstrated efficacy, strategies to broadly implement and disseminate such interventions offer the potential to further reduce the prevalence of new HIV infections. Further, there is a need to consider factors that would affect widespread dissemination when a particular biomedical HIV prevention approach is included in a combination prevention program [70, 85]. As identified by others, there are a number of challenges that may adversely impact widespread dissemination of biomedical HIV prevention methods including access, cost, provider and patient comfort discussing these methods, and need for ongoing maintenance and monitoring [85].

There is also a paucity of research investigating medical providers and other stakeholders' acceptability of biomedical HIV prevention approaches. Since providers will be instrumental in the provision and recommendation of these products when they are available for use [12, 86], greater understanding of providers' knowledge and acceptability for biomedical HIV prevention methods is essential in future research efforts. Further, there is a need for providers to have clear recommendations for best practices in the management of biomedical HIV prevention technologies that also incorporate behavioral HIV prevention strategies [81]. Such guidelines should also consider routine screening for HIV and other STIs along with monitoring of relevant side effects (e.g., toxicity) [78]. Additionally, assessing the acceptability of combination prevention programs by key community stakeholders may influence their acceptability and uptake in the communities they serve.

Conclusions

There is a need to consider how acceptability data from biomedical HIV prevention approaches at various stages of development may affect uptake and adherence to those methods as they become available. For example, Buchbinder and colleagues [73] identified younger, ethnic minority individuals, and those reporting lower HIV risk behaviors as less likely to enroll in an HIV vaccine trial. Thus, behavioral intervention strategies to increase use of specific biomedical HIV prevention approaches may need to be tailored to specific populations. Use of theory-informed behavioral interventions could be particularly effective to address health-related beliefs that may adversely affect the acceptability and uptake of these methods. Furthermore, hypothetical willingness to use a biomedical product or engage in a study trial may not translate to actual uptake and use of the product and/or willingness to participate in a trial for a given biomedical prevention approach.

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