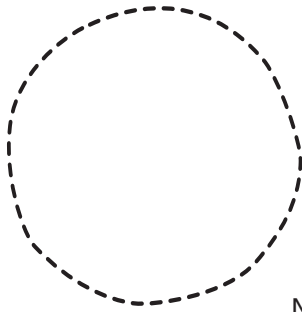


DATELINE **2013**

LOCATION **Sub-Saharan Africa**



Principal Investigator Wilhemina X is the head of a center of research excellence in a sub-Saharan African country where prevalence has stabilized at an estimated 10 percent and incidence continues to be high among adolescents, young married women, internally-displaced people and other high risk groups.

For the past several years, her center has participated in vaccine trials, including early safety studies of *Vaxino*—an experimental AIDS vaccine candidate that showed unprecedented levels of immune responses in human volunteers in Phase I and Phase II trials.

Now, the time has come to evaluate *Vaxino* in efficacy trials. PI Wilhemina's site is one of those considered for inclusion in the multi-site trial. She is profoundly hopeful that her country will be included. It is a great opportunity to use the expertise and capacity of her team. And having lost a sister and several cousins to HIV/AIDS, she is personally aware of the disease's impact on women, and on the limitations of current prevention options, particularly for married women.

PI Wilhemina and her team have been working hard to prepare for the study. They have conducted community outreach activities to explain the trial and its questions, and have held dialogues with medical professionals, politicians and community leaders about the implications of identifying a vaccine candidate that might reduce the risk of HIV infection without completely preventing infection. They've also discussed the ethical and practical dimensions of the prevention, treatment and care provided to trial participants, their families and their communities.

In the midst of this activity, results are released from a microbicide efficacy trial that was also conducted in Wilhemina's country. The trial showed that the candidate is partially-effective; similar studies have had the same finding in other parts of the world. The WHO has yet to approve the product, but Wilhemina's country is a priority for rollout of an expanded access program, pending full regulatory approval.

On a conference call, Wilhemina and her colleagues discuss the implications of this development. If her site is included in the *Vaxino* trial, and the microbicide is available, there may be an ethical obligation to offer it to all trial participants. This means the site will have to recruit twice as many individuals as originally anticipated. It also means the site would be offering a different standard of prevention care than that provided at other locations, where the microbicide is not yet available.

The investigators consider their options: introduce the microbicide as part of the protocol in all countries, invest the resources needed to set up a nested sub-study of the combination strategy at Wilhemina's site, or exclude the site and move forward with the original protocol—the most efficient and least expensive option.

"What do you think?" an investigator asks PI Wilhemina.

She stays silent for a moment, weighing the options. The site has been gearing up for this trial for two years. This is the moment they have been waiting for. On the other hand, the network will have to scramble to find resources to fund the expansion of the trial site—and an answer could come more swiftly from another country where the microbicide is still not available on a national level. Then again, Wilhemina is concerned that population-level efficacy of the microbicide may be lower than what was observed in the highly-controlled clinical trial setting—and holds firm to her hope for identifying a vaccine for her country.

She takes a deep breath and begins to speak.

04. AIDS Prevention Evolves (Again): Why we are on the verge of an era of new complexity

What do AIDS prevention and the theory of evolution have in common?

One answer is that both have come under fire from right wing Christian fundamentalists in the White House and Capitol Hill.

Another is that one of the tenets of AIDS prevention, and evolution, is that things get more complex over time.

Both of these answers are of great importance today. 2006 brought a number of reports about how US government policies have threatened implementation of AIDS prevention and sexual and reproductive health services. Demanding that the interventions that we know to work—condoms, clean needles, mother-to-child transmission prevention—are made widely available is a top priority for every prevention advocate.

The issue of increasing complexity is also timely and highly significant. The next two to three years will bring the release of data from an array of studies including male circumcision, microbicides, AIDS vaccines, pre-exposure prophylaxis (PrEP) and treatment of HSV-2 infection (see Figure 6). These data will indicate whether any of these strategies provide protection against HIV infection.

Here, the key word is *indicate*. While data from some of these studies may give definitive answers about whether or not an intervention works, other studies have been deliberately designed to provide preliminary answers, which will need to be confirmed in further studies. One example of this is the ongoing “STEP” study of the Merck adenovirus-based AIDS vaccine candidate (for more on this, see chapter 1). This test-of-concept trial will give an early indication

of whether or not the vaccine candidate is effective. But no matter what, more studies will need to be done. Still other studies may yield data that are indeterminate or statistically hard to analyze.

Even when the data are clear-cut, they are expected to demonstrate only a partial efficacy. None of the interventions under study are going to be the silver bullet that provides complete protection against HIV infection for everyone under every circumstance. And so there are going to be additional challenges as the field works to provide clear messages about these new interventions to multiple audiences.

