

## Research on adolescents and microbicides: A review.

By: Amanda E. Tanner, Mary B. Short, Gregory D. Zimet, and Susan L. Rosenthal

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### **Abstract:**

Adolescents are an important target for microbicide research, as they are disproportionately affected by sexually transmitted infections and currently are underrepresented in the microbicide research literature. Furthermore, adolescents are psychosocially and biologically different from adults, and findings from adult research cannot be assumed to apply universally to adolescents. Adolescents, to date have rarely been included in clinical trials and acceptability research for microbicides, in part because their participation requires attention to unique developmental issues, including parental consent and confidentiality. Despite these challenges, adolescents should be included in microbicide clinical research. If adolescents are ultimately expected to use microbicides, it is essential that we understand the developmental, contextual, and relationship variables that may influence use and acceptability. Accordingly, the goal of this paper was to examine the issues affecting the inclusion of adolescents in microbicide clinical research as well as review the existing adolescent-specific microbicide research, which highlights the various factors that may influence use and acceptability. It is hoped that this review can provide guidance for future work with this important, specialized population.

**Keywords:** microbicides | adolescents | HIV/AIDS | sexually transmitted infections | adolescent gynecology | adolescent sexuality

### **Article:**

Introduction

Sexually Transmitted Infections and Microbicides

Globally and in the United States, sexually active adolescents and young adults are at a high risk of acquiring sexually transmitted infections (STIs), including human immunodeficiency virus (HIV).<sup>1</sup> and <sup>2</sup> For example, a recent US Centers for Disease Control and Prevention (2008) study reported that 1 in 4 adolescent women between the ages of 14 and 19 is infected with an STI. Given that women share a disproportionate burden of STIs compared to men, it is critical

that women have methods they can initiate to protect themselves. The female condom provides a potential option, but it has not gained widespread acceptance.<sup>3 and 4</sup> Although correct and consistent use of male condoms effectively reduces the risk of STIs,<sup>5</sup> regular use of condoms is limited by women's need to negotiate condom use with their male partners,<sup>6 and 7</sup> and even when women are able to negotiate condom use, they may choose not to out of a desire for intimacy, increased physical sensation, or to please their partner.<sup>8 and 9</sup> Thus, microbicides may be useful in increasing women's ability to protect themselves.<sup>10</sup>

Microbicides are creams, gels, films, or foams that can be inserted into the vagina or rectum to protect against STIs and, in some cases, pregnancy.<sup>11</sup> Currently there are more than 10 microbicide formulas in clinical trials, including 1 product in a phase III trial.<sup>12</sup> Microbicide production delays have been attributed primarily to the complex physiology of the vaginal and rectal environments and the lack of research funding mechanisms.<sup>13</sup> In addition to prevention properties, microbicides may affect sexual comfort and pleasure, as most formulas will have lubricating qualities.<sup>14, 15, 16 and 17</sup> Microbicides, then, offer a unique compromise between the reduction of infection risk and potential influence on sexual performance and pleasure, thereby highlighting the importance of research. If safe, effective, and acceptable microbicides can be developed, then these woman-initiated methods have the potential to limit the transmission of STIs, including HIV.

Microbicides have great promise for adolescents; however, the majority of microbicide research has been conducted with adults. Thus, the purpose of this paper is to explore the adolescent-specific issues that influence the inclusion of adolescents in microbicide clinical research as well as review the extant adolescent microbicide research. It is hoped that this review can provide guidance for future work with this important, specialized population.

## Adolescence

Adolescence is a phase of physical and psychosexual maturation as well as a transitional period into adulthood. There are distinct issues affecting adolescent sexual risk and protective behaviors, including parent relationships, limited sexual experience, lower usage of disease- and pregnancy-prevention methods, often spontaneous sexual opportunity, and lack of information regarding protective behaviors in school sexuality education programs.<sup>18, 19, 20 and 21</sup> The key areas of adolescents' developmental changes include biology, cognition, and social behavior and functioning, which have implications for the use of vaginal microbicides by adolescent women.

