Talia Elliott

Mr. Speice

ISM 1

13 September 2017

Research Assessment #2

Date: September 13, 2017

Subject: AIDS and HIV

MLA citation:

Piot, Peter. "AIDS: a global response." *Science*, vol. 272, no. 5270, 1996, p. 1855. *Academic OneFile*, go.galegroup.com/ps/i.do?p=AONE&sw=w&u=j043905010&v=2.1&id=GALE%7CA18480751&it=r&asid=6f956acd1cdc15422205623c5daec245. Accessed 13 Sept. 2017.

Stone, Alan. "Microbicides: a new approach to preventing HIV and other sexually transmitted infections." *Nature Reviews Drug Discovery*, vol. 1, no. 12, 2002, p. 977+. *Academic OneFile*, go.galegroup.com/ps/i.do?p=AONE&sw=w&u=j043905010&v=2.1&id=GALE%7CA185694816&it=r&asid=8729c267689673f49ab2d598462c2ac4. Accessed 15 Sept. 2017.

Assessment:

I chose to do this research assessment over the immune disorders HIV and AIDS. Because I am interested in immune related medical research, this research topic was fitting. The articles listed above provided information from research studies conducted by professionals. The first article focuses on how AIDS affects developing countries, and how industrialized countries

could help areas most affected by AIDS. Since close to 90% of people with AIDS are in developing countries, there are multiple things that could be done to provide aid to these people. The second article focused on one of the theories currently being tested for prevention of AIDS: microbicides. Although microbicides sound promising, the study referenced in the second article was unsuccessful. I found the information in these articles both interesting and relevant to my studies in ISM.

The issues discussed in the first article were interesting to me because they deal more with the medical ethics side of research, as opposed to the scientific side. The information given by the article, such as the fact that, "Globally, over 8500 newly infected people daily join the ranks of the 21 million already living with one of the 10 known subtypes of the virus" (Piot), was interesting, but provided evidence to Piot's more important point; little is being done to help developing countries with the issues surrounding HIV and AIDS. The article made the point that little research is done in developing countries for an issue that affects them most. This means that some of the solutions created are not accessible to the people of these countries. I thought this was extremely important to consider, for trials not only trials done on HIV and AIDS , but other medical topics of interest also. Accessibility and affordability should be kept in mind when creating prevention and treatment options for medical disorders because, if the solution is not viable for all people being affected by the issue, then is it really a solution? I would like to keep this in mind as I begin looking for a research study I would like to be a part of; I am researching to help people, so shouldn't I find a trial whose main goal is to help *all* people?

The second article introduced several points that I thought related to me in my research this year. The first was a further continuation of the idea above; helping people in disadvantaged situations. One of the reasons the article cited for the importance of developing microbicides (an

alternate form of prevention for women at risk for AIDS, HIV, and pregnancy because of sexual relations) was to allow women control of their bodies. In many areas where AIDS and HIV are common, women are not given much say in their lives. This means that condom usage may be up to the men, which can cause unwanted pregnancies and STDs. By giving these women a product which they can control the usage of, medical professionals are liberating them. I am extremely excited by the idea of being able to aid groups and individual people in need through medical work. To make a difference like that in the lives of even just a few people would give my life an important purpose, and I think that is part of the reason I am drawn to the medical research field. The second interesting point the article made was something I have been thinking about since the start of the year: failure is always an option. Although I believe failure should be avoided, it is sometimes inevitable, and this article proved that even professional medical scientists are sometimes incorrect. In their testing of the microbicide nonoxynol-9, "the World Health Organization released a report containing the recommendations of a meeting of experts who had concluded, after careful scrutiny of all the available evidence on the potential benefits and hazards of nonoxynol-9, that this substance should not be used as a microbicide (although it remains a contraceptive option for women at low risk of HIV) [16]" (Stone). The researchers developed a hypothesis but were proven incorrect. This does not, however, mean that all research on microbicides will halt—and nor should it. It simply means that the research scientists will form a new hypothesis and continue their research. I think that this proves there is always something to be learned from failure, and, in the research field, it is even an important step. This makes me excited to be able to develope my own hypothesis and even face failure in the pursuit of innovation.

Both the documents, in my opinion, proved important points about the medical field that I will carry with me as I begin the journey of finding a mentor and working in a lab this year. In addition, the information about AIDS and HIV in these articles were very interesting, and I enjoyed getting to learn more about these disorders. I think my interest in these articles has also allowed me to be sure of my interest in medical research and immune disorders. Overall, these articles were useful and a reminder of what I want to do with my time in ISM this year.

AIDS: a global response

Comment [1]: Found on Academic OneFile, a database listed on Mackinvia, so the source can be assumed to be credible.

Abstract:

The new joint United Nations Program on HIV/AIDS (UNAIDS) should assure that plans for global AIDS/HIV research are designed to meet the needs of developing countries not just those of the richer nations. Ninety percent of people with AIDS or HIV live in developing nations.

Full Text:

The U.S. Centers for Disease Control and Prevention estimate that 40,000 U.S. citizens became infected last year with the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS). Globally, over 8500 newly infected people daily join the ranks of the 21 million already living with one of the 10 known subtypes of the virus. In heavily affected countries in Africa and Asia, where one out of three urban adults may be infected, AIDS deaths among young and middle-aged adults--workers, managers, political leaders, and military personnel--are threatening health systems, economies, and national stability. With the current scale of global travel, the largely invisible, shifting, and expanding global epidemic of HIV makes the planet a more dangerous place for all.

