

# Insights

POLICY BRIEF | SEPTEMBER 2015

## Research and Development of New Biomedical HIV Prevention Tools for Women and Girls

Combating the global AIDS epidemic through a more empowered response in Sub-Saharan Africa



Photo by UNAIDS/R. Cangale

High HIV prevalence and incidence puts a disproportionate burden on girls and women in Sub-Saharan Africa and threatens to reverse current success in combating the global AIDS epidemic. Programs to fight HIV/AIDS among women and girls can be bolstered by new biomedical prevention tools including pre-exposure prophylaxis, microbicides and vaccines that enhance women and girls' ability to protect themselves. Better aligning research and development efforts with the needs of women and girls can accelerate the introduction of a wider, more effective array of HIV prevention tools to enhance the health of girls and women, as well as the global response to HIV/AIDS.

### NINE RECOMMENDATIONS TO BETTER ALIGN HIV PREVENTION R&D WITH THE NEEDS OF WOMEN AND GIRLS IN SUB-SAHARAN AFRICA

1. Better understand women and girls' needs.
2. Invest in and act on social science research.
3. Keep research close to women's community health resources.
4. Incorporate health and science literacy into research programs.
5. Align research efforts with programs addressing social and economic issues.
6. Put a female face on research efforts.
7. Engage HIV-positive women as a critical peer group.
8. Consider critical differences in designing research studies for young women and girls.
9. Ensure the sustainability of community benefits.

### The feminized epicenter of the global epidemic

Unprecedented humanitarian, political, financial and scientific mobilization over the last 15 years has changed the trajectory of the global AIDS epidemic, providing 15 million people access to antiretroviral treatment (ART), and reducing AIDS-related deaths and new infections significantly. Despite this progress, in 2014 22 million of the 37 million people living with HIV did not have access to ART, 1.2 million died and 2 million newly contracted the virus.<sup>1</sup>

Further, global gains obscure a disproportionate burden on women and girls, especially in Sub-Saharan Africa where two-thirds of all AIDS-related deaths and new HIV infections occur and where women represent 59 percent of people living with HIV, a proportion likely to rise given even higher prevalence and incidence in young women and girls. Currently, 80 percent of newly infected adolescents in eastern and southern Africa are female, and women between the ages of 15 and 24 are twice as



Photo by Vanessa Vick

likely to be living with HIV as their male peers. Women in Sub-Saharan Africa are enrolled in ART at a higher proportion than men, but AIDS remains the region's number one killer of women of reproductive age.<sup>2,3</sup> Children are 10 times more likely to die within two years of their mothers' deaths.

Women are more physically susceptible to HIV infection than men.<sup>4</sup> Structural, social and cultural factors such as child marriage, violence, limited access to education, isolation from families and friends and enforced economic dependency on men that can include engagement in transactional sex, further exacerbate their vulnerability.<sup>5,6</sup> Prevention methods such as male condoms and circumcision can reduce HIV transmission, but require male consent or initiation. Low regional HIV testing rates for men mean a high risk of contact with a sexual partner unaware that he carries the virus.<sup>7</sup>

### Urgent efforts and long-term approaches

Failure to further improve HIV prevention for women and girls in Sub-Saharan Africa also holds the potential to stymie international goals to reduce new infections or worse to roll back gains of the global AIDS response to date. A recent report from *The Lancet* and UNAIDS noted that, "to attain these aspirational United Nations goals and targets the spread of HIV among young women in southern and eastern Africa must be stopped."<sup>8</sup>

Advocacy, leadership and action by women and girls has raised the profile of this issue and fueled demands for more inclusive and proactive approaches. One such example is the DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored and Safe) Initiative launched in 2015 by the United States President's Emergency Plan for AIDS Relief (PEPFAR), the Bill & Melinda Gates Foundation and the Nike Foundation to which over half a billion dollars has been committed, and which represent the first programmatic targets designed specifically to reduce HIV infections in young women.<sup>5,9</sup> DREAMS aims to focus educational, economic and social resources on "hot spots" in 10 countries\* where HIV incidence is highest among girls and young women to reduce HIV incidence by 40 percent in three years.<sup>5</sup>

The mobilization of such resources is critical to diminish the impact of HIV/AIDS in the near-term while building momentum of long-term programs in the future. The sustainability of such long-term efforts will also demand a wider range of new HIV prevention tools, recognizing that no one option will fit all needs and that individual circumstances require customizable choices. This policy brief explores areas where biomedical HIV prevention research can better engage – and be engaged by – women and girls to improve outcomes in the short-term while accelerating progress for new tools more specific to the needs of women and girls in Sub-Saharan Africa in the mid- to long-term.