With regard to biological factors, adolescence is a time of hormonal changes, cervix maturation, and varying menstrual patterns.<sup>13</sup> It is unknown whether the immature and developing gynecological tract of the adolescent woman would have an influence on safety or efficacy of microbicides. For instance, during the period after menarche, the columnar epithelium extends to the outer surface of the cervix, potentially increasing susceptibility to infection. Additionally, there may be aspects of adolescents' sexual behavior that influence microbicide efficacy or safety. Adolescent women, for example, may be less likely to be sufficiently aroused at the time of sexual intercourse and therefore have less vaginal lubrication. This lower level of lubrication may make a microbicide with lubricating qualities more acceptable and desirable,<sup>16</sup> and <sup>17</sup> but it may also have an impact on safety and efficacy. It is possible with less natural fluid in the genital tract that the product would not spread sufficiently to provide protection. These key developmental factors highlight the need for adolescents to participate in, and benefit from, microbicide research.<sup>19</sup> and <sup>22</sup>

### Inclusion of Adolescents in Clinical Research

It is necessary to include adolescents in reproductive health research, as they appear to have unique vulnerabilities to STIs. With increased cognitive skills, adolescents have a greater capacity to be involved in decision making about participation in research, including clinical trials. However, adolescents' involvement in decision making occurs within a social and legal context in which parental consent is required. Therefore, the prospect of including adolescents in clinical trials raises a variety of legal, ethical, and practical issues (eg, how, when, and where to obtain parental consent and how to ensure protection of minors, who are considered vulnerable persons). The necessity of parental involvement is complicated by issues related to informed consent, confidentiality, and promotion of adolescent autonomy.<sup>22, 23</sup> and <sup>24</sup> The challenge in including adolescents in microbicide trials, therefore, is how to obtain parental and adolescent consent while protecting participant privacy and confidentiality.<sup>13</sup>

Although adolescents are developing the necessary skills to be more involved in decisions related to research participation, the need to negotiate the social and legal context continues. An approach that has been suggested to include adolescents in microbicide clinical trials is to conduct adult-only phase I and II trials to determine safety.<sup>13</sup> Once safety is confirmed, a combined phase I/II trial could be conducted with adolescents, with movement toward an integrated adult/adolescent phase III trial.<sup>13</sup> Once adolescents are recruited, there will be other issues to be considered, including retention, access to health care, and maintaining confidentiality. These issues are important but do not preclude including adolescents in the research. Requiring parental consent for safety and efficacy studies should not detract from the study results, as adolescent women's anatomy and physiology are relatively similar to each other

(although different from those of adults). Issues such as the waiving of parental consent will be most pertinent in acceptability studies, where there may be important differences (eg, sexual experience, parent-child communication) between adolescents who are willing and not willing to obtain parental consent.

The requirement of parental consent in microbicide research may pose a barrier to inclusion for adolescents who do not wish to disclose sexual behaviors to their parents.<sup>13, 19, 22 and 24</sup> The (inadvertent) exclusion of a subsample of sexually experienced adolescents, who choose not to get parental consent, means that their experiences and attitudes, which are particularly relevant, remain unknown. It may be necessary to wait until microbicides are approved to examine this group's assessment, as waiving parental consent for an approved product would be less difficult. It is notable, however, that there have been microbicide studies that have required parental consent and have included women as young as 14.<sup>25 and 26</sup> These studies demonstrate that parental consent can be obtained from parents of younger adolescents and highlight the importance of not shying away from requiring parental consent, but recognizing and acknowledging the implications in terms of the potential for selection bias.