This is not to say that there is no hope. For the first time, a number of developing countries are registering a genuine drop in new HIV infections, which shows that prevention efforts focused on safer sexual and drug-related behavior are beginning to pay off. The clearest indications come from Thailand, where the reductions in incidence and prevalence are most dramatic among young men. In cities in Uganda, one of the hardest-hit countries in the world, the number of HIV-infected pregnant women is lower now than 5 years ago. Existing prevention approaches, though imperfect, demonstrably work. But maximizing protection from HIV over future decades of foreseeable transmission calls for improved approaches and technologies. Research is key to making a serious dent in the unstable global HIV situation and bringing the numbers down to stable and safer levels.

Comment [2]: Understandable why just developed countries...however efforts need to begin to be made in undeveloped countries. Maybe research on more affordable options needs to occur?

Comment [3]: how much lower?

Recent scientific breakthroughs are encouraging. For example, combination therapy with antiretroviral drugs now promises not only to defer disease progression and improve quality of life but perhaps even to turn HIV infection into a chronic nonprogressive condition. Progress in the development of HIV prevention technologies has been slower than was once hoped, but again there are encouraging advances, particularly the discovery that zidovudine can interrupt mother-to-child transmission. If these and other potential breakthroughs are to result in a safer world, the global research agenda needs to be turned on its head. Immediately. Fact 1: The AIDS problem is overwhelmingly concentrated in the developing world, where more than 90% of all HIV-infected people now live. Fact 2: AIDS intelligence and R&D are overwhelmingly concentrated in the industrialized world, where the problem, though serious, is only a small fraction of the global epidemic.

Scientists urgently need to focus epidemic intelligence on the constantly shifting global picture (as is now done for influenza virus subtypes), direct R&D to technologies that will be globally relevant and affordable, and carry out product evaluation together with the developing countries. This calls for the establishment of partnerships, including innovative joint ventures between the public sector and the pharmaceutical industry. Without them, there is little hope of developing accessible vaccines and vaginal microbicides, which are the main hopes for the future. Equally important, if not more so, partnerships must be forged between developed and developing countries. Basic laboratory research will probably continue to be conducted mainly in industrialized countries, but the developing countries have the most to gain from research. They also have a great capacity to contribute, particularly in the evaluation of new therapeutic and preventive approaches.

The new Joint United Nations Program on HIV/AIDS (UNAIDS), itself cosponsored by six UN agencies with mandates ranging from health to development, has a role to play in bringing these partners together. UNAIDS and other research sponsors and funders also bear a responsibility for ensuring that the global HIV/AIDS research agenda--in particular, any research conducted with and in developing countries--genuinely responds to developing countries' needs, not just those of the richer nations. Ignoring the AIDS research needs of 90% of the epidemic is not just unethical. It is plain irrational. The task is to make the global epidemic less dangerous; anything else offers false security for all.

A rationally prioritized AIDS research agenda would offer hope to the whole planet. It would indeed be **"One world, one hope":** the theme of this year's International Conference on AIDS, now about to begin in Vancouver, and of World AIDS Day 1996.

Comment [4]: This is important because for a long time AIDS was a death sentence; this promises the return of a quality of life to a number of people.

Comment [5]: further research on zidovudine might be interesting.

Comment [6]: research and development

Comment [7]: research (generally in a university setting); a.k.a. where I would like to work

Comment [8]: further research into these solutions may also be interesting.

Comment [9]: Need participants in studies to verify success (or failure)

Microbicides: a new approach to preventing HIV and other sexually transmitted infections

Full Text:

Author(s): Alan Stone [1]

Vaginal medications containing the spermicidal surfactant nonoxynol-9 have been used for more than 50 years to reduce the risk of unwanted pregnancy. The demonstration that nonoxynol-9 not only attacks sperm but can also destroy the human immunodeficiency virus (HIV) [1, 2] provided the initial stimulus to search for products that, when used vaginally, would prevent the sexual transmission of this deadly virus. Initially termed 'virucides', the name now commonly accepted for such products is 'MICROBICIDES', reflecting the intention that they should protect not only against viruses, such as HIV and genital herpes, but also against common bacterial infections, such as gonorrhoea and chlamydia.

The basic concept is simple. Anti-infective chemicals, selected from the great variety of substances that are known to block HIV and other sexually transmitted PATHOGENS in the laboratory, are formulated to create products suitable for insertion into the vagina before intercourse. These can be in the form of gels, creams, foams, impregnated sponges, suppositories or films. The chemical and physical actions of the product will protect the uninfected person, man or woman, from infectious agents that might be present in the genital secretions of his or her sexual partner. Microbicides will also protect HIV-infected people from other sexually transmitted infections (STIs), including possibly drug-resistant or more virulent HIV strains. This will be particularly important in immunocompromised individuals, who are especially vulnerable to infections. Research is also under way on microbicides for use in rectal sex.

Although this might sound straightforward, the process of developing and evaluating microbicides is highly complex. As well as providing effective protection, they must also be safe to use, chemically and physically stable, compatible with latex and other materials used in barrier devices, and affordable and acceptable to the end-user.

The need for microbicides

Why do we need to develop microbicides given that efforts to produce anti-HIV vaccines are under way and, in addition, the condom is known to offer good protection against HIV and other STIs? Regrettably, the development of an AIDS vaccine -- which will ultimately have a crucial role in the

Comment [10]: The previous article listed microbicides and vaccines as being one of the most promising treatments for AIDS; therefore, I decided to research microbicides.

Comment [11]: Also found on Academic OneFile, so the source can be assumed similarly credible.

Comment [12]: Reasoning for hypothesis and research.

Comment [13]: goal of the research.