### HIV prevention R&D efforts in a female context

Research on new HIV prevention technologies (NPTs) began in the late 1980s. Efforts to develop **microbicides** – creams, rings, films or suppositories applied vaginally or anally containing HIV-preventing compounds – grew out of the contraceptive field. After early microbicide candidates failed to provide protection in clinical trials, a microbicide gel containing antiretroviral compounds for the first time reduced HIV acquisition among women in a clinical trial in 2010.<sup>10</sup> Low adherence among participants kept subsequent trials from confirming those results, prompting greater emphasis on social and behavioral research to better understand users' needs to improve

\* Kenya, Lesotho, Malawi, Mozambique, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe

adherence, and increased attention on other formulations and regimens in development designed to reduce the need for daily use or maintenance. Results from two Phase III clinical trials of one such product, a monthly ARV-based vaginal ring, are expected in 2016.<sup>11</sup>

Research into the use of ART by HIV-uninfected persons to reduce the risk of infection — **pre-exposure prophylaxis (PrEP)** — has shown that Truvada™ (taken orally) can reduce infection risk by up to 92 percent, assuming regular adherence to regimens. Studies have also shown that young women in Africa can adhere to daily PrEP in trials, although further research into how to best utilize PrEP for young women is warranted.<sup>12,13</sup> Demonstration projects involving women and girls are currently underway in Kenya and South Africa, and PrEP has been incorporated as a non-required component of DREAMS.<sup>14,15,16</sup> Effectively implementing PrEP in female populations could be facilitated through synergies with school-based health and sexual and reproductive health (SRH) services, but will also likely require parallel programs, including social marketing and behavioral interventions, to combat many of the structural issues that place women and girls at risk in the first place.<sup>17,18</sup> Research into long-acting injectable formulations of ART for PrEP offers the promise of increased adherence, with one trial currently enrolling volunteers in South Africa and Malawi.<sup>19</sup>

Efforts to develop **preventive HIV vaccines** build on the inspiration from vaccines against other infectious diseases, including recently introduced vaccines against human papillomavirus (HPV), which causes cervical, vulvar and vaginal cancer. HIV vaccines could be administered confidentially (together with other vaccines or as part of other public health interventions) prior to exposure to HIV and — provided they offer lasting protection with a reasonable number of doses — increase adherence. HIV vaccines may also build on learnings from HPV vaccine demonstration projects, and infrastructure built through broad implementation of HPV vaccination, and the high acceptability of injectable contraception on the continent.<sup>20</sup>

To date, one HIV vaccine candidate has shown moderate efficacy in Thailand in 2009, in a trial involving 16,000 volunteers, 40 percent of whom were women.<sup>21</sup> Follow-on trials with modified candidates to prevent infection by HIV subtypes common in southern Africa and to do so with higher and longer lasting efficacy are scheduled to enroll both men and women beginning at the end of 2016. Additionally, promising research into vaccines likely to induce broader and lasting protection with a minimal number of doses, or passive immunization approaches,

is also concurrently moving toward, or entering, early clinical development.

In addition to PrEP, microbicides and vaccines, research to bolster usage of existing female-controlled tools such as the early initiation of ART to reduce infectiousness, female condoms and diaphragms continues. Multipurpose technologies meant to provide simultaneous protection against other sexually transmitted infections and pregnancy are also under development in a number of forms.<sup>22</sup>

### Ongoing R&D challenges for female-controlled NPTs

Research and development of HIV NPTs for girls and women have accelerated in recent years, energizing discussions regarding the potential impact of an enhanced, comprehensive response to HIV/AIDS.<sup>23</sup> At the same time, disproportionately high prevalence and incidence rates in women and girls is fueling an increased urgency to transform promise into reality for women and girls and in turn avert a potential reversal of gains by global HIV/AIDS programs. A number of persistent issues identified across the NPT R&D field must be addressed in order to most effectively add HIV NPTs to the existing response:

- **Low trial participation by women and girls.** Gender balance is critical to assessing whether a candidate product has the same effectiveness and acceptability among women and girls as in men and boys. With the exception of microbicide research, women have generally been under-represented in



NPT clinical trial enrollment, representing just 19 percent of participants in ART trials and 38 percent in vaccine trials.<sup>24</sup> Female underrepresentation is driven by relatively lower autonomy and mobility. Also, researchers are reluctant to enroll participants who may have to leave the trial due to pregnancy and are further challenged with ensuring consistent use of contraception during the trial.