The field is on the verge of an era of increased complexity and, potentially, increased confusion. Will this result in progress (à la evolution) or chaos? AVAC believes that the answer depends on the willingness of various stakeholders to begin discussing and dissecting some of the key issues that will arise as data emerge from these new studies. This has already started in the context of circumcision. We believe that more efforts like these are needed, and on a larger scale. Here are some of the areas where attention is needed today:

ETHICS

We start our list with ethics because in the face of data that are indeterminate or preliminary—and so require confirmation in additional studies—consensus on ethical issues will be of paramount importance.

Take, for example, the hypothetical case of a microbicide “X,” which reduces the risk of HIV infection by 30 percent among women volunteers who used the product consistently and correctly in the context of a prevention trial. In many instances, product developers

TABLE 4 TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE (AUGUST 2006)

| Country | Male Circumcision | Female Diaphragms | PrEP | Herpes Suppression | Microbicides | Vaccines |
|--|-------------------|-------------------|------|--------------------|--------------|----------|
| AFRICA | | | | | | |
| Benin | | | | | • | |
| Burkina Faso | | | | | • | |
| Botswana | | | • | • | | • |
| Cameroon | | | | | • | |
| Ghana | | | • | | | |
| Kenya | • | | | • | | • |
| Madagascar | | | | | • | |
| Malawi | | | | | • | • |
| Nigeria | | | | | • | |
| Rwanda | | | | • | | • |
| South Africa | | • | | • | • | • |
| Tanzania | | | | • | • | • |
| Uganda | • | | | • | • | • |
| Zambia | | | | • | • | • |
| Zimbabwe | | • | | • | • | |
| ASIA | | | | | | |
| China | | | | | | • |
| India | | | | | • | • |
| Thailand | | | • | | | • |
| AUSTRALIA | | | | | | |
| Carlton, Victoria | | | | | • | |
| Sydney | | | | | | • |
| EUROPE | | | | | | |
| Belgium | | | | | • | • |
| Finland | | | | | | • |
| France | | | | | | • |
| Germany | | | | | | • |
| Sweden | | | | | | • |
| Switzerland | | | | | | • |
| United Kingdom | | | | | | • |
| LATIN AMERICA & THE CARIBBEAN | | | | | | |
| Dominican Republic | | | | | | • |
| Haiti | | | | | | • |
| Jamaica | | | | | | • |
| Puerto Rico | | | | | | • |
| NORTH AMERICA | | | | | | |
| Canada | | | | | | • |
| United States | | | • | • | • | • |
| SOUTH AMERICA | | | | | | |
| Brazil | | | | | • | • |
| Peru | | | • | • | | • |

might then proceed with a second or even third efficacy trial to confirm the initial findings and to gather more information about how the product works in different populations with different HIV risk factors.

Suppose, now, that another microbicide or vaccine trial is being launched in the same country or region where the first study was conducted. Should microbicide “X” be included in that study, even if it has yet to be licensed and made available for widespread use? Scientists and trial planners might argue convincingly that this would be premature. But would communities see it the same way? Perhaps. But in the context of a broader array of prevention tools, it will be essential to use dialogue and consultation to define research questions that are relevant to scientists *and* communities.

At issue is how different communities interpret the state of equipoise (the technical term for a state of being equally balanced; or, not knowing the answer to a scientific question). This issue has already emerged in the context of PrEP trials, where some community advocates have asked why trials of mono- and duo-therapy for PrEP are happening at the same time.

As Susan Buchbinder, director of the HIV Research Section at the San Francisco Department of Health and a principal investigator on the STEP study (see chapter 2), explains, “There may be differences between ‘scientific’ equipoise and ‘community’ equipoise.”

There will also be ethical issues when the data are clear-cut, and a strategy is deemed effective. How will the poorest and most vulnerable populations be guaranteed swift access to these interventions? There will be an inevitable delay as manufacturing capacity is scaled up and individual countries deliberate over regulatory approval, financing and delivery. During this gap period, trial sites will face many specific questions, including:

- Can/should research sponsors wait until a product or strategy that shows efficacy in clinical trials is licensed, before considering it as part of an add-on trial of other interventions (see “Trial Design” section)?
- Once an intervention is licensed, should trial sites add it to volunteers’ prevention package regardless of whether it is adopted by the country as part of a national program—or will this provide undue inducement for volunteers to enroll?
- Couple-, family-, and community-oriented voluntary counseling and testing (VCT) all have potential to increase VCT impact on prevention; yet these interventions compromise the confidentiality of the trial volunteer, which is central to ethical conduct of all research. Is there a role for trial sites in expanding availability of enhanced VCT to larger community?
- If ethical obligations related to any or all of above questions slow or prevent effective AIDS vaccine trials, in spite of overwhelming need for this research, what are the ethical consequences, if any, of this type of delay?