Comment [14]: Not a cure as I assumed from the other article, but a type of prevention from further spread of AIDS and other STIs

Comment [15]: Affordable relates to the other article...if microbicides are made accessible and inexpensive enough, these products can be useful for a large amount of people not in industrialized nations or economically stable positions.

war against the HIV pandemic -- is proving to be a great deal more technically challenging than many had expected. Vaccines suitable for large-scale administration over diverse geographic regions might be many years away. Furthermore, condoms are effective against these infections only if they are used consistently and correctly [3, 4], and this is seldom the case. Unprotected sex remains widespread, as can be judged from the continuing growth of the global HIV epidemic (4.3 million new adult cases of HIV during 2001, 1.8 million of them in women [5]) and from the annual burden of around 340 million cases of other STIs [6]. Intensive campaigns to promote condoms remain as important as ever, and there have been some successes; most notably in Thailand and Uganda. But the fact remains that they are not popular, particularly with men, and in many of the societies in which HIV is prevalent, women lack the power to negotiate their use.

By contrast, microbicides will provide a user-friendly technology that will widen the range of protective options and, importantly, will be under the control of women. Several studies predict that they will be widely acceptable to both men and women [7, 8, 9]. Unlike condoms, microbicides will not create a physical barrier to intimate contact, and women will be able to apply them a considerable time before intercourse takes place. Ideally, they will be colourless, odourless and tasteless, and non-messy to use. Moreover, the use of a microbicide need not necessarily prevent conception, as the intention is to develop both contraceptive and non-contraceptive products.

Studies with nonoxynol-9

The need for microbicides is urgent. A fast-track approach is to investigate products that are already licensed for vaginal use, such as the spermicidal contraceptives that are now on the market, and find out whether they will protect individuals in a population at high risk of HIV infection. Nonoxynol-9 is a surfactant that works as a spermicide by disaggregating the lipid membranes of spermatozoa. It has a similar effect on the lipid membranes of HIV, the genital herpes virus and sexually transmitted cellular pathogens, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (Fig. 1a).

The first large-scale (Phase III) clinical trial to evaluate nonoxynol-9 involved female sex workers in Nairobi [10]. To be statistically significant, such trials typically require several thousand female volunteers who are willing to be randomized to use either the microbicide or a placebo, and who are also willing to undergo regular testing for HIV and other STIs over many months.

Phase III trials are usually designed to provide information on the long-term safety and acceptability of a product, as well as its effectiveness. However, a trial on this scale, with its logistical complexities and exacting ethical requirements [11], is justified only if the product has previously been shown to be safe and acceptable in smaller trials. A Phase I trial provides initial data in perhaps 10-20 healthy women at low risk of infection. This is followed by a Phase II trial to confirm the findings over a longer period in perhaps 200-300 women -- including some HIV-positive women -- preferably in a population similar to that in which it is intended to carry out the Phase III trial. Safety endpoints include the absence of systemic toxicity and local adverse effects on the EPITHELIUM that lines the vagina and cervix, and minimal disturbance of the bacterial flora normally resident in the healthy vagina. Penile safety studies are also necessary. Detailed information about clinical studies in microbicide development is available in a document prepared for the International Working Group on Microbicides [11].

In the Nairobi trial, the product being tested was a commercially available contraceptive sponge impregnated with 1,000 mg of nonoxynol-9. The outcome was disappointing: the product did not protect against HIV, gonorrhoea or chlamydia, and seemed to be responsible for genital ULCERS in some of the women [10]. Several subsequent Phase III trials of different nonoxynol-9 formulations also failed to show any benefit. These included a study in the Cameroon of a vaginal contraceptive film incorporating 70 mg of nonoxynol-9 (Ref. 12) and a trial of a contraceptive gel (known as COL-

Comment [16]: What make the development of an AIDS vaccine so complicated?

Comment [17]: Microbicides-reliant completely on the woman-will allow progress of women in areas where they are not given much freedom. Any way to give women more say in their own health should be prioritized.

Comment [18]: interesting medical ethics point

Comment [19]: The failure may be due to a number of reasons, but the fact that the researchers are willing to keep working towards a successful product illustrates my quote for the year: failure is accessible if you keep trying.

1492) containing 52.5 mg of the substance, which was carried out in several African sites [13]. In the latter trial, use of the surfactant was associated with a significant increase in the incidence of HIV infection. This was particularly pronounced among the women who were more frequent users of the product (mean use >3.5 times a day), and in the same group, there was a higher incidence of genital ulcers than in the equivalent placebo group. In neither trial was there an effect on gonorrhoea or chlamydia infection rates. It is unclear why the earlier safety studies with COL-1492 failed to show an excess of ulcers [14], but this was probably because of their short duration and insufficient power to detect an effect of the size seen in Phase III studies. In a further study carried out in the Cameroon, a different gel containing 100 mg nonoxynol-9 also failed to protect women against the two bacterial infections (HIV was not a primary end point in this trial) [15].

After the initial announcement of the COL-1492 result in 2000, several national and international bodies issued statements advising on its implications for the use of nonoxynol-9 in both stand-alone products and condom coatings. In June 2002, the World Health Organization released a report containing the recommendations of a meeting of experts who had concluded, after careful scrutiny of all the available evidence on the potential benefits and hazards of nonoxynol-9, that this substance should not be used as a microbicide (although it remains a contraceptive option for women at low risk of HIV) [16]. The report stresses that alternative microbicides, which are safe and effective, need to be developed as a matter of urgency.

There is insufficient information to be able to offer definitive guidance about the value of other surfactants as microbicides, although research is continuing with a number of them. For example, C31G, an equimolar mixture of the amphoteric surfactants cetyl betaine and myristamine oxide, has successfully completed a Phase I safety study (A.-M. Corner, personal communication).

