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Acceptability in Microbicide and PrEP Trials: Current Status and a Reconceptualization

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Abstract

Purpose of Review—Assessment of acceptability is a central component of most oral PrEP and microbicide trials. In this paper we review current definitions and frameworks employed in acceptability research, discuss findings from recent studies of product acceptability and summarize trends in acceptability research. We conclude by offering a new framework for investigating product acceptability within clinical trials, one which considers product acceptability to be conceptually distinct from adherence.

Recent Findings—While numerous studies have investigated product acceptability, a consensus is lacking regarding the definition and operationalization of the concept. In addition fewer than half of the studies reviewed investigated actual candidate products. To the extent that an overall measure of acceptability is considered, the consensus is that most participants find the products acceptable. However, it is the rare study that investigates whether product adherence is associated with acceptability.

Summary—Given the critical role of adherence to the success of clinical trials, it is important to identify the extent to which acceptability is a factor in product usage and to ascertain which dimensions of acceptability — product attributes, dosing regimen, delivery mechanism, use attributes, partner's attitudes, effect of product on the sexual encounter, product-related norms — if any, affect adherence.

Keywords

Acceptability; microbicide; PrEP; adherence

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Conflicts of Interest

In selecting papers of special interest, authors did not vote on their own work. There are no other conflicts of interest.

Introduction

Assessment of acceptability is a central component of most PrEP and microbicide trials. It stands to reason that many participants will not be adherent to product use during the course of a trial, nor will many of those at risk of HIV use the product when it becomes available if it is considered unacceptable. However, while numerous PrEP and microbicide studies have investigated product acceptability, a consensus regarding the definition and operationalization of the concept does not exist [1, 2]). A theoretical muddiness plagues discussions and investigations of acceptability as many researchers equate acceptability with use and focus studies that investigate acceptability on identifying factors that motivate or undermine use. Indeed, a recent review paper considered use-associated factors, and willingness to use in the future, key elements in an “integrated” approach to acceptability [3]. The observation from contraceptive research that perceived method attributes are only weakly predictive of product use [4] and the finding in a study of barrier methods and STD prevention, that acceptability — measured either as hypothetical willingness to use or as product satisfaction — was not associated with subsequent method use [5], may also have contributed to some skepticism regarding the utility of measuring acceptability rather narrowly and to the incorporation of product usage in recent definitions. In this paper we will review current definitions and frameworks employed in microbicide and PrEP acceptability research. We will then examine recent empirical studies that include assessments of product acceptability —variously operationalized— and will summarize trends in acceptability research based on 18 papers (from 15 unique studies) published in 2011 and 2012. We are focusing primarily on studies where the product is a drug or chemical barrier, whether actual or hypothetical, although the issues we discuss apply to acceptability of physical barrier methods as well. We will conclude by offering a new framework for investigating product acceptability within clinical trials, one which avoids the inherent circularity of current definitions and considers product acceptability to be conceptually distinct from adherence.

Current definitions and frameworks

Fifteen years ago, in an attempt to “re-orient” research on contraceptive choice, Heise [4:p. 7] argued that acceptability is not a feature “inherent in a product or a method” that could be adjusted if it is lacking; rather it is “relative, conditional and user-driven.” She considered acceptability to be an “interplay” between the user, the technology, the service delivery system and the social environment. Context —type of partnership (primary or casual), nature of relationship (new or established), and gender-power dynamics — mattered. This conceptualization has influenced behavioral and social scientists involved in microbicide acceptability research: Elias and Coggins [6] posited that acceptability is more than just the “method continuation rate,” and broadened their definition to include the knowledge regarding potential benefits, correct usage, potential side effects and alternative products. Equally important is the service delivery system, that is, “whether and how the product is provided to potential users” [6:p.164]. In 2005, Severy and Newcomer [7:p.49] argued for “a sense of acceptability demonstrated by long-term use,” noting that use depends on product characteristics, (which will affect individuals differently across cultures), partner dynamics, and other actors including family members and health care providers. Their definition of