As with many other realms of research-related ethics, there are no black-and-white answers to these questions—at least for the moment. But it should be possible to reach consensus on some of the critical issues by engaging and educating various audiences, constituencies and groups of decision-makers. AVAC commits to working with partners in various forums to initiate and inform these dialogues.

ETHICS RECOMMENDATION:

Convene WHO/UNAIDS/Civil society-sponsored ethical consultations on issues related to introduction and evaluation of new partially-effective prevention strategies

Develop an infrastructure that will allow for ongoing review of these issues, so that consultations are not held at a single time point, but can be revisited and updated on a regular basis

TABLE 5 CONSIDERATIONS FOR USE OF A PLACEBO VERSUS AN ACTIVE CONTROL*

| | YES | NO |
|---|-------------------------------|------------------------------------|
| Is there effective treatment? | • | |
| Does the treatment affect survival or irreversible morbidity in the population to be studied? | • | |
| Is "effective" treatment accepted uniformly as standard treatment? | Active control in all studies | Placebo control where doubt exists |

* Adapted from Ellenberg et al. *Annals of Internal Medicine* 2000; 133: 464-470

TRIAL DESIGN

Right now, all of the prevention trials that are being conducted address more or less the same question: Does this strategy decrease the risk of HIV infection more than the standard prevention package provided by the study? Or, more simply put: Does it have an added benefit?

The standard prevention package also looks more or less the same for most of these studies. It includes: risk-reduction counseling, condoms or clean needles or both (depending on the study population), and treatment for sexually-transmitted infections.

But as data are released from these studies, prevention trial planners may find themselves posing new questions and revisiting the components of a given study's prevention standard of care.

New Trial Questions

"Knowledge begets knowledge," astronaut John Glenn said. "The more I see, the more impressed I am—not with what we know—but with how tremendous the areas are as yet unexplored." And when a new AIDS prevention intervention is identified, it will bring as many new questions as it does answers: Is a second-generation candidate better than a first generation candidate—and if so, how much better? Is a combination of strategies—for example, a vaccine plus a microbicide—better

than either one on its own? Or: What is the overall public health impact of a package of interventions? To answer a different question, you need a different trial design. And a scenario in which there are one or more partially-effective "first generation products"—as well as a pipeline filled with as-yet untested second generation candidates will add complexity to the work of trial planners and product developers.

This is a welcome challenge since it would only emerge in the context of evidence that one or more strategies has some level of efficacy. "I would give anything to have my life be more complicated," says Benoit Masse, chief statistician for the newly-formed Microbicide Treatment Network (MTN), who, along with colleague Steve Self at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP), is exploring the trial design issues that could arise when one or more partially effective interventions are identified.

But as welcome as this challenge might be, it must still be addressed with careful, coordinated planning. The ethical consultations recommended above are one aspect of this planning. It is also important to begin to explore the different trial designs that might be employed to get answers about new candidates, and to take steps to ensure that communities, political leaders and other audiences understand the rationale behind these various studies and the questions that they can (and cannot) answer.

TABLE 6

PRESENT AND FUTURE PREVENTION TRIAL DESIGNS

| QUESTION POSED/ANSWERED BY THIS TYPE OF TRIAL | DESCRIPTION | STATISTICAL AND OTHER CONSIDERATIONS |
|---|---|---|
| Trial type: ADD-ON TRIALS | | |
| Does adding experimental intervention “x” to the existing standard of care have a significant benefit (i.e., reduction in risk of transmitting or acquiring HIV)? | Most prevention trials use this strategy, i.e., <i>adding on</i> an experimental vaccine to proven interventions like condoms and clean needles and measuring any change, in incidence. In the future, add-on trials might involve a vaccine added on to a partially effective microbicide. | Sample size smaller in general than non-inferiority trials (see below); unable to provide answers about individual components of a given intervention. |
| Trial type: SUPERIORITY TRIALS | | |
| Is one intervention better than another of the same type or category (i.e., an experimental microbicide/vaccine versus a partially effective microbicide/vaccine) when each is added to the current standard of care? | Trials that determine whether one intervention is more effective than another. | Sample size smaller in general than non-inferiority trials (see below) and similar in size to current Phase IIb/III trials; must be willing to drop intervention that might be ‘non-inferior’ to a partially effective intervention. |
| Trial type: NON-INFERIORITY TRIALS | | |
| Is one intervention better or non-inferior than another of the same type or category (i.e., an experimental microbicide/vaccine versus a partially effective microbicide/vaccine) when each is added to the current standard of care? | Trials that determine whether one intervention is more, or at least as effective (within a certain margin) than another. | Can be very large (hundreds of thousands of people), particularly if the proven product has only low to moderate efficacy. Sample size for these trials is primarily determined by the anticipated magnitude of the effect of the new candidate and the size of the “non-inferiority” margin. If a first-generation candidate has a low level of efficacy (30-50%) then the non-inferiority margin will have to be small since the new intervention efficacy cannot get too close to, say, 20%. |

**QUESTION POSED/ANSWERED
BY THIS TYPE OF TRIAL**

DESCRIPTION

**STATISTICAL AND OTHER
CONSIDERATIONS**

Trial type: **FACTORIAL DESIGN**

How do several different experimental strategies interact with each other and with the current standard of care?