Mechanism of HIV transmission

To understand why nonoxynol-9 failed to protect against HIV in the above trials, and why there is considerable optimism about the eventual success of some of the alternative microbicides that are under investigation at present, we need to consider the biological mechanism by which HIV is transmitted sexually. Potential sources of transmissible HIV are free virus particles and infected LYMPHOID CELLS in semen, in cervicovaginal secretions and in blood or other fluids present as a result of physical trauma or genital infections. The first steps in HIV infection normally involve the attachment of the virus, through the gp120 GLYCOPROTEIN on its outer membrane, to its primary receptor, CD4, on the surface of the host cell. This is followed by an interaction between a specific gp120 domain and a cellular co-receptor, which triggers a conformational change in the viral envelope that leads to fusion of the viral and host-cell membranes and entry of the viral genome into the host cell [17]. Two CHEMOKINE receptors on the cell surface -- CCR5 and CXCR4 -- serve as co-receptors for HIV, and different HIV strains tend to have a strong preference for one or the other.

The epithelium that lines the vagina and the external surface of the cervix is multilayered, and is relatively strong and durable. Beneath this is a layer of connective tissue -- the lamina propria. Within these structures are several classes of lymphoid cell, including dendritic cells, macrophages, T lymphocytes and Langerhans cells (Fig. 2). Much has been written about the role of these tissues and cells in the transmission of HIV from males to females, and some aspects are controversial. (The detailed mechanism by which penile tissue becomes infected is also unclear, although there are likely to be some similarities.) A considerable body of evidence has been derived from experiments on EXPLANTS of human vaginal and cervical tissues infected with HIV *in vitro* , and from studies in macaque monkeys infected vaginally with the simian immunodeficiency virus (SIV). Most of the findings support the view that the primary initial sites of HIV infection are lymphoid cells in the lamina propria -- dendritic cells and macrophages in particular, but possibly also T

Comment [20]: How did they get an increase in the incidence?!

Comment [21]: Nonoxynol-9 was completely ineffective, which makes me wonder why scientists believe this is a promising option for AIDS prevention. Maybe another method would be more effective...in other words, maybe not a drug but a technology women can use? Or simply a different combination of drugs would be better?

Comment [22]: How HIV infection happens

Comment [23]: Possible research topic? I wonder if any studies/ which studies are being done on this currently.

Comment [24]: Comparable to HIV?

lymphocytes -- that have both CD4 and the co-receptors for the virus [18, 19, 20]. The Langerhans cells in the genital epithelium (in contrast to those in human skin) do not seem to be as readily infectable by the incoming virus, probably because, although they express CD4, they express little of the co-receptors [18]. However, the possibility that they have a role in the infection process cannot be ruled out.

Infected dendritic cells can migrate to the local lymph nodes, where extensive HIV replication takes place, leading to generalized systemic infection. HIV particles can also attach to the surface of dendritic cells, without infecting them, through an interaction between mannose-rich residues in gp120 and specific lectins in the cell membrane, including one known as DC-SIGN. The significance of this finding is not yet clear, but it is possible that this is an important route by which non-replicating, but infectious, HIV could be carried to the lymph nodes and be presented to susceptible cells [21]. If so, it provides another potential target for microbicide intervention.

The non-lymphoid squamous cells, which comprise the bulk of the multilayered genital epithelium, have none of the necessary receptors for HIV and -- subject to the technical limitations of the assay systems -- seem to be resistant to infection [18]. Furthermore, these cells (unlike the cells of the epithelium that lines the gastrointestinal tract [22]) do not allow the virus to migrate through them by passive transcytosis. This raises the question of how HIV -- whether the free virus particles or HIV-infected lymphoid cells -- manages to pass through the resistant epithelial barrier. Studies in tissue explants have given rise to several proposals [18, 23, 24, 25]. One is that Langerhans cells and T lymphocytes in the epithelium might have the capacity to bind the virus and migrate with it to the lamina propria. However, several observations indicate that HIV can reach its subepithelial target cells only if there are physical breaches in epithelial integrity [18]. Clearly, such lesions will make it easier for HIV to infect cells in the lamina propria even if there are other routes through the epithelium. They can result from infection with other pathogens, from physical trauma or, as we have seen, from the use of the surfactant nonoxynol-9.

Surfactant-induced ulcers take several days to heal, so in clinical trials in populations in which sex is frequent, it is perhaps not surprising that nonoxynol-9 showed no net benefit [26]. Phase I studies have shown that nonoxynol-9 can also give rise to localized inflammation [27], and it is likely that this also enhances the risk of HIV infection; for example, by CYTOKINE activation of potential target cells [18]. Moreover, nonoxynol-9 adversely affects the lactobacilli that live in the healthy vagina and whose secretion of lactic acid and hydrogen peroxide creates a second line of defence against invading pathogens [27, 28, 29].

Microbicides under investigation

The problems experienced with nonoxynol-9 have focused attention on microbicides that work by different mechanisms, and which neither damage the vaginal lining nor affect the lactobacilli. Many such agents are now under investigation. To prevent HIV transmission, a microbicide must either inactivate the virus (both free and cell-associated) while it is still in the vaginal lumen, prevent the virus from attaching to and fusing with its host cells (or attaching to DC-SIGN) or prevent the virus from replicating if it should succeed in infecting these cells. Table 1 includes examples of substances that have the potential to intervene at one or other of these stages of the HIV infection process. Many are active against a wide range of HIV strains, and most also show some activity against other STI organisms. The latter are responsible for substantial morbidity and mortality. There is also evidence that STIs enhance the susceptibility of an affected person to infection by HIV [30]. So, at the community level, by protecting against these infections, it is likely that microbicides will have an indirect impact on HIV levels as well as a direct impact on the transmission of the virus.