acceptability — “the voluntary sustained use of a method in the context of alternatives” — still prevails today. Severy and his colleagues [8:p.127] subsequently proposed an “expanded framework” for assessing acceptability, one that re-conceptualized sustained acceptability as a dynamic and sequential process, and incorporated a leading behavior change theory, the AIDS Risk Reduction Model [9, 10]. Their framework also goes beyond product attributes to identify the “individual, couple and socio-cultural factors that make [sustained] use possible.” More recently, Woodsong and Alleman [11] developed a framework for clinical trials that views acceptability as “a continuum of behavioral and attitudinal changes” strongly influenced by context. It has been applied and adapted in several qualitative inquiries in clinical research, for different types of products and delivery modes [12*, 13*, 14]. The most recent conceptual model of microbicide acceptability, developed by Coly and Gorbach [2], emphasizes stages of product development and also considers context and trial phases to be important. They note, however, that despite its importance, context has “received little attention in the literature.” Acceptability “as measured by single or short-term use of a product in a phase I or phase II trial, should be measured as adherence in phase IIb or phase III trials that require extended product use...” ([2]: pp.584-585). Coly and Gorbach do not provide their own definition of acceptability; rather their model outlines the factors that influence acceptability.

These current frameworks, which broaden the definition and move beyond physical characteristics and pharmacological properties, consider acceptability as the bundle of individual, interpersonal, contextual factors, as well as product attributes, that support or hinder use. For all intents and purposes acceptability is defined in terms of use or, in the language of clinical trials, product adherence.

Measurement of acceptability: review of recent studies

The 15 unique studies presented in the 18 publications reviewed vary markedly in terms of sample size, population, product, definition of acceptability, and methodology. See Table 1. As such, it is not possible to generalize about acceptability, specifically which product attributes — e.g. color, smell, texture, viscosity, size— delivery mode, or dosing regimen might be viewed as desirable or problematic in specific settings and among particular populations. However, one can summarize components of the study designs and make some general statements about findings:

- Only seven of the 18 papers [12*, 17*, 19, 21, 26, 27, 29] investigate acceptability of actual candidate products. Eight papers [15, 16, 18*, 20, 22-24, 30] examine hypothetical acceptability— typically investigating whether respondents would be willing to use a product, and attitudes and beliefs about the hypothetical product.
- Three of the 18 [13*, 25, 28], examine acceptability of a placebo or proxy product focusing on product attributes.
- Three of the 18 [12*, 19, 28*] ask participants to compare multiple products or dosing regimens and indicate their preference, rather than to evaluate a single product or individual features of a product.

- To the extent that an overall measure of acceptability is included in studies, the proportion of participants who indicate a “willingness to use” the product is the most common summary construct. Fifteen publications [13*, 15, 16, 17*, 18*, 19-24, 26, 27, 28*, 30] contain such a measure with some variability in responses; in five [13*, 15, 22, 27, 28*] of the 15 studies at least 80% expressed a willingness to use. In another [17*], 59% reported that they would be likely to use in the future. In yet another [18*], which interviewed nearly 1800 high risk participants in seven countries, 61% indicated they would definitely use. In the one acceptability study that was conducted in China [30] over two-thirds indicated a willingness to use. Another study [29] asked about overall satisfaction and whether the participant would recommend the product to a friend; here again, the product was considered “highly acceptable.” Interestingly, despite the range in the percentages willing to use that are reported, the conclusion is the same, namely that participants find the products under investigation to be acceptable.
- It is the rare study in which researchers feature negative findings; only one trial [17*, 21, 26] devoted considerable space to problems, noting that participants reported issues with the three gels under investigation (one active, two placebo), complaining about leakage, and interference and decreased satisfaction with sex.
- Two studies [18*, 20] used conjoint analysis to assess the relative importance participants assign to various attributes or features of a product, whether positive or negative. Participants were presented with hypothetical scenarios with different combinations of attributes involving such dimensions as cost, efficacy, side-effects, duration of administration, dosing regimen, dispensing process, time spent obtaining the product, frequency of resupply and frequency of HIV testing. They were then asked to rate these scenarios. One of these studies [20] reported the results for eight different hypothetical scenarios and observed enormous variability across scenarios—ranging from nearly 20 to over 80 percent acceptable—with out of pocket cost, efficacy and side effects exerting the greatest effect on PrEP acceptability. These results suggest that acceptability is determined by numerous attributes and that an overall measure of “willingness to use” or “liking the product” may be insufficiently nuanced to explain adherence.
- Implicitly acknowledging the limitations of narrow measures of acceptability, such as physical properties or side effects, all but one of the 18 papers we reviewed assesses multiple, broader dimensions of the concept. While the measures are not standardized, the results are informative. The most common elements considered include “use attributes” (15 papers), followed by “partner's attitudes” (13 papers), “efficacy” —hypothetical— (11 papers) and “effects of product on the sexual encounter” (10 papers).