Factorial trials can have multiple arms. For example, a 4-arm trial might test the following combinations:

- 1) Experimental microbicide + placebo
- 2) Experimental vaccine + placebo
- 3) Experimental microbicide + experimental vaccine
- 4) All placebo

Factorial clinical trial designs allow an assessment of interactions among the interventions.

Sample size can be smaller than with superiority trials, but it is usually difficult to predict favorable conditions for efficiency; potential efficiency gains should be weighed against potential loss of power under possible scenarios. (See Green et al. in *Journal of Clinical Oncology*, 20(16), 2002.)

Trial type: **COMMUNITY-LEVEL TRIALS**

How does a specific package of care provided to an entire community affect HIV incidence and prevalence in a population?

Randomization of communities to receive different interventions. Already being used to evaluate two VCT strategies, it could be adapted to evaluate various prevention "packages" including a range of components. Community randomized trials typically allow the assessment of direct and indirect effects of an intervention.

Provides a "real world" picture of the combined impact of an array of services. Because the measurement is at the population-level (incidence and prevalence), these large trials could be less expensive than superiority trials of a similar size which measure individual impact (a given individual's risk of HIV infection). They could not be used for licensure of a single product (similar to add-on trials). Also, in today's global environment, it may be increasingly difficult to find two comparable communities which do not have some degree of "cross talk" (knowledge of/access to what is happening in the neighboring site) which could complicate data analysis.

Work of this kind has already been done in Thailand around the ongoing prime-boost trial. The study tests a combination that includes AIDSVAX, a candidate that failed to show efficacy when it was tested alone. If the ongoing trial does show some efficacy, it may be difficult to determine whether that is the result of the vaccine combination or solely of the ALVAC vCP1521, which is the other component of the prime-boost strategy.

More of this kind of work will need to be done on this front as various situations arise. Table 6 describes some of the different types of trial designs which might be employed to answer various questions.

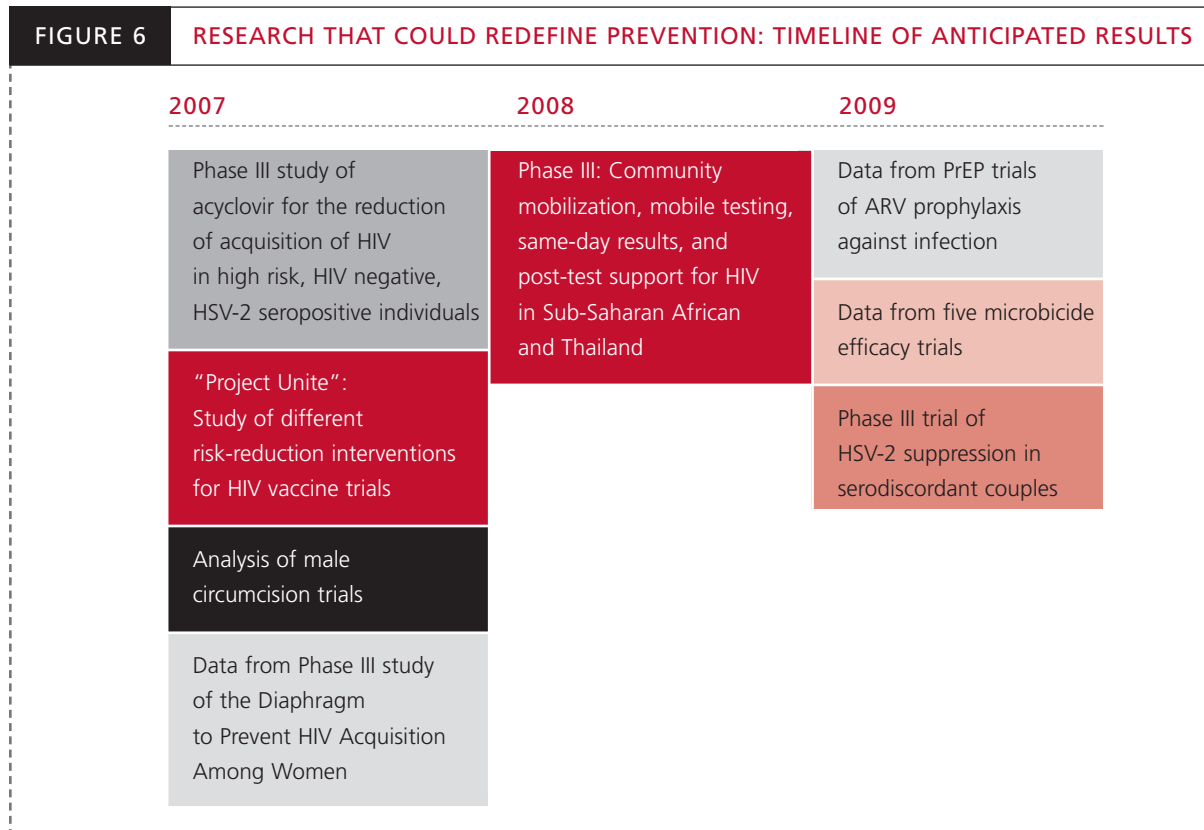
A New Standard of Prevention?