The future

Comment [25]: I think it's interesting how findings by one group can lead to developments by another group. I think that's part of what's so cool about science.

Comment [26]: Why are they resistant? And could this resistance be used?

Comment [27]: Definition: Transcytosis is a type of transcellular transport in which various macromolecules are transported across the interior of a cell. Macromolecules are captured in vesicles on one side of the cell, drawn across the cell, and ejected on the other side. Examples of macromolecules transported include IgA, transferrin, and insulin.

Comment [28]: learning from research

Comment [29]: the multiple strains make prevention difficult because, similar to the flu, there is no way to tell which strain might threaten the patient.

Several microbicides are scheduled to enter Phase III clinical trials over the next year or so, including carrageenan, BufferGel, PRO 2000 and dextrin-2-sulphate. Others will follow. The report of a recent international consultation sponsored by the Rockefeller Foundation [62] concluded that these first-generation microbicides might be no more than 60% effective against HIV transmission, but they would meet the urgent need for this kind of intervention and would have a major public health benefit. The results of epidemiological modelling indicate that such a microbicide could avert 3.7 million infections globally over a three-year period if it were used in only 50% of sex acts not protected by condoms, and assuming that it was used by only 30% of individuals easily reached by existing health services [63]. Concern has sometimes been expressed about the possibility that the introduction of such a product could lead to migration away from condom use and thereby increase overall HIV risk. Mathematical modelling indicates that although this might be a problem if there is a high level of condom use, say in more than 70% of sex acts, if condoms are used fairly infrequently, say in 30% of sex acts, a considerable level of migration to microbicide could be tolerated without increasing HIV risk [64].

Second-generation products could soon be on the market [62]. These might be 70-90% effective against HIV, with good activity against gonorrhoea, chlamydia, genital herpes and papilloma virus. The Rockefeller report further predicted that by 2017, microbicides would be 85-97% effective against HIV, and a 90-97% contraceptive option would be available.

In reality, how soon these benefits materialize will depend on how successful we are in tackling not only the scientific challenges but also several societal issues. The level of funding for microbicide development needs to be greatly increased. The Rockefeller consultation estimated the requirement over the next five years to be US $775 million, whereas the overall level of public support for the field over that period stood at approximately US $230 million [62]. This can be compared with an estimated US $400 million per annum of public support for AIDS vaccine development [65].

Microbicide advocacy needs to be intensified so that health policy officials, health providers and potential end-users are properly informed. Knowledge and expertise must be shared internationally. Finally, there is growing evidence that in the longer term, microbicides could be highly profitable [8, 9, 62], and the current reluctance of the major pharmaceutical companies to engage seriously in this field needs to be overcome. The ultimate objective is to provide a user-friendly option that sexually active people might choose to use to protect themselves against HIV, other sexually transmitted diseases and unwanted pregnancy. Microbicides will not solve the immense problem of HIV and AIDS alone, but together with condoms, and eventually AIDS vaccines, they will give people a wider choice of protective technologies.

Comment [30]: more research might be interesting to see how effective products are right now and whether the predictions of the Rockefeller report were correct.

Comment [31]: Maybe this makes makes sense, though, because vaccines could completely inoculate, whereas microbicides require frequent reapplication. While I agree that microbicides have promise as a part of preventing AIDS, I think the vaccine might be more promising. However, I should do some more research on the vaccine option before stating that conclusively.

Comment [32]: One benefit to the microbicides is that they protect against more than just AIDS

Definition List:

MICROBICIDE: (Virucide). An anti-infective medication formulated for topical self-administration before intercourse to protect against HIV and other sexually transmitted pathogens.

PATHOGEN: A microorganism that causes disease.

EPITHELIUM: The tissue that covers the surface of the body and lines hollow structures, including the male and female genital tracts and the rectum. Its structure varies depending on location and role.

ULCER: A lesion in the epithelium that extends through to the underlying connective tissue.

LYMPHOID CELLS: Types of immune cell, including macrophages, lymphocytes, Langerhans cells and dendritic cells, that have specific roles in the diverse components of the immune response to foreign antigens.

GLYCOPROTEIN: A protein combined with a carbohydrate, such as mannose or galactose.

CHEMOKINES: A group of small proteins involved in intracellular signalling -- a subgroup of the cytokines.
EXPLANT: Living tissue excised from the body and maintained in culture medium.
CYTOKINES: Small protein molecules that control the activity of immune cells, produced, for example, as part of the inflammatory response.
XENOGRAFT: Living tissue from one species grafted into or onto another.
ANIONIC POLYMER: A long-chain molecule composed of linked, negatively charged units.
STERIC HINDRANCE: Interference with a molecular interaction by the spatial arrangement of the structures involved.
MONOCLONAL ANTIBODY: Multiple copies of a single antibody derived from the identical descendants of a single antibody-producing cell.

DATABASES

Comment [33]: Citations from here down.

