HIV Topical Microbicides: Steer the Ship or Run Aground

Six HIV candidate microbicides are scheduled to enter 6 large-scale effectiveness trials in the next year. The selection of products for testing and the design of this group of trials should be reconsidered to provide an answer to a key question now before the field: Does a sulfonated polyanion, delivered intravaginally as a gel, block HIV attachment to target cells with sufficient potency to protect women from sexually acquired HIV infection?

Paradoxically, entering more candidates into more trials may confuse or compromise efforts to identify an effective product. Instead, a single trial of the most promising product(s) best serves the current candidates while also preserving resources needed to promptly advance innovative new protective concepts into future large-scale trials. (*Am J Public Health.* 2004;94:1085–1089)

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I TOLD MY FRIEND I WAS thinking of referring to microbicides—in comparison with preventive HIV vaccines—as "the other white meat." Without a moment's hesitation, she waggishly shot back, "Yes, but vaccines have all the pork."

As soon as HIV was isolated in the early 1980s and methods were devised for producing large quantities of the virus for diagnostic tests and laboratory studies, preventive vaccines emerged as a paramount research goal because they were considered the optimal means of controlling the HIV pandemic. Topical microbicides—vaginally/rectally administered agents designed to block HIV access or attachment to or insertion in the genome of susceptible target cells—for the most part languished: unfamiliar, unpronounceable, marginalized, typically ignored or neglected in public by officials who played a predominant role in establishing research priorities and discounted or trivialized in private. Although, like vaccines, microbicides can interrupt mucosal transmission of HIV in animal models, they long remained overshadowed as a biomedical means of preventing HIV infection.

With the annual National Institutes of Health (NIH) budget for HIV vaccine research projected to exceed half a billion dollars in the upcoming fiscal year, routine increases in the vaccine budget in the neighborhood of $50 million[1] per year approximate the entire amount annually designated for microbicides, estimated at $68 million in fiscal year 2003.[2] In the past decade, NIH has spent tens of millions more on preparations for HIV vaccine efficacy trials that have never taken place than on the few microbicide trials that have. Federal bureaucrats learn to recite the magic sentence that exorcises complaints of insufficient resources: current funding is adequate to support any research worth pursuing. Because availability of funds motivates researchers to take risks and devote the substantial effort required to apply for grants and contracts, lack of funding and lack of ideas worth funding stall a research field in a vicious circle of apathy.

MORE IS LESS?

However, by early 2004, persistence in the face of an unremitting pandemic affecting ever larger proportions of women finally seemed to have paid off. Six new microbicide candidates that had been painstakingly brought through preclinical and early clinical development were poised to enter large-scale effectiveness trials in the subsequent 12 months. Sponsors had secured sufficient funding from government and foundation donors—the Department for International Development of the United Kingdom, the Bill and Melinda Gates Foundation, NIH, and the US Agency for International Development—to launch the trials, with the expectation that donors who provided the down payment would follow through with the $250 million or more likely to be required for their completion.

Sponsors have worked closely with donors to secure the extensive resources required for such a costly undertaking. Field sites have been identified and prepared to begin the trials, and communities have been informed about and mobilized to support these studies. Unless plans change, more than 20 000 women, mostly in developing countries, will be asked to volunteer for these trials in the next several years and to sustain participation for periods of up to 2 years and, sometimes, even longer (Table 1).

At a historical moment that seems well worth celebrating, microbicide research has reached a crossroads where the momentum of a decade or more of effort is sending it down the wrong path. By testing too many products in too many separate clinical trials, the field is mortgaging its future. Not only is the multitrial strategy flawed, but the scope and duration of these trials may stall the evaluation of even more promising, innovative candidates now progressing through preclinical and early clinical development. The field stands to benefit from pausing to compare available candidates and to consider proceeding only with the best-performing one(s). Sound research design and resource management imply that such a portfolio review should in turn lead to a better coordinated, more efficient clinical testing strategy.