The field must also plan for the scenario in which a new intervention is proposed as part of the standard of prevention services and interventions for trial volunteers. Such an intervention would then be

added to the package provided to volunteers in both the active and the placebo arm.

In some cases, there could be a clear-cut argument for adding this intervention. If, for example, treatment of HSV-2 in HIV-uninfected people slashes the risk of HIV infection, then this could become part of the standard of care for all prevention programs in a relatively short amount of time. After all, the drug acyclovir is already on the market and approved for exactly this use.

But here again, the field should also be planning for confusion. What if circumcision shows a high level of efficacy in protecting men against HIV infection? A trial site could not require that all of its participants be circumcised, but should it offer the service on site? How much counseling time should be devoted to helping men and their partners make this decision?



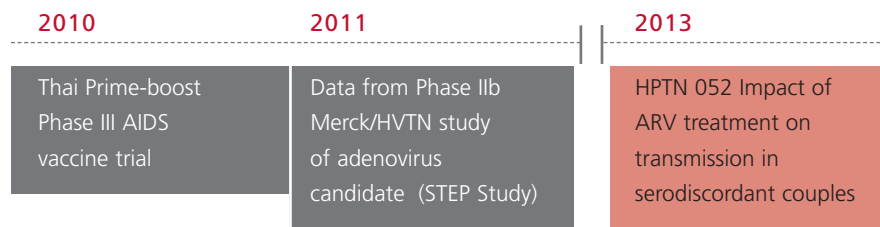
Or, what if one of the first-generation microbicides shows a low to moderate level of efficacy among women in serodiscordant relationships? Would it be ethical to conduct a placebo-controlled trial of another candidate in commercial sex workers, or should all trials going forward provide the first generation microbicide as an “active control”?

The above question is particularly difficult to answer prior to regulatory, licensing and manufacturing issues being addressed. During the limbo period prior to approval by the FDA, EMEA or other national regulatory authorities, how should these decisions be made? And in a situation of limited manufacturing capacity and finite quantities of product, should trial participants be prioritized to receive it?

The list of hypothetical situations and open questions is long. But given that we are likely to have several years to consider and prepare for them, we should use this time well. This means exploring how decisions about including a new product as an “active control” in a trial or in a country’s standard of care might be made.

Ben Masse and Steve Self have proposed the diagram in Table 5 as a starting point for these deliberations, but it’s important to note that these decisions will vary from country to country—especially in the period before so-called “normative” agencies like the World Health Organization, UNAIDS or PAHO have made decisions on a global or a regional scale.

In making these decisions, country- and community-level stakeholders (both policy makers and opinion leaders) will need a range of information including:



The strength of the data from the efficacy trial

- Is it conclusive? If so, for which populations? Are additional confirmatory trials needed? Does the level of efficacy meet community expectations—for example, is a 30% efficacious product or intervention desirable in all settings in the same way that, say, an 80% efficacious intervention might be?

The safety profile of the candidate

- Is the population in which product was evaluated similar in risk profiles, background disease, etc., to the one in which it might be used as an active control?

Community input

- What are the perspectives of potential trial participants, political leaders, and medical professionals?

Product availability

- Is there sufficient manufacturing capacity and supply to meet immediate and long-term needs? Is it licensed in the country where it would be used? Is it approved by international regulatory agencies?

It is important to plan for and discuss situations in which trial sponsors decide not to include a newly-identified intervention as the active control in a particular trial. This will not be the first time that such decisions were made; and they have drawn controversy in the past, as with the Ugandan study HIVNET 012, which compared the efficacy of single-dose nevirapine in mother-to-child transmission (MTCT). In that study, the control arm received a modified short course of AZT, which had shown efficacy in a recent Thai trial, rather than the extended regimen then used in the US and elsewhere in the developed world.