Linking acceptability to product use

As Table 1 indicates, only one of the 18 studies attempted to link acceptability to use. van der Straten et al. [12*] examined whether dosing preference —precoital or daily— was associated with self reported adherence of the Duet, a cervical barrier and microbicide

delivery system; self-reported adherence was not found to significantly vary by use regimen, although women preferred the precoital regimen. Of note, this study had a small sample size, and was of short duration. A couple of studies, published prior to 2011, have analyzed the association between acceptability and adherence. Joglekar et al. [31] assessed whether various dimensions of acceptability, including physical characteristics, use-related issues, sexual experience with the product, genital symptoms, and partner acceptability affected self reported adherence to a candidate vaginal microbicide tablet; only sexual experiences with the product were significantly associated with adherence in a multivariate model. van der Straten et al. [32] examined whether consistent use of a gel with or without a diaphragm was associated with several dimensions of acceptability — liking product, sexual pleasure, reasons for use, recommendation to a friend, partner's knowledge of use, partner's reaction to product, and experiencing a problem with study product. No association was observed. A major limitation of both these studies is the reliance on self reports to measure adherence.

New definition and conceptual model for investigating microbicide acceptability

As reviewed above, consensus is lacking about the definition and measurement of acceptability. It is a complex construct, which has been equated to a behavior (use or sustained use) combined —or not—with a set of attitudes influenced by a given context. The reduction of acceptability to attitudes or hypothetical intentions (e.g. willingness to use in the future), which may have little relevance to (future) reality, has not strengthened support for the value of measuring this concept in clinical trial research.

Within the conduct of clinical trials, we propose a revised definition of acceptability that clearly and operationally separates product acceptability from product adherence, and the factors that may influence these two constructs. See Figure 1. We define acceptability as the product-related attributes and perceptions that *potentially* influence (i.e. act as facilitators and barriers) to product adherence. In this revised framework, product acceptability is a proximal determinant to use. Background and contextual factors also may influence use directly or indirectly through product acceptability. We adapted a socio-ecological model, which recognizes that various agents and factors are operating at different levels (individual, household, partner, organizational, contextual/structural) and may influence an individual's behavior (adherence to product use) as well as his/her product-related attitudes and perceptions (acceptability). While erring on the side of being exhaustive, Table 2 presents examples of variables that could be measured under each level of influencing factor and component of product acceptability. This model recognizes the importance of participants' agency in the use of the product or an alternative, as even in clinical trials, participants have the option to use nothing, or to only use condoms. Finally, as previously defined [33] adherence is operationalized as initiation (uptake or not of the product), execution (whether the product is taken as directed), and discontinuation. These three components highlight the dynamic aspect of adherence as a behavioral process taking place overtime. The importance of trial phases, noted by Coly and Gorbach [2], is highlighted in several ways: for the adherence components, while initiation, and persistence will be more critical in longer duration trials, quality of execution is critical in all trial phases. Also some acceptability

attributes are more important to measure in early phase I trials (e.g. physical characteristics and delivery mode), when product modification may still be feasible [3]), while others will be more relevant to measure in later phases (e.g. sexual encounter attributes, partner's attitude about product, community associated norms about products). Finally, some levels of influence may figure more prominently in different trial phases (e.g. individual characteristics in phase I, versus partner and contextual factors in later phase trials).

We believe this model is an improvement over previous models because it clearly separates acceptability from adherence, and highlights how influencing factors can affect product use directly or indirectly through acceptability. It also incorporates participants' agency and choice (or lack of thereof) as a central concept on the pathway between acceptability and adherence. This model may help explain why unsatisfactory products, such as condoms can still be used, despite low acceptability [5, 34], or, alternatively, why despite "high" reported acceptability, study products in clinical trials may not be consistently used because of contextual influences, alternative choices or competing life priorities [13*, 35].