A strategy to ease the parental consent process and enhance participant privacy is to allow obtaining consent over the phone.<sup>22</sup> This strategy limits the degree to which parental consent is a barrier by allowing the participation of adolescents whose parents did not accompany them to the study site. Another strategy is to discuss with parents the need to keep confidential the information provided by their child. If a parent agrees, his or her daughter can be informed prior to beginning the study that confidentiality is protected. This issue is especially relevant when exclusion criteria include such things as a positive pregnancy or HIV test. It is essential that confidentiality discussions with the parent and adolescent be extremely open and detailed before study initiation. Understanding the complex nature of adolescent-parent relationships and working to balance parental involvement and adolescent autonomy is necessary to ensure their privacy and navigate inclusion in studies.<sup>19 and 22</sup>

An additional challenge to including adolescents in research is how to access their sexual partners, in terms of both the relational and the legal issues. Adolescents tend to have shorter-term and less involved relationships,<sup>27</sup> which can complicate the identification of partners and impede efforts to recruit them. In addition, a legal issue was identified in attempts to recruit adolescent women's partners.<sup>28</sup> The Institutional Review Board expressed concerns regarding adolescent women identifying older partners and thereby inadvertently raising the issue of statutory rape.<sup>28</sup> A continuing dialogue regarding how to address this issue will be important, as it is essential that adolescents (both women and men) have the opportunity to freely choose to

participate in microbicide research to ensure that it is consistent with the research principles of respect, justice, and beneficence.<sup>18</sup> and <sup>29</sup> Again, to meet these overarching research principles,<sup>29</sup> adolescent women (and their partners) should have the chance to participate in microbicide research. The practical realities of the need to know about microbicide safety, efficacy, and acceptability require that we ask how to include adolescents, not whether to include them.

## Existing Adolescent Microbicide Research

### Microbicide Acceptability

A significant amount of funding, including federal monies, is currently being devoted to microbicide production.<sup>30</sup> Once microbicides are proven safe and effective, they need to be acceptable and usable.<sup>31</sup> Dimensions of acceptability will likely differ based on the cultural and developmental characteristics of the population.<sup>32</sup> Acceptability research, then, is particularly crucial for adolescents, as they remain a population that is disproportionately influenced by the burden of STI/HIV<sup>33</sup> and could greatly benefit from a woman-initiated prevention method, particularly with the challenges that can arise around discussing condom use with a partner.<sup>34</sup>

As microbicides are not currently commercially available, most of the adolescent/young adult acceptability work has assessed hypothetical product characteristics to predict use<sup>26</sup> and <sup>35</sup> or used vaginal moisturizers or lubricants as proxy microbial products to assess behavioral correlates of use.<sup>16</sup> and <sup>22</sup> As microbicides will be used within sexual partnerships, it is important to explore the ways in which microbicides will be negotiated within the sexual interaction. Therefore, an understanding of preferences for specific microbicide qualities, as well as how other people may influence adolescent women's decision to use microbicides, is essential.

### Product Characteristics

Extant microbicide acceptability research with adolescent women has reported varied individual preferences regarding product characteristics. Adolescent women generally favored both pregnancy and disease prevention in a single product,<sup>26</sup> and <sup>35</sup> however, this preference changed with reproductive health goals. Women who were trying to become pregnant, for instance, preferred a product with STI/HIV prevention properties only.<sup>16</sup> and <sup>20</sup> Previous research indicated that potential side effects may influence microbicide acceptability and use, including yeast infections, vaginal itching, penile irritation, and allergic reactions.<sup>20, 26</sup> and <sup>36</sup> In addition, associations with the microbicide proxy to other products influenced use; for example, if a microbicide seemed to have similar properties to a yeast infection medication, it

was a perceived barrier to use.<sup>17</sup> Adolescent women indicated that microbicides should be promoted through youth-specific venues, such as magazines.<sup>36</sup> There was also a reported desire for microbicides to be small enough to carry in a pocket, bra, or within a cell phone or palm pilot case.<sup>36</sup>

Timing of microbicide application preferences varied. Some young women reported a preference for insertion up to 8 hours in advance of coitus.<sup>35</sup> Other young women, however, did not appreciate the prescribed waiting period and preferred application right before intercourse, as sex was not always planned.<sup>16</sup> and <sup>20</sup> Post-coital application was appealing to some women, as they could avoid having a conversation about use with their partner<sup>16</sup> and in case they forgot to apply the product in the “heat of the moment.”<sup>36</sup> In addition, there was a desire for lubricating products,<sup>16</sup> and <sup>17</sup> but with minimal messiness<sup>17</sup> and leakage.<sup>35</sup> and <sup>37</sup> For some young women and their partners, the lubricating properties were thought to be beneficial in increasing sexual comfort and pleasure.<sup>16</sup> and <sup>17</sup> Overall, adolescent women wanted microbicides to be affordable, discreet, effective, comfortable, flexible, and without side effects.