LocusLink
CCR5: http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=1234
CD4: http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=920
CXCR4: http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=7852
FURTHER INFORMATION
Alliance for Microbicide Development: http://www.microbicide.org/
Global Campaign for Microbicides: http://www.global-campaign.org/
International AIDS Vaccine Initiative: http://www.iavi.org/
International Family Health: http://www.ifh.org.uk/
Rockefeller Foundation: http://www.rockfound.org/
World Health Organization: http://www.who.int/en/
Encyclopedia of Life Sciences
acquired immune deficiency syndrome: http://www.els.net/els/FDA/default.asp?id=A2B16F08-AC8C-4E01-A434-76604AD6AA08
AIDS as a world health problem: http://www.els.net/els/FDA/default.asp?id=454E04F2-7B30-4699-BFCB-12465A6FCDE7
human immunodeficiency viruses: http://www.els.net/els/FDA/default.asp?id=05FF011B-5CE9-45F4-A289-B3CBCC350A95
Caption(s):
Illustration 1: TIMELINE [see PDF for image]
Key events and predictions in the development of microbicides; 1980-2017
Figure 1: Some microbicides work by damaging the lipid membrane of the pathogen. [see PDF for image]
a | Surfactants, such as nonoxynol-9 and C31G, disaggregate the membranes of cells and enveloped viruses. **b** | Certain antibiotic peptides, such as gramicidin and defensins, act as ionophores and create holes in the membrane.
Figure 2: Structure of the human vaginal epithelium. [see PDF for image]
The multilayered epithelium and the underlying connective tissue contain several types of potential target cell for HIV.
Figure 3: Comparison of nonoxynol-9 with the anionic polymer PRO 2000: anti-HIV potency and cytotoxicity *in vitro* . [see PDF for image]
a | Nonoxynol-9 inactivates both the virus and the cells. **b** | By contrast, PRO 2000 affects only the virus. A450, optical absorbance at wavelength 450 nm; dpm, disintegrations per minute.

Figure 4: Anionic polymers as microbicides: mechanism of action. [see PDF for image]
The precise mechanism is unclear. **a** | The charged polymer might bind non-specifically to the viral and cell surfaces and prevent the close encounter required for infection to take place. **b** | The polymer might block the interaction between a specific gp120 domain and the HIV co-receptor on the cell surface. (The diagram shows only one of numerous gp120 'spikes' on the lipid envelope of HIV.)
Figure 5: Antiretroviral drugs (reverse-transcriptase inhibitors) as microbicides. [see PDF for image]
These drugs enter the cell and lie in wait for any HIV genomes that manage to get in. Some of them, such as UC781, can penetrate the intact HIV particle and disable its reverse-transcription mechanism even before the virus infects a cell.
Table: Examples of substances under investigation as potential microbicides * [see PDF for image]
Acknowledgement:
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References
1. Hicks, D. *et al* . Inactivation of HTLV-III/LAV-infected cultures of normal human lymphocytes by nonoxynol-9 *in vitro* . Lancet 2, 1422-1423 (1985).
2. Malkovsky, M., Newell, A. & Dalgleish, A. Inactivation of HIV by nonoxynol-9. Lancet 1, 645 (1988).
3. Saracco, A. *et al* . Man-to-woman sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. J. Acquir. Immune Defic. Syndr. 6, 497-502 (1993).
4. de Vincenzi, I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. N. Engl. J. Med. 331, 341-346 (1994).
5. Joint United Nations Programme on HIV/AIDS and World Health Organization. *AIDS Epidemic Update: December 2001* (Joint United Nations Programme on HIV/AIDS and World Health Organization, Geneva, 2001).
6. Gerbase, A., Rowley, J., Heymann, D., Berkley, S. & Piot, P. Global prevalence and incidence estimates of selected curable STDs. Sex. Transm. Infect. 74 (Suppl. 1), S12-S16 (1998).
7. Coggins, C., Blanchard, K. & Friedland, B. Men's attitudes towards a potential vaginal microbicide in Zimbabwe, Mexico and the USA. Reprod. Health Matters 8, 132-141 (2000).
8. Darroch, J. & Frost, J. Women's interest in vaginal microbicides. Fam. Plann. Perspect. 31, 16-23 (1999).
9. Hill, R., Ryan, J., Stone, A. & Fransen, L. Vaginal microbicides for the prevention of HIV/AIDS: assessment of the potential market. Int. J. Pharm. Med. 14, 271-278 (2000).
10. Kreiss, J. *et al* . Efficacy of nonoxynol-9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. JAMA 268, 477-482 (1992).
11. Rosenberg, Z., Van Damme, L. & Mauck, C. Recommendations for the clinical development of topical microbicides: an update. AIDS 15, 857-868 (2001).
12. Roddy, R. *et al* . A controlled trial of nonoxynol-9 film to reduce male-to-female transmission of sexually transmitted diseases. N. Engl. J. Med. 339, 504-510 (1998).