Conclusion

In their 2008 review of microbicide acceptability research, Coly and Gorbach [2] observed that: 1) a consensus did not exist with regard to the definition and operationalization of acceptability; 2) "as currently measured" vaginal microbicides have been found to be acceptable; and 3) the association between microbicide acceptability and adherence in clinical trials has yet to be determined.

Four years later, these same conclusions hold; moreover, we can extend the second point to include oral PrEP. While several trials have demonstrated efficacy since that earlier review — CAPRISA 004 (Tenofovir gel), iPrEX (Truvada), Partners PrEP (oral Tenofovir and Truvada, and TDF2 (Truvada) — two trials or arms of a trial investigating the same products have been stopped for futility— FemPrEP (Truvada) and VOICE (Tenofovir gel and oral). One partial explanation for the disparate findings is differential adherence [36]. Efficacy has been shown to be associated with detectable levels of study drug in plasma [37]. Indeed, fewer than 40% of participants had significant plasma drug levels in FemPrEP. Given the critical role of adherence to the success of clinical trials, it is important to identify the extent to which acceptability is a factor in product usage and to ascertain which dimensions of acceptability — product attributes, dosing regimen, delivery mechanism, use attributes, partner's attitudes, effect of product on the sexual encounter, product-related norms — if any, affect adherence. We have been hampered in the past by reliance on self reported measures of adherence, which have been shown to be flawed [37-39]. And we have been hindered in our investigation of the linkages between acceptability and adherence by defining the former in terms of the latter. With the validation of and increased ability to measure drug levels in trials, as well as inclusion of more objective measures of adherence (e.g. unannounced product counts, electronic monitoring, applicator insertion assays), researchers will be in a better position to understand the degree to which adherence is driven by acceptability and the degree to which it is influenced by individual and contextual factors.

Finally, similar to Severy and Newcomer [7] who contend that “we cannot be certain about a product's acceptability” in the absence of choice, we think an important case can be made for consideration of choice and product preferences, wherever feasible in clinical trials, as a means of advancing our understanding of product acceptability.

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Key Points

- While numerous studies have investigated product acceptability, a consensus is lacking regarding the definition and operationalization of the concept.
- While most studies recognize that acceptability is multidimensional, a majority assess “willingness to use” as their overall acceptability measure, leading most investigators to conclude that products are acceptable.
- Within the conduct of clinical trials, it is important to separate product acceptability from adherence, and the factors that may influence these two constructs.
- It is critical to identify the extent to which acceptability is a factor in product usage and to ascertain which dimensions of acceptability — product attributes, dosing regimen, delivery mechanism, use attributes, partner's attitudes, effect of product on the sexual encounter, product-related norms — if any, affect adherence.
- With the increased ability to measure drug levels in trials, as well as inclusion of more objective measures of adherence, researchers will be able to assess the degree to which adherence is driven by acceptability and the degree to which it is influenced by individual and contextual factors.

Figure 1.
Conceptual model identifying the potential role of product acceptability in adherence