#### Adolescents and Social Network Influence on Microbicide Acceptability and Use

Existing research suggests that sexual partners, family, and health care providers will affect the acceptability and use of microbicides by adolescents. Issues associated with microbicide acceptability have focused on these important people as influential in decision making, encouraging use, communication, and information dissemination.

#### Male partners and microbicide acceptability

As microbicides will be used within a dyadic sexual interaction, adolescent women and men are both important targets for microbicide promotion. Little work has directly addressed young men's acceptability of microbicides. The few studies reported, similar to young women's evaluations, considerable variation in young men's evaluations of and concerns related to microbicides. The results indicated young men placed an emphasis on sexual enhancement, had concerns regarding microbicide safety, and wanted their partners to tell them about use.<sup>28</sup> and <sup>38</sup>

Male partners' attitudes toward microbicides or to similar products (eg, vaginal moisturizers) have also been explored indirectly through young women's reports. Comparable to adults,<sup>39</sup> adolescent women's specific relationship dynamics, including perceptions of male partners' assessment, communication ability, and comfort with covert use, influenced use of microbicide

surrogates.<sup>25</sup> and <sup>40</sup> Positive male evaluations resulted in an increased likelihood of use of a microbicide surrogate, whereas negative evaluations decreased the likelihood of use.<sup>40</sup> Similar to discussions regarding other contraceptive and disease prevention methods,<sup>4</sup> adolescent women described a variety of expectations and experiences when talking to their partners about microbicide/moisturizer use. Some young women reported ease in discussing microbicide surrogate use with their partners, whereas other women struggled with initiation of these discussions. <sup>17</sup> and <sup>40</sup> Young women in more established relationships or those who had known their partner for an extended period of time tended to be more comfortable communicating about microbicide surrogate use in comparison to women who defined their relationships as more casual.<sup>40</sup> In addition, there was a reported willingness by some adolescent women to have their partner be present for microbicide application or let the partner insert the product.<sup>41</sup>

Consistent with adult findings,<sup>3, 42</sup> and <sup>43</sup> some adolescents expressed an interest in the potential of surreptitious microbicide use,<sup>16</sup> though the majority of women reported telling their partners about use of the microbicide surrogate.<sup>17</sup> and <sup>40</sup> The women who reported a desire for covert use said that they were motivated by a lack of trust in their main partner and reported wanting to do what they could to protect themselves.<sup>40</sup> This desire for covert self-protection may arise from the real and perceived challenges that these women encounter in trying to negotiate male condom use, making microbicides, a woman-initiated method of STI prevention, an attractive option.

#### Parents and microbicide acceptability

Parents are frequently relied upon for health care information and decision making. Mothers have been identified as the most often accessed and most positive source of sexual health information.<sup>36</sup> They also have a significant impact on adolescent women's decision making.<sup>44</sup> Consistent with this notion, adolescents have reported that parents will influence microbicide acceptance.<sup>16</sup> and <sup>44</sup> When an adolescent woman had a positive relationship with her mother, they were more likely to discuss the use of a microbicide surrogate.<sup>44</sup> These findings suggest that mothers, as relatively frequent providers of sexual health information, may be an effective avenue for promotion of microbicide use by their adolescents.<sup>44</sup>

#### Health care providers and microbicide acceptability

Health care providers are in a unique position to confidentially inform adolescent women (and men) about, as well as encourage use of, microbicides. One study of general health care providers reported that the majority would be comfortable counseling individuals about

microbicide use.<sup>45</sup> It is noteworthy that this was an adult-specific study and that providers may have more hesitation about encouraging use for adolescent women. Some health care providers, for instance, reported a concern that adolescents will prefer to use microbicides (likely a less effective prevention method) and will stop using condoms.<sup>20</sup> It has been demonstrated, however, that providing adolescents with multiple contraception and disease prevention method options (eg, hormonal methods) does not decrease condom use.<sup>46</sup> Therefore, it will be essential to work with providers to counsel and teach adolescent women and men about all of the available STI/HIV prevention methods, including microbicides. Overall, health care providers would be able to educate adolescents about microbicides, answer questions related to safety and efficacy, and monitor potential side effects.<sup>36</sup>