A 6-PRODUCT, 6-TRIAL PILEUP

Five of the 6 products about to enter large-scale trials belong to

TABLE 1—Microbicide Effectiveness Trials Scheduled to Begin in 2004

Sponsor (Manufacturer)	Product	Sample Size (Design)	Country (City/Region)	Estimated Start
NIAID/HPTN (Indevus; Reprotect)	Pro2000/5; BufferGel	3100 (phase IIb; 4 arm)	India (Pune) Malawi (Blantyre, Llongwe) South Africa (Durban, Hlabisa) Tanzania (Moshi) Zambia (Chililabombwe, Lusaka) Zimbabwe (Chitungwiza, Harare)	Q3
USAID (Biosyn)	Savvy (C31g)	4284 (2-arm phase III × 2)	Ghana (Accra, Kumasi) Nigeria (Lagos, Ibadan)	Q1
USAID/GMP (CONRAD)	Cellulose sulfate	2500 (2 arm)	India (Chennai) Kenya (Nairobi) Uganda (Kampala) Benin	Q2–3
USAID/GMP (CONRAD)	Cellulose sulfate	2700 (2 arm)	Cameroon (Yaounde)	Q4?
Population Council	Carraguard	6260 (2 arm)	South Africa (Cape Town, Durban, Soshanguve)	Q1
DFD/MRC (Indevus; ML Labs)	Pro2000/5; Emmelle (dextrin-2-sulfate)	6000 (3 arm)	South Africa (Durban, Johannesburg, Mtubatuba) Zambia (Mazabuka) Tanzania (Mwanza) Uganda (Masaka) Cameroon (Yaounde)	Q2–3

Note. NIAID = National Institute of Allergy and Infectious Diseases; HPTN = HIV Prevention Trials Network; Q = quarter; USAID = US Agency for International Development; GMP = Global Microbicide Program; DFD = Department for International Development (United Kingdom); MRC = Medical Research Council.

the same class of compound, sulfonated polyanions. Their protective activity depends on the same mechanism of action: interference with HIV attachment to susceptible immune cells. One of the 5 also lowers pH in the vaginal milieu to levels expected to be virucidal. The detergent action of the sixth compound, a surfactant, purportedly will disrupt the envelope of HIV yet spare the membranes of healthy cells (Table 1).

The first product scheduled to enter a large-scale trial is the surfactant Savvy. Only 4 years ago, the field recoiled from news that even at the lowest dose tested, a previous surfactant candidate, nonoxynol-9 (N9), increased susceptibility to HIV infection among the most frequent users of the product.[3] The same detergent action that disrupts the HIV envelope also may cause lesions in the vaginal epithelium, the principal physical barrier between HIV and susceptible immune cells. Published studies suggest that Savvy may[4] or may not[5] be as injurious to healthy tissue as N9.

It is impossible to overstate the potential harm to future microbicide research and perhaps other research on preventive biomedical technologies—not to mention the very real risks to participants in the trials—should field testing of another surfactant product reveal an adverse safety profile. Safety assessment procedures used in N9 trials will remain unchanged in upcoming trials of Savvy, which means that thousands of women might be exposed for months or even years before such adverse effects became identifiable. No evidence of superior efficacy relative to other advanced microbicide candidates counterbalances concern about Savvy's potential toxicity.

HOW NOT TO SELECT AMONG "ME TOO" PRODUCTS

No industrial sponsor would commit the extensive resources required for efficacy trials to 5 products of the same type. Rather, the most promising candidate would be sought through comparative preclinical and early clinical tests—considered the most plausible indicators of clinical safety and efficacy. Development of the 5 polyanions has been supported by separate sponsors in vertical alliances that have precluded or discouraged cross-product comparisons. When a single donor has supported multiple products, the donor has not always had the independent scientific capacity to assess the comparative merits of products it supports. Although almost all trial funding comes from public coffers, the available data on these products have not been brought together in a single forum that would allow direct head-to-head comparisons.

Carraguard is the only product in this category to have completed a stand-alone phase II trial. The product and placebo arms registered the same number of infections.[6] Although an insufficient number of cases are available to provide definitive evidence that Carraguard lacks protective efficacy, this finding supports further comparative testing versus other products of the same class. In vitro assays of multiple products indicate that they are not equivalent in their virucidal potency,[7] suggesting that comparative preclinical data would support selection of the most promising from among the group.

New insights into the fundamental molecular mechanisms of HIV infection indicate that the laboratory-adapted variant of HIV used in previous preclinical efficacy studies differs importantly from the variant of HIV most often implicated in sexual transmission. This difference is pivotal, because polyanions may be less effective in inactivating the sexually transmitted variant (known as CCR5) than the laboratory-adapted variant (CXCR4). Suitable viral stocks now make it possible to evaluate candidate microbicides using CCR5 variants for both in vitro studies and a low-dose, multiple-challenge non–human-primate test, one considered to be a more relevant

model for human sexual transmission than previous such tests.[8]

HOW NOT TO COMPARE MULTIPLE PRODUCTS

The question to be answered at the present stage of product development for this particular concept—nonspecific blocking of HIV attachment to target cells—is whether the most compelling candidate in the class, based on comparative preclinical efficacy and preclinical and early clinical safety, protects uninfected women from HIV acquisition during unprotected vaginal intercourse. Testing more than one product of the same class requires an explicit rationale, including analyses assessing cross-product differences to inform the field and guide further product development.