The world has changed dramatically since these early trials. ARVs are becoming increasingly available in resource-poor settings, and some MTCT programs have now expanded to MTCT-Plus, which provides combination treatment to the mother, father and children as needed after delivery. But future prevention

trials are still likely to face challenging decisions about *what* to add to the general standard of prevention care—or to the trial protocol—and *when* to add it. It will be absolutely critical that stakeholders on all levels contribute to the dialogue and decision-making process.

Adding an active control to a trial has an impact on the size and cost of the study. A new, additional effective intervention will ideally lower incidence in the trial population, thereby requiring larger numbers of participants and/or additional sites.

Depending on the trial design selected, the size of these trials could grow to greatly exceed that of current studies. Budgets for various trial networks, including the MTN and the HVTN, may be impacted by these findings—since most financial projections do not take into account the adjusted trial sizes suggested by early projections.

Large trials enrolling tens and hundreds of thousands of people are not unheard of, and have been conducted for other vaccines, like the Salk Polio vaccine, which was tested in hundreds of thousands of US children in the 1950s. More recently, the Merck HPV vaccine was tested in upwards of 20,000 young women. However, none of these interventions is a direct analog to HIV prevention, and much preparation is needed to ensure that there is capacity and political will for such trials to be done.

Getting regulatory guidance on the types of trial design that will be considered for licensure of a product is also important. If an add-on trial finds efficacy in a combination microbicide-vaccine, for example, where one component of the combination has not been tested on its own, how will the final product be licensed? This question will also be raised if there is an efficacy finding from the Thai prime-boost trial. Even though such questions may still be several years in the future, it is imperative that discussions among trial planners, funders, communities and regulatory authorities start now to avoid future confusion and delay.

It is also important to note that the majority of the new interventions currently under study are being evaluated for the prevention of sexual transmission of HIV. PrEP, HSV-2, and vaccine trials are all enrolling heterosexuals and men who have sex with men; and there is growing attention being paid to the issue of testing rectal microbicides in men who have sex with men. PrEP is also being studied in injection drug users, but this is the exception rather than the rule.

Cohorts of IDUs might therefore be recruited and ethically enrolled in trials that focus on efficacy of new interventions in preventing injection-related HIV transmission. But if these trials are to happen, it is critical that prevention-research sponsors and their partners in government and international health agencies do a better job of delivering proven interventions such as clean needles, syringe exchange sites, and drug replacement therapy using buprinorphine or methadone to trial participants. Twenty-five years into the epidemic, these proven interventions are still out-of-reach, if not illegal, in the vast majority of countries where injection drug use is driving the epidemic, and there is an urgent need to address this gap, both in the context of trials and on a broader policy level.

TRIAL DESIGN AND PLANNING RECOMMENDATIONS:

A series of expert consultations on trial design- and planning-related issues, with results widely-disseminated to prevention research stakeholders

Regulatory guidance from FDA, EMEA and other authorities about trial designs that can be used for licensure applications of candidates and/or combination strategies

Develop a coordinated advocacy agenda designed to document best practices and improve prevention services offered to IDU cohorts

VOLUNTEER COUNSELING AND TESTING AND RISK REDUCTION FOR VOLUNTEERS

All volunteers in prevention trials receive intensive risk reduction counseling as well as condoms and, in some instances, clean needles. These are provided at every study visit. As a result, volunteers often receive a higher standard of prevention care and support on a more regular basis than is available to or accessed by the general community.

But while there is general consensus about the high-quality and standard of VCT and risk-reduction counseling in the context of vaccine trials, there is surprisingly little research evaluating the efficacy of these trial-specific interventions.

Nor is there any common mechanism for quality assurance or control that could be used to evaluate or review services at the time of site initiation or throughout a trial.

There are some analogies from outside the AIDS vaccine field. The “Explore” study recently completed in six U.S. cities was the first trial to prospectively evaluate the impact of two different risk reduction interventions on HIV incidence in MSMs. This trial enrolled 4295 men and followed them for more than four years. Ultimately, it found no significant difference in HIV infection rates between the two arms.

The “Explore” experience underscores the reality that it can be very difficult to gather definitive data on the different behavioral interventions. But there is still a need to improve our understanding of what constitutes quality risk-reduction counseling for trial volunteers.

Dr. Beryl Koblin and her team at the New York Blood Center are attempting to answer this question in the context of high-risk women, through a study

called UNITY, which is comparing two different types of HIV risk-reduction and vaccine-education interventions in high-risk women in New York City. The women will be offered hepatitis B vaccine as a surrogate for an AIDS vaccine. The trial will measure levels of comprehension about key aspects of vaccine research and number of unprotected vaginal and anal sex acts in the two arms.