13. Van Damme, L. *et al* . Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. Lancet 360, 971-977 (2002).
This large-scale (Phase III) clinical trial of nonoxynol-9 gel helped to drive home the message that products that contain this surfactant are not only ineffective in protecting against HIV and other STIs, but can actually increase HIV risk, probably by causing ulcers in the genital epithelium.
14. Van Damme, L. *et al* . Safety of multiple daily applications of COL-1492, a nonoxynol-9 vaginal gel, among female sex workers. AIDS 14, 85-88 (2000).
15. Roddy, R., Zekeng, L., Ryan, K., Tamoufe, U. & Tweedy, K. Effect of nonoxynol-9 on urogenital gonorrhoea and chlamydial infection. JAMA 287, 1117-1122 (2002).
16. World Health Organization/Contraceptive Research and Development Program. *WHO/CONRAD Technical Consultation on Nonoxynol-9* (World Health Organization, Geneva, 2002).
A report of an expert consultation that took place in October 2001 to consider the available evidence on the efficacy and toxicity of nonoxynol-9, both as a microbicide and as a spermicidal contraceptive. The report concluded that nonoxynol-9 should not be used for HIV/STI prevention, and that there is an urgent need to develop safe and effective microbicides. It also recommended that nonoxynol-9 spermicides, although inefficient contraceptives, should be retained as a female-controlled contraceptive option provided that HIV risk is low.
17. Brelot, A. & Alizon, M. HIV-1 entry and how to block it. AIDS 15 (Suppl. 5), S3-S11 (2001).
18. Greenhead, P. *et al* . Parameters of human immunodeficiency virus infection of human cervical tissue and inhibition by vaginal virucides. J. Virol. 74, 5577-5586 (2000).
Explants of human vaginal and cervical epithelium maintained in culture fluid are used to study their infectability by different HIV strains, the effects of immune activation and the locations and types of cell initially infected. Several microbicides are shown to be active in preventing infection in this system.
19. Spira, A. *et al* . Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. J. Exp. Med. 183, 215-225 (1996).
20. Zhang, L. *et al* . *In vivo* distribution of human immunodeficiency virus/simian immunodeficiency virus coreceptors: CXCR4, CCR3 and CCR5. J. Virol. 72, 5035-5045 (1998).
21. Geijtenbeek, T. *et al* . DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances transinfection of T-cells. Cell 100, 587-597 (2000).
This paper describes a potential new route of HIV sexual transmission. HIV particles can bind to a specific lectin, DC-SIGN, which is present in the membrane of human genital dendritic cells. HIV particles so bound retain their infectivity for several days and can be efficiently transmitted to T cells.
22. Bomsel, M. Transcytosis of infectious human immunodeficiency virus across a tight human epithelial cell line barrier. Nature Med. 3, 42-47 (1997).
23. Collins, K., Patterson, B., Naus, G., Landers, D. & Gupta, P. Development of a new *in vitro* organ culture model to study transmission of HIV-1 in the female genital tract. Nature Med. 6, 475-479 (2000).
24. Shattock, R., Griffin, G. & Gorodeski, G. *In vitro* models of mucosal HIV transmission. Nature Med. 6, 607-608 (2000).
25. Gupta, P., Collins, K., Patterson, B., Naus, G. & Landers, D. *In vitro* models of mucosal HIV transmission. Nature Med. 6, 607-608 (2000).

26. Stone, A. Microbicides: the UNAIDS-sponsored trial of nonoxynol-9 gel. IPPF Med. Bull. 34, 3-4 (2000).
27. Stafford, M. *et al* . Safety study of nonoxynol-9 as a vaginal microbicide: evidence of adverse effects. J. Acquir. Immune Defic. Syndr. 17, 327-331 (1998).
28. Klebanoff, S., Hillier, S., Eschenbach, D. & Waltersdorph, A. Control of the microbial flora of the vagina by $H_2 O_2$ -generating lactobacilli. J. Infect. Dis. 164, 94-100 (1991).
29. Ongradi, J., Ceccherini-Nelli, L., Pistell, M., Spector, S. & Bendinelli, M. Acid-sensitivity of cell-free and cell-associated HIV-1: clinical implications. AIDS Res. Hum. Retroviruses 6, 1433-1436 (1990).
30. Wasserheit, J. in *AIDS and Women's Health: Science for Policy and Action* (eds Chen, L., Sepulveda, J. & Segal, S.) 47-72 (Plenum, New York, 1991).
31. O'Connor, T., Kinchington, D., Kangro, H. & Jeffries, D. The activity of candidate virucidal agents, low pH and genital secretions against HIV-1 *in vitro* . Int. J. STD AIDS 6, 267-272 (1995).
32. Miller, C., Alexander, N., Gettie, A., Hendrickx, A. & Marx, P. The effect of contraceptives containing nonoxynol-9 on the genital transmission of simian immunodeficiency virus in rhesus macaques. Fertil. Steril. 57, 1126-1129 (1992).
33. Weber, J. *et al* . 'Chemical condoms' for the prevention of HIV infection: evaluation of novel agents against SHIV (89.6PD) *in vitro* and *in vivo* . AIDS 15, 1563-1568 (2001).
34. Lewis, M. *et al* . Efficacy of PRO 2000 gel in a macaque model for vaginal HIV transmission. 8th Conference on Retroviruses and Opportunistic Infections Abstract 721 (2001).
35. Manson, K., Wyand, M., Miller, C. & Neurath, R. Effect of cellulose acetate phthalate topical cream on vaginal transmission of simian immunodeficiency virus in rhesus monkeys. Antimicrob. Agents Chemother. 44, 3199-3202 (2000).
36. Tevi-Benissan, C. *et al* . Protection of cynomolgus macaque against cervicovaginal transmission of SIVmac251 by the spermicide benzalkonium chloride. J. Acquir. Immune Defic. Syndr. 24, 147-153 (2000).
37. Di Fabio, S. *et al* . Vaginal transmission of HIV-1 in hu-SCID mice: a new model for the evaluation of vaginal microbicides. AIDS 15, 2231-2238 (2001).
38. Kish, T., Budgeon, L., Welsh, P. & Howett, M. Immunological characterisation of human vaginal xenografts in immunocompromised mice: development of a small animal model for the study of human immunodeficiency virus-1 infection. Am. J. Pathol. 159, 2331-2345 (2001).
39. Bourne, N. *et al* . The topical microbicide PRO 2000 protects against genital herpes infection in a mouse model. J. Infect. Dis. 180, 203-205 (1999)
40. Zacharopoulos, V. & Phillips, D. Vaginal formulations of carrageenan protect mice from herpes simplex virus infection. Clin. Diagn. Lab. Immunol. 4, 465-468 (1997).
41. Gyotoku, T., Aurelian, L. & Neurath, R. Cellulose acetate phthalate (CAP): an 'inactive' pharmaceutical excipient with antiviral activity in the mouse model of genital herpesvirus infection. Antivir. Chem. Chemother. 10, 327-332 (1999).
42. The International Working Group on Vaginal Microbicides. Recommendations for the development of vaginal microbicides. AIDS 10, 1-6 (1996).
This was the first such compilation to be published, providing useful guidance to those involved in microbicide development. The group has since published more comprehensive and up-to-date clinical recommendations (reference 10), and updated preclinical recommendations will appear shortly.