If multiple products are to be tested, they should be entered into a single randomized trial that ensures equal distribution among all products of any factors that may influence effectiveness other than the product itself. Only a single trial that randomizes all products can distribute confounding factors—measured and unmeasured—equally among all products. Testing multiple products in multiple trials simply because they are ready, the sites are ready, and the funding agencies have signed the checks does not exemplify good science, sound policy, or responsible ethics.

In the case of a patchwork of trials, there seems no evident rationale for decisions to test some candidates in multiple trials and others in only a single trial or to test some products in concurrent trials with different designs and other products in paired trials with identical protocols. Differences among trials may complicate, and even preclude, direct comparisons. For example, products may perform differently not because of differences in their biological efficacy but because of differences among women enrolled in different trials in terms of, for example, product acceptability or consistency or contexts of condom use. Comparative analyses will be especially difficult, because these separate trials lack common methods and instruments with which to measure such key behavioral indicators.

Some trials have been designed in conjunction with the input of regulators and are based on plans for submitting applications for licensure based on specified study outcomes. Other trials have no clear linkage to a plan for subsequent regulatory review. In countries with rampaging epidemics and an underdeveloped public health infrastructure, regulators are apt to look to the Food and Drug Administration or the European Agency for the Evaluation of Medicinal Products for guidance. But few of these trials have been designed to address specifications for US or European licensure or registration, leaving a policy vacuum. Consequently, the outcome of a single trial, for instance, may indicate enough of a protective benefit from an experimental microbicide to suggest that it would contribute usefully to HIV prevention efforts, even though the results may lack the strength of evidence required to convince regulators to approve such a candidate for licensure.

HOW TO AVOID BETTER SAFETY ASSESSMENT METHODS

Researchers acknowledge weaknesses of the key outcome measure used to monitor product safety: pelvic examinations with visual inspection and colposcopy to detect lesions. A method that depends on clinical examinations is difficult to standardize, labor intensive, burdensome for study participants, and very costly. Furthermore, the N9 experience suggests that this is not an optimally sensitive way to monitor product safety. Although sponsors have sought to standardize colposcopy by including the same trainers for all trials, plans for periodic assessments of "drift" from the prescribed clinical examination procedure and implementation of corrective mechanisms have not been elaborated with an equal amount of comprehensiveness.

Large-scale trials with HIV infection as a primary outcome provide the best opportunity to assess the performance of biomarkers that may be superior safety indicators. Specimens required for such studies can be collected readily, sometimes even by study participants themselves without the assistance of a clinician. Because laboratory-based biomarkers involve the use of reproducible assays, they are intrinsically more reliable than clinical observations made by multiple practitioners. They can be selected so as to be more sensitive than overt tissue damage detectable during clinical examinations. From the perspective of quality control, they are simpler to assess, and inconsistencies in implementation can be more easily remedied.

Pressured by a sense of urgency to move their studies into the field, reluctant to incur even marginal added costs, and unwilling to task already overburdened field sites with any additional procedures required for such "ancillary studies," sponsors have made no provisions to exploit a unique opportunity to improve the efficiency and increase the sensitivity of safety monitoring in future trials. Selecting fewer products, which would reduce the total required sample size, and consolidating operations in a single multicenter trial might provide a more suitable context for any additional specimen collection and storage required to support such studies.

MORTGAGING THE FUTURE

More worrisome than a group of trials in which all fail to demonstrate the efficacy of any single candidate would be a trial program that generates ambiguity while delaying entry of the next generation of candidates into large-scale trials. These risks are all too real, because the proposed set of trials places unprecedented demands on individual clinical trial sites.

Few of the sites that are slated to participate in these trials have previously attempted the massive effort required to recruit and retain 500 to 2000 women in a study. Few sites have conducted prior studies intended to support a regulatory submission for registration or licensure. These requirements translate into the need for flawless conduct of study procedures, accuracy of data capture, integrity of specimen management, and administration of regulated investigational products.