VCT AND RISK REDUCTION COUNSELING

RECOMMENDATION: Develop a fully-funded and coordinated research agenda geared towards defining the effects of various risk-reduction counseling strategies in context of HIV/AIDS vaccine trials

REGULATORY AND IMPLEMENTATION ISSUES

If a new intervention is identified, it will not automatically be adopted by all countries at the same time. As experience with HPV vaccine is showing, initial introduction may be in specific pilot countries; other countries may conduct cost-benefit analysis and determine that the value added by the new strategy—particularly one that is only partially effective—is not sufficient to justify the costs of introducing it at a country level.

Situations in which a new intervention has not been introduced as part of a national program, or is only available in select pilot sites, present a unique challenge to trial planners. “One of the questions you have to ask at a site and a country level is: ‘At what point would a research team have to say there is enough evidence for this to be [part of the trial] standard of care?’” says Helen Rees principal investigator at the Reproductive Health Research Unit in Soweta, South Africa. “Can a research team put in a prevention standard of care that is not programmatic in the country? At what point does that become a perverse incentive?”

These decisions bear strong similarities to the debates around provision of ARVs as part of the treatment

standard of care for prevention trial volunteers and communities. Here, sponsors are already grappling with questions like: What happens if ARVs are not widely available in the community or at country-level? What kinds of strategic partnerships can be leveraged to expand access to a given service, so that inequities between volunteers and their communities are minimized?

As trial sponsors face these decisions, so, too, do countries. And here there is an important role to be played by the World Health Organization in issuing and updating guidance notes on specific interventions. Given the planning and logistical requirements of introducing new prevention approaches, these documents should, in some instances, be issued before or at the same time as results from confirmatory trials are released.

REGULATORY AND IMPLEMENTATION

RECOMMENDATION: Regularly-updated WHO guidance notes on new and emerging prevention interventions including male circumcision, PrEP, HSV-2 treatment, couples counseling, enhanced VCT to support country-level decision making about adding new interventions to national programs

COMMUNICATIONS AND ADVOCACY

The foundation for all of these action items is a clear and coordinated communications effort that conveys consistent messages about partial effectiveness, evolving standards of care and the need for trials of multiple prevention interventions—even after first-generation strategies have been identified. This effort can build on the strong work to date done by the microbicides and vaccine fields. But it must go further: in an era where there is a partially effective microbicide or vaccine, or PrEP intervention, the boundaries between the fields will all but vanish. It is incumbent on all prevention-research stakeholders to coordinate and prepare for this convergence.

COMMUNICATIONS AND ADVOCACY

RECOMMENDATION: Form a prevention research advocacy network that brings together stakeholders from all the various fields and regions to discuss communications and messaging strategies and to share best practices from around the world

THE AIDS VACCINE ADVOCATES' CHALLENGE

In just a few years, the context for conducting prevention trials may be dramatically different from what it is today. But one thing is certain: there will still be a need for a safe, effective and affordable AIDS vaccine as an element of a comprehensive prevention package. Just as effective family planning programs rely on providing women with a “menu” of options for different times and situations in their lives, so, too, must AIDS prevention continually aspire to identifying a complete array of strategies and choices.

Given the history of vaccines as the most powerful tool for ending epidemics that the world has ever known, it is absolutely imperative that these trials continue to be prioritized and conducted, with the goal of identifying candidates with ever-increasing levels of efficacy. One reason for this is that challenges

of conveying the realities of partial efficacy will always be many—and hard to overcome.

AIDS vaccine advocates have a critical role to play in ensuring that research continues with speed and the highest ethical standards. To help contribute to this, AVAC commits to:

- **Create clear, user-friendly materials explaining the consequences of findings from trials of various interventions including circumcision, HPV vaccine, HSV-2 treatment, PrEP, microbicides and vaccines**
- **Support and/or convene a prevention research advocacy network that facilitates and disseminates results from expert consultations on cross-cutting ethical, community and trial design issues**
- **Develop, field-test and update initiatives to expand comprehension of partial efficacy and its implications for public health and future trial design**
- **Advocate at WHO level and elsewhere as appropriate for guidance notes on relevant topics**

Future AVAC Reports and publications will measure our progress on these goals and provide updates on the state of the field in achieving research milestones, while also providing excellent prevention services for every population, every place in the world.

ABOUT AVAC

Founded in 1995, the non-profit AIDS Vaccine Advocacy Coalition (AVAC) seeks to create a favorable policy and social environment for accelerated ethical research and eventual global delivery of AIDS vaccines as part of a comprehensive response to the pandemic. This work is guided by the following principles:

- Translate complex scientific ideas to communities AND translate community needs and perceptions to the scientific community.
- Manage expectations.
- Hold agencies accountable for accelerating ethical research and development.
- Expand international partnerships to ensure local relevance and a global movement.
- Ensure that policy and advocacy are based on thorough research and evidence.
- Build coalitions, working groups and think tanks for specific issues.
- Develop and widely disseminate high-quality, user-friendly materials.