Table 1

Summary of acceptability articles published in 2011 and 2012

Authors	Publication Date	Country(ies)	Population(s)**	Product Type	Route of Administration	Product	Acceptability Measure(s) [†]	Analysis Linking Acceptability to Use/Adherence	Data Collection Method(s)
Brooks et al. [15]	2012	US	25 GBM SDC	Hypothetical	Oral	PrEP tablet	C, E, F, H, I	No	Mixed Methods
Brooks et al. [16]	2011	US	25 GBM SDC	Hypothetical	Oral	PrEP tablet	C, E, F, G, H, I	No	Qualitative
Carballo-Diéguez et al. [17*]	2011	US/Puerto Rico	61 WSM	Actual	Vaginal	VivaGel®	A, D, E, F, G, I	No	Mixed Methods
Eisingerich et al. [18*]	2012	Botswana, India, Kenya, Peru, Uganda, South Africa	1790 FSW, IDU, MSM, SDC, WSM	Hypothetical	Oral/parenteral	PrEP tablet, Injection	B, C,D, E, G, H, I	No	Quantitative
Frezieres et al. [19]	2012	US	34 heterosexual couples	Actual	Vaginal	BufferGel, SILCS diaphragm	A, B, C, E, F, G, I	No	Mixed Methods
Galea, et al. [20]	2011	Peru	45 FSW, TG, MSM	Hypothetical	Oral	PrEP tablet	C,D, E, G, H, I	No	Mixed Methods
Giguere et al. [21]	2012	US/Puerto Rico	61 WSM	Actual	Vaginal	VivaGel®	A, D, E, F, G, H, I	No	Mixed Methods
Heffron et al. [22]	2012	Kenya	181 heterosexual SDC	Hypothetical	Oral	Early ART or PrEP tablet	C, E, D, G, I	No	Quantitative
Hoel et al. [23]	2011	South Africa	29 WSM	Hypothetical	Vaginal	Microbicide	G, H, I	No	Qualitative
Kohli et al. [24]	2011	India	15 MSW	Hypothetical	Vaginal	Microbicide	E, F, G, H, I	No	Qualitative
Mahan et al. [25]	2011	US	10 WSM	Proxy/Placebo	Vaginal	Lubricant	A (perceptual differences)	No	Quantitative
McGowan et al. [26]	2011	US	61 WSM	Actual	Vaginal	VivaGel®	C, E, I	No	Quantitative
Mutua et al. [27]	2012	Kenya	67 MSM, 5 FSW	Actual	Oral	FTC/TDF tablet	C, D, I	No	Quantitative
Nel et al. [28*]	2011	Burkina Faso, Tanzania, Zambia	526 WSM, 31 MSW partners	Proxy/Placebo	Vaginal	Film, soft-gel capsule (SGC), tablet	A, B, D, E, F, G, I	No	Quantitative
van der Straten et al. [12*]	2012	Zimbabwe	80 WSM, 20 MSW partners	Actual	Vaginal	BufferGel/Duet cervical barrier	D, E, F, G	Yes	Mixed Methods
van der Straten et al. [13*]	2012	South Africa, Tanzania	157 WSM, 19 MSW partners	Proxy/Placebo	Vaginal	Silicone elastomer ring	C, D, E, F, G, H, I	No	Mixed Methods
Whitehead et al. [29]	2011	Thailand	60 HIV+ WSM	Actual	Vaginal	Carraiguard® gel	A, C, E, F, G	No	Quantitative
Zhou et al. [30]	2012	China	152 MSM	Hypothetical	Oral	PrEP tablet	C, E, H, I	No	Quantitative

** Female sex workers (FSW), Gay and bisexual men (GBM), Injecting drug users (IDU), Men who have sex with men (MSM), Men who have sex with women (MSW), Sero-discordant couples (SDC), Transgender (TG), Women who have sex with men (WSM)

[†] (A) Product characteristics (color, smell, size, volume, consistency); (B) Delivery mechanism, (tablet, gel, ring, film, suppository); (C) Efficacy (hypothetical); (D) Dosing regimen, (daily, precoital, percoital, intermittent) ; (E) Use attributes, (physical sensation *in situ*, ease and comfort of use, discreteness/secretcy leakiness, side effects, ancillary benefits); (F) Effects of product on the sexual encounter (lubrication, effect on sexual pleasure); (G) Partner's attitude, (awareness, support, approval/disapproval); (H) Product-associated norms (stigma, community attitudes about formulation); (I) Willingness to use

Table 2
Examples of measurable items included in influencing factors and components of acceptability in the conceptual framework

Influencing factors: level	Examples	Components of Acceptability	Examples
Individual	Age, ethnicity, education, income, labor force participation, marital status, religiosity, religious affiliation, risk perception	Product characteristics	Color, smell, size, volume, consistency
Household	Resources, living conditions (toilet, water) sleeping arrangements, number and type of household residents	Delivery mechanism	Tablet, gel, ring, film, suppository
Partner	Number, type, communication, decision-making power	Efficacy (if known)	
Organizational	Trial phase (phase I, II, IIB, III, IV) Clinic features (quality of staff, waiting time, access); Workplace (schedule, relationship with co-workers, organizational culture); Community group membership	Dosing regimen	Daily, precoital, percoital, intermittent
Contextual/structural	Socio-cultural norms, local practices, HIV prevalence, urban/rural location	Use attributes	Ease and comfort of use, physical sensation in situ, discreetness/secretcy leakiness, side effects, ancillary benefits
		Effects on the sexual encounter	Lubrication, effect on sexual pleasure, timing of use
		Partner's attitude about product	Awareness, support of product use, approval/disapproval
		Product associated norms	Stigma, community norms about product formulation