43. Javan, C., Gooderham, N., Edwards, R., Davies, D. & Shaunak, S. Anti-HIV type 1 activity of sulphated derivatives of dextrin against primary viral isolates of HIV type 1 in lymphocytes and monocyte-derived macrophages. AIDS Res. Hum. Retroviruses 13, 875-880 (1997).
44. Profy, A. *et al* . PRO 2000 gel, a potential topical microbicide for HIV prevention, can block infection by other sexually transmitted disease pathogens. XII International AIDS Conference Abstract 33146 (1998).
45. Neurath, R., Strick, N., Li, Y.-Y., Lin, K. & Jiang, S. Design of a 'microbicide' for prevention of sexually transmitted diseases using 'inactive' pharmaceutical excipients. Biologicals 27, 11-21 (1999).
46. McClure, M. *et al* . Investigations into the mechanism by which sulphated polysaccharides inhibit HIV infection *in vitro* . AIDS Res. Hum. Retroviruses 7, 3-16 (1992).
47. Neurath, A., Strick, N., Li, Y.-Y. & Debnath, A. Cellulose acetate phthalate, a common pharmaceutical excipient, inactivates HIV-1 and blocks the coreceptor binding site on the virus envelope glycoprotein gp120. BMC Infect. Dis. 1, 17 (2001).
48. Moulard, M. *et al* . Selective interactions of polyanions with basic surfaces on human immunodeficiency virus type 1 gp120. J. Virol. 74, 1948-1960 (2000).
49. Shattock, R. & Doms, R. AIDS models: microbicides could learn from vaccines. Nature Med. 8, 425 (2002).
50. Coggins, C. *et al* . Preliminary safety and acceptability of a carrageenan gel for possible use as a vaginal microbicide. Sex. Transm. Infect. 76, 480-483 (2000).
51. Stafford, M. *et al* . A placebo-controlled, double-blind prospective study in healthy female volunteers of dextrin sulphate gel: a novel potential intravaginal virucide. J. Acquir. Immune Defic. Syndr. 14, 213-218 (1997).
52. Van Damme, L. *et al* . A Phase I study of a novel potential intravaginal microbicide, PRO 2000, in healthy sexually inactive women. Sex. Transm. Infect. 76, 126-130 (2000).
53. Mauck, C. *et al* . Single and multiple exposure tolerance study of cellulose sulfate gel: a Phase I safety and colposcopy study. Contraception 64, 383-391 (2001).
54. Mayer, K. *et al* . Safety and tolerability of BufferGel, a novel vaginal microbicide, in women in the United State. Clin. Infect. Dis. 32, 476-482 (2001).
55. Dey, B. *et al* . Multiple antiviral activities of cyanovirin-N: blocking of gp120 interaction with CD4 and coreceptor, and inhibition of diverse enveloped viruses. J. Virol. 74, 4562-4569 (2000).
56. Cole, A. *et al* . Retrocyclins: circular minidefensins with potent activity against HIV-1. Microbicides 2002 Conference Abstract A-048 (2002).
57. Zeitlin, L. *et al* . A humanized monoclonal antibody produced in transgenic plants for immunoprotection of the vagina against genital herpes. Nature Biotechnol. 16, 1361-1364 (1998).
58. Balzarini, J. *et al* . Preclinical studies on thiocarboxanilide UC-781 as a virucidal agent. AIDS 12, 1129-1138 (1998).
59. Barnhart, K. T., Pretorius, E. S. & Malamud, D. Non-invasive imaging of the spread of microbicides with magnetic resonance imaging. Microbicides 2002 Conference Abstract B/C-283 (2002).
60. Phillips, D. & Zacharopoulos, V. Nonoxynol-9 enhances rectal infection by herpes simplex virus in mice. Contraception 57, 341-348 (1998).
61. Phillips, D., Taylor, C., Zacharopoulos, V. & Maguire, R. Nonoxynol-9 causes rapid exfoliation of sheets of rectal epithelium. Contraception 62, 149-154 (2000).
This study showed that two over-the-counter nonoxynol-9 products caused considerable damage to the human rectal epithelium within 15 minutes of being applied by volunteers. This

finding, together with the material in references 13 and 16, have led to calls for a ban on condoms coated with nonoxynol-9 and sex lubricants containing this substance.
62. Rockefeller Foundation. *Mobilization for Microbicides: the Decisive Decade* (Rockefeller Foundation, New York, 2002).
63. Watts, C. The public health impact of microbicides: model projections. Microbicides 2002 Conference [online] (cited 15 Oct 2002) <http://www.itg.be/micro2002/pages/presentations.html>.
An influential study that used epidemiological modelling techniques to show that a microbicide of only moderate efficacy could have substantial public health benefits in terms of HIV infections averted, provided that, as a female-controlled method, it is used more consistently than condoms.
64. Foss, A., Vickerman, P., Heise, L. & Watts, C. Will shifts from condom to microbicide use increase HIV risk? Model projections. XIV International AIDS Conference Abstract WeOrD1319 (2002).
65. International AIDS Vaccine Initiative. When Will an AIDS Vaccine be Found? The State of Global Research (International AIDS Vaccine Initiative, New York, 2002).
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