AVAC CURRENTLY FOCUSES IN FOUR PRIORITY AREAS:

01. Develop and advocate for policy options to facilitate the expeditious and ethical development, introduction and use of AIDS vaccines and other new prevention technologies.
02. Ensure that rights and interests of trial participants, eventual users and communities are fully represented and respected in the scientific, product development, clinical trial and access processes.
03. Monitor the AIDS vaccine field and mobilize political, financial and community support for AIDS vaccine research as part of a comprehensive response.
04. Build an informed, action-oriented global coalition of civil society and community-based organizations exchanging information and experiences.

A major part of AVAC's work is to translate complex scientific ideas to communities through the development and wide dissemination of high-quality, user-friendly materials. In addition to our annual report that analyzes progress toward the development of an HIV/AIDS vaccine and makes recommendations for actions in the coming year, AVAC publishes the AIDS Vaccine Handbook and operates the AIDS Vaccine Clearinghouse (www.aidsvaccineclearinghouse.org), a comprehensive and interactive source of AIDS vaccine information on the internet.

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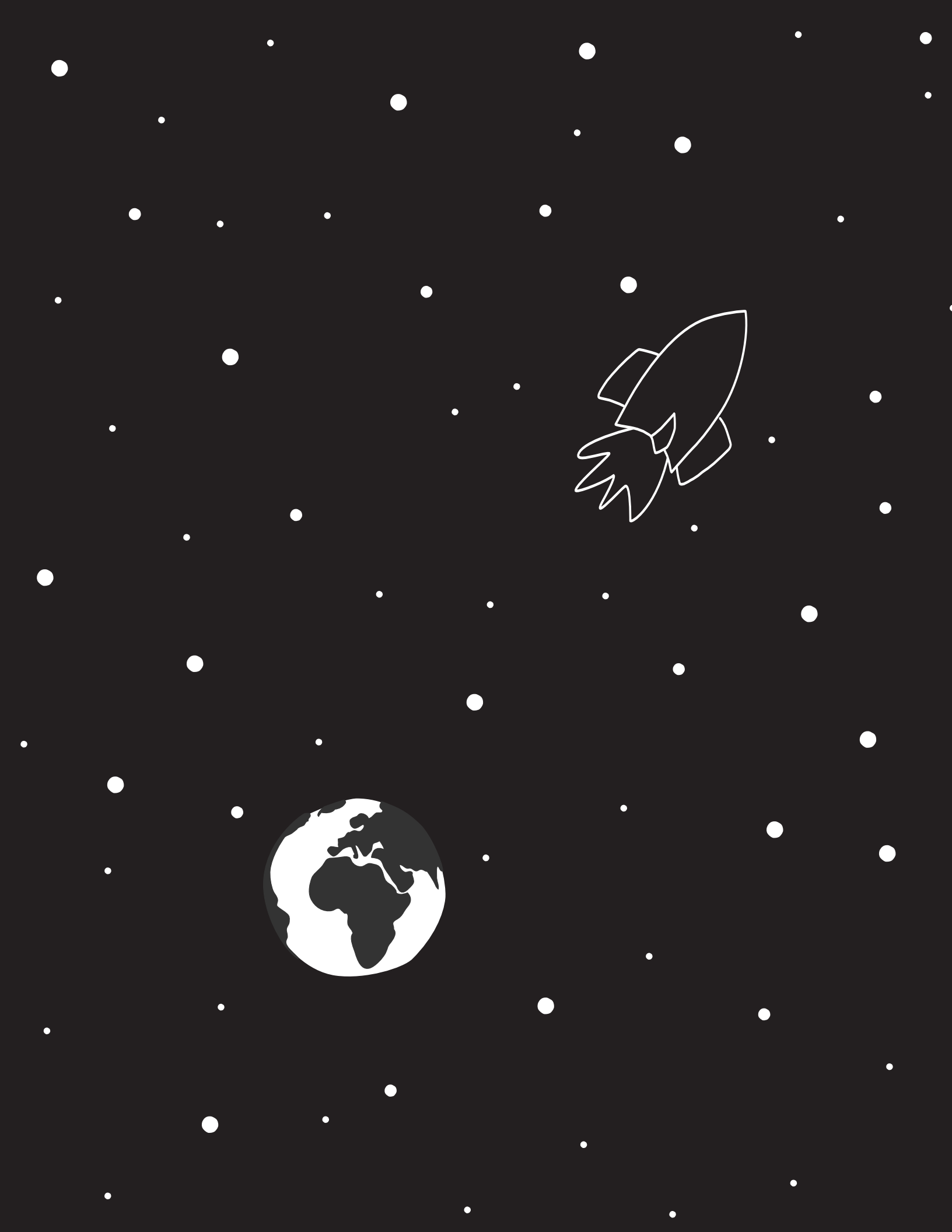
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