- **Product profiles and study protocols that insufficiently respond to the needs of women and girls.** Both product design as well as trial design and conduct can be hindered by a lack of understanding of the context in which it will be used. The practical (and critical) urgency to test available product candidates must be balanced with strong consideration for the end users' needs. Otherwise, research efforts risk low adherence to regimens, inconclusive results and misspent scientific, financial and social resources.
- **The continued need for sustainable relationships between communities and research efforts.** The willingness of women to engage with research is heavily influenced by familiarity and trust between the research enterprise and its host community.<sup>25</sup> If research fails to link women and girls to community benefits such as health literacy programs and referrals to health services when trials end, they risk discouraging participation.<sup>26</sup>
- **Health systems that are insufficiently prepared to incorporate new interventions.** Strengthening weak or overburdened health systems in low- and middle-income countries can facilitate and sustain

improvements across a broad spectrum of health issues. The introduction of prevention technologies for women and girls can pose unique challenges to existing health systems, including the need to train health workers on product use and specific infrastructure or storage requirements.<sup>27</sup> Weak health systems in low- and middle-income countries have been identified as a specific barrier to uptake of HPV vaccines by women and girls.<sup>28</sup>

### Aligning HIV NPT R&D with the needs of women and girls

The identification and reduction of barriers to engaging HIV prevention research by women and girls in Sub-Saharan Africa have been subject to research for a number of years. However, the still-pervasive threat represented by HIV/AIDS, the continued evolution of NPT R&D, and the potential application of new insights provide a useful and timely backdrop on which to revisit, refine and expand research approaches.<sup>29,30</sup> The following recommendations draw on past and present efforts to describe opportunities to enhance NPT R&D for women and girls while simultaneously improving the research community's ability to derive meaningful results and accelerate future product research, development and introduction.

#### 1. Better understand women and girls' needs.

Recent experience in HIV prevention trials in Africa underscores a continued need to better engage women and girls earlier in R&D to ensure that their specific needs inform target product profiles that will lead to widely acceptable, impactful products. The CAPRISA 004 trial in South Africa utilized a coitally related dosing strategy based on consultations with the participating communities, and enrolled women 18-35 years of age at two sites (the majority at a rural site), many of whom had infrequent high-risk sex with migrants. This trial was the first to show efficacy for an ART-based vaginal microbicide when used before and after sex.<sup>31</sup> However, the FACTS 001 trial utilizing the same microbicide and dosing strategy was unable to achieve sufficient adherence to determine efficacy in younger women across nine sites in South Africa.<sup>32</sup> Daily dosing with the same microbicide in the VOICE trial after consultations with younger women in Uganda, South Africa and Zimbabwe also failed to achieve sufficient adherence to determine efficacy.<sup>33</sup> These divergent results reflect both the benefits of early engagement with women and girls participating in trials, and the need for more granular research into drivers and barriers of adherence, and earlier consideration in the R&D process.



**2. Invest in and act on social science research.** Social research to identify gender-related barriers to trial participation and product uptake, and the utilization of community advisory boards (CABs) inclusive of women and girls and responsive to gender issues have helped increase enrollment of other women and girls in vaccine trials in Kenya. Social research can also help identify the motivations of women who take part in clinical research, and increase our understanding of how they differ from women who decline to be in trials since the latter may actually be in greater need of improved prevention.<sup>34</sup> Partnerships between research organizations and women's advocacy groups can promote critical dialogue, utilizing good participatory practice guidelines.<sup>35</sup> Such front-loaded investments in community engagement can facilitate participation by women and girls, successful conduct of trials and accelerated development of acceptable products.<sup>36</sup>

**3. Keep research close to women's community health resources.** Locating research sites within clinics that provide SRH services can foster durable researcher/host relationships. Linking research to community health can ensure better access to HIV prevention options benefiting women and girls, including HIV testing, voluntary testing and counseling for couples, screening and treatment of sexually transmitted infections, and prevention of mother-to-child transmission. This can reinforce to the community that research efforts are responsive to the current needs of women and girls in regard to HIV/AIDS and that research is a critical part of adding new interventions to those that already exist.

Linking HIV prevention research with access to SRH services and other public health programs is important given that HIV/AIDS represents one of many critical health issues for women and girls in Sub-Saharan Africa. As illustrated by the University of Witwatersrand's Reproductive Health and HIV Institute, among others, significant synergies result from embedding clinical trials in settings delivering ongoing health care and health education to communities, along with other services such as child care. Women who use these services may not choose to participate in clinical trials, but such co-location builds community awareness and trust of research efforts based in reliable, helpful facilities.<sup>37</sup>

**4. Incorporate health and science literacy into research programs.** Sustained health and science literacy programs targeting women and girls can improve uptake of biomedical HIV/AIDS interventions while laying important groundwork for research. Providing accessible information on how HIV/AIDS and



other health conditions proliferate and how scientific research contributes to improved health and well-being can raise awareness of health issues, improve uptake of health interventions, lower barriers to engage with researchers and facilitate adoption of products more broadly. Preparatory and participatory activities to familiarize women and girls with the function of the trial can provide reassurances to families and neighbors that participation in a trial is safe.

**5. Align research efforts with programs addressing social and economic issues.** Opportunities for HIV prevention research to respond to the needs and priorities of women and girls include potential collaborations with efforts focusing on fighting structural drivers of HIV infection. Such engagement can also indicate which benefits are most valued by women and what practical steps can be taken to facilitate their participation in clinical trials.