### Microbicide Access and Marketing

Access to microbicides will be an important gauge of acceptance for adolescents.<sup>36</sup> Research suggests that young women preferred a range of access venues, for instance, some wanted microbicides to be available by prescription<sup>35</sup> or distributed through clinics.<sup>16</sup> Others preferred over-the-counter availability of microbicides, yet they stated they would be embarrassed if purchasing the product in the presence of others.<sup>35</sup> and <sup>36</sup> Finally, some adolescent women believed that microbicides should be distributed through schools and sexuality education classes.<sup>36</sup> Thus, a variety of distribution options, as well as attractive packaging,<sup>3</sup> may be necessary to increase adolescent women's and their partners' access to and likelihood of purchasing microbicides.

The likely influence of partners, family, and health care providers on adolescents' microbicide acceptance and ongoing use suggests that microbicide marketing and educational campaigns should be directed to influential adults as well as adolescents and their partners. In addition, it may be necessary to develop multiple targeted strategies. For instance, health care providers are in a position to introduce products to adolescents and inform them about potential side effects. However, parents and teachers should also be informed about microbicides, as they have vital roles in the lives of adolescents and may be in a better position than health care providers to address issues around sustained use of microbicides. Additionally, the incorporation of male partners into microbicide promotion efforts will be critical.<sup>3</sup> The use of media, including magazines and television, would also allow for creative options for the dissemination of information.<sup>41</sup> and <sup>44</sup>

The introduction and promotion of microbicides as a disease-prevention method focusing on HIV may be met with some resistance due to the well-documented stigma associated with

HIV,<sup>47</sup> and <sup>48</sup> especially for adolescents who may face challenges in communicating with partners about the use of contraceptives and disease prevention methods.<sup>25</sup> and <sup>40</sup> It may be important, therefore, to approach microbicide promotion by noting that disease prevention is only 1 of several attractive characteristics of microbicide use, which may include contraception and lubrication. Recent work has suggested that including sexual pleasure messaging in STI/HIV prevention campaigns may increase condom use rates<sup>15</sup> and <sup>49</sup> and will likely also be a useful strategy in microbicide promotion. In addition, the promotion of microbicides will need to include adolescents' broader environmental, structural, social, and cultural context. For example, HIV prevalence will likely have implications for microbicide marketing based on geography; highlighting potential for HIV protection may be more useful in higher prevalence areas, whereas highlighting other characteristics (eg, lubrication for sexual comfort and pleasure) may be more beneficial in other areas.

### Conclusions and Recommendations for Future Research

Adolescents are an important target for microbicide research, as they are disproportionately affected by STI and currently are underrepresented in the microbicide research literature. Furthermore, adolescents are psychosocially and biologically different from adults, and findings from adult research cannot be assumed to apply universally to adolescents. Moreover, the period of adolescence is not internally homogeneous, as 14-year-olds, for instance, are in a distinct developmental period from that of their 18-year-old counterparts. Therefore, it is essential to ensure that adolescents across a broad range of ages be included in microbicide research. The inclusion of adolescents in clinical trials would allow safety and efficacy information to be combined with what is known about acceptability of hypothetical and surrogate microbicides to create targeted microbicide promotion campaigns. Although first generation microbicides will likely be less effective than condoms at STI/HIV prevention,<sup>50</sup> even a lower efficacy microbicide could have a significant public health impact, particularly when combined with condom use.<sup>35</sup> and <sup>51</sup> We strongly recommend, therefore, that adolescents be included in future clinical trials and acceptability research,<sup>52</sup> and <sup>53</sup> which will allow for an examination of adolescent developmental issues related to safety, efficacy, and acceptability, as well as developing targeted educational and promotional materials.

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