When the next generation of compounds—now progressing into late preclinical or early clinical testing—become available for entry into large-scale trials, the sites that are now being committed may still be engaged in completing the current generation of studies. With new clinical trial

capacity just beginning to be cultivated, inadequate infrastructure may result in the next generation of candidates remaining in limbo while the current set of trials draw to a close. Yet, these candidates are apt to be more promising than the current group of advanced candidates because they benefit from insights and opportunities unavailable even a few years ago.[9]

Much more now is known about the process of HIV infection secondary to sexual exposure, particularly the importance of R5 versus X4 coreceptor usage. In vitro challenge studies with subtypes representative of those in circulation in the regions where products are to be tested and an improved non–human-primate model can provide more useful guides to potential field efficacy. New agents specifically active against HIV at diverse stages of its replication cycle have joined the array of compounds available for evaluation. At last, products being considered as microbicides have induced participation in the field by some of the industry giants that have, until now, scrupulously refrained even from licensing abandoned compounds for public sector development as HIV preventive products.

Knowledge of principles and techniques for developing topical formulations fundamental to the cosmetic and skin care industries now informs microbicide development. Long-acting delivery systems such as relatively unobtrusive vaginal rings that may require replacement monthly or even less often are being carefully scrutinized; these systems would greatly reduce adherence burdens on users while offering a truly inactive placebo that will simplify clinical trial design. Increasingly, product designers appreciate (and development strategies anticipate) that the most effective products are likely to combine multiple active ingredients and mechanisms of protection to achieve broad coverage.

However, the proposed trials have enlisted virtually every potential field site believed to have access to suitable populations of high-risk trial participants and capable of ensuring that their participation meets the highest scientific and ethical standards. These sites will be engaged in enrolling or following participants through 2006 to 2008, or even longer if accrual is slower or retention more problematic than currently contemplated in ambitious study parameters and timetables. It typically requires 2 or more years to identify, develop, and qualify new clinical sites that can participate in efficacy trials.

THE PAUSE THAT REFRESHES

Sponsors might argue that the additional delay in implementing large-scale microbicide trials required to reconsider product selection and rework clinical trial design also will delay progress by 1 to 2 years. Certainly, it will take time to assemble data, perform any additional preclinical studies that seem especially critical for decisionmaking, finalize a revised trial protocol, secure regulatory review, and implement a different field site distribution than that currently planned. The time required depends on how quickly people can mobilize and become motivated to address the future instead of defending well-intentioned decisions made years ago that no longer serve the field.

Any pause is vexing. It imposes major disruption on field sites, host communities, sponsors, and donors. Imposing a further cycle of scrutiny or wholesale revision of research protocols is especially difficult for sponsors who sacrificed much and struggled long and hard to bring a candidate to this most advanced stage of product development. But the risks and costs of pausing must be contrasted with the risks and costs of proceeding. On both sides, imponderables weigh heavily. People may die because research delays defer answers that could have spared them. People also may die because research proceeds down a blind alley or stalls progress in more promising avenues of investigation. Perfection may be the enemy of the good. But hunkering down in dogged determination to proceed, while refusing to take the measure of obstacles that threaten further progress, is called a shipwreck.

POSTSCRIPT

As this paper was going to press, both of the developments alluded to above subsequently unfolded. In February, as informal discussions with donor organizations moved toward some sort of mobilization to review the overall research strategy being implemented, the potential challenge to existing plans became known to trial sponsors. Sponsors of 2 of the proposed trials redoubled efforts to insure that accrual would begin without any further delays, just in time for word to spread at the biennial Microbicides 2004 meeting of virtually every investigator and organization committed to this area of research and development. There can be no more effective way to discourage a modification of the study design or data collection instruments and methods than to begin enrolling volunteers based on the existing protocol and case report forms.

Nevertheless, the Alliance for Microbicide Development and Gates Foundation did orchestrate a consultation April 12–13, 2004 on behalf of the trial donors (Polly F. Harrison, PhD, Executive Director, Alliance for Microbicide Development, Silver Spring Md, oral communication, May 12, 2004). The program (Memorandum from Renee Rizdon and Polly Harrison to Participants in Funder's Consultation April 5, 2004) implied no challenge to the selection of products entering testing or the assemblage of trials being implemented, seeking instead to "extract the maximum possible benefit out of the trials going forward." Despite the complexity of issues associated with the existing menu of trials, the brief meeting also sought to "seek consensus on next best steps for development and testing of future microbicide candidates." ■

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