Programs such as the FRESH study (Females Rising through Education, Support and Health), coordinated by the Ragon Institute, address the link between poverty and HIV infection through the engagement of women in research through concurrent programs that provide job and life-skills training for those who take part in the study, which aims to identify HIV infection and initiate ART very early after exposure. FRESH enrolls 18-23-year-old women in the Umlazi Township in KwaZulu-Natal, South Africa, where HIV prevalence among 15-year-old girls is 1 percent, but jumps up to over 60 percent by the time



they turn 23. Linking visits with educational opportunities also supports frequent trial visits for regular sampling and consistent follow-up.<sup>38</sup> Engagement of other ongoing efforts such as DREAMS also offer additional opportunities for program synergies.

6. **Put a female face on research efforts.** Increased employment of and involvement by female scientists and research staff can support research efforts for women and girls in a number of ways. Putting women at the forefront of research efforts builds understanding of and openness to women's and girls' needs in decision-making processes, and lowers barriers for women and girls to speak about their fears, issues and wishes. It also provides job opportunities and training for women living in the communities where research is taking place.
7. **Engage HIV-positive women as a critical peer group.** HIV positive women participating in formative research, CABs and other community engagement mechanisms as part of good participatory practices can provide critical first-hand knowledge of structural and social factors contributing to women's vulnerability to HIV and important retrospective views on how these factors contributed to their own HIV acquisition. Their experience also makes

them experts on how stigma is manifested in their communities and what steps a trial can take to avoid or lessen the impact that trial-associated stigma may have on participants and their families. Further, engagement of HIV-positive women can increase overall community interest and literacy around both HIV/AIDS and research and development.

8. **Consider critical differences in designing research studies for young women and girls.** As recently articulated in guidance for engagement of adolescents in HIV prevention and reproductive health research trials in Kenya, program and study design should take into consideration the physiological, psychological and social differences between young people and adults. Work engaging young women and girls should consider critical differences that include higher physical susceptibility to sexually transmitted infections, exacerbated vulnerability to partner violence, and lower relative awareness of long-term health risks (as recently observed for HPV diseases such as cervical cancer). Further, obtaining ethical informed consent for trial participation by young women and girls may require engagement of families and tailored programs.<sup>39</sup> Studies involving young women and girls should ensure their inclusion in CABs, and where necessary, implement differentiated designs between women and girls.
9. **Ensure the sustainability of community benefits.** Ensuring that trial sites remain engaged with host communities even between active studies can strengthen ties between researchers and host communities. Partnerships between researchers, domestic agencies and external funders to sustain benefits provided by the site between trials can facilitate re-initiation of trial activities through accelerated enrollment and increased retention. Trial capacity originally built to conduct HIV prevention trials could be utilized by groups focused on other regional health issues when HIV prevention trials are not active; commitments by these non-HIV groups to maintain adjoining community engagement efforts could be an agreed-upon prerequisite for access to that trial infrastructure. One useful example is the Kenya AIDS Vaccine Initiative's Institute of Clinical Research, which initially focused solely on HIV vaccine R&D, and has since expanded its research portfolio to include a wider number of diseases while maintaining strong community ties.<sup>40</sup> Commitments for post-trial access to products proven to be effective could also contribute to strengthening community relationships with researchers.

## A singular opportunity

An expanded, customizable HIV prevention toolbox deployed in tandem with programs to address structural, social and cultural issues offers a more comprehensive and effective response to the disproportionate burden the epidemic places on women and girls in Sub-Saharan Africa by offering more flexibility and choice of options which fit individual needs and constraints. This can be achieved through continued, strengthened leadership by women and girls and enhanced collaborations between communities, researchers, advocates and policymakers to better align research agendas and activities with female populations.

The combined impact of such actions offers the promise of improvements to the health of women and girls, increased control over their health and reproductive rights and strengthened support for their children, families and communities. In turn, successfully

reversing the epidemic in women and girls in Sub-Saharan Africa would help stabilize or even accelerate the downward trend for the global AIDS epidemic and promote sustainable development for some of the most impoverished countries of the world.

*IAVI would like to thank Anna Forbes for implementing research and outreach activities and for content development. Special thanks to those who took part in consultations on this work, including Judith Bruce, Elizabeth McGrory, and Naomi Rutenberg (Population Council), Barbara Mensch (Microbicides Trials Network/Population Council), Janet Fleischman (Center for Strategic and International Studies' Global Health Policy Center), Holly Seltzer and Sharyn Tenn (International Partnership for Microbicides), Kari Stoeber (Girl Effect) and Sydney Hushie (Global Youth Coalition on HIV/AIDS).*

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IAVI gratefully acknowledges the generous support provided by the following major donors



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