Microbicides: User-controlled HIV prevention

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Learning Objectives

* Explain the need for user-controlled HIV prevention methods
* Be able to answer “What is a microbicide?”
* Be able to list and describe the mechanisms of action of potential microbicides
* Illustrate differences between vaginal and rectal microbicides
* Describe the timeline and challenges for microbicides research and clinical trials

For the curious, extensive supplementary notes follow most slides. These can be skipped if time is short.
Over the last quarter century nearly 65 million people were infected with HIV and an estimated 25 million have died of AIDS-related illnesses. In 2006, it is estimated that close to 40 million people live with HIV, yet the vast majority are unaware of their status. Below is a brief timeline that walks you through highlights of the epidemic, from the beginnings to the present.
The Global Challenge

38.6 million people [33.4–46.0 million] living with HIV, 2005

Supplementary notes on next slide
Supplementary notes

• An estimated 38.6 million (33.4 million-46.0 million) people world-wide were living with HIV at the end of 2005. An estimated 4.1 million (3.4 million-6.2 million) became newly infected with HIV and an estimated 2.8 million (2.4 million-3.3 million) lost their lives to AIDS.

• To bring into relief the severity of the AIDS crisis, we shall look at South Africa. South Africa’s AIDS epidemic, one of the worst in the world, shows no evidence of a decline. Based on its extensive antenatal clinic surveillance system, as well as national surveys with HIV testing and mortality data from its civil registration system, an estimated 5.5 million (4.9 million to 6.1 million) people were living with HIV in 2005. An estimated 18.8% (16.8% to 20.7%) of adults (15 to 49 years) were living with HIV in 2005.1 Almost one in three pregnant women attending public antenatal clinics were living with HIV in 2004 and trends over time show a gradual increase in HIV prevalence.

• These numbers are stark and striking at best. Let us focus for a moment on the epidemic from a women’s perspective.

Source: UNAIDS, World Health Organization
HIV/AIDS is rapidly becoming a women’s epidemic. Of the approximately 14,000 individuals infected with HIV every day, more than half of them are women worldwide. As of 2005, 57% of the people living with HIV/AIDS in sub-Saharan Africa were women and girls. Among 15-25 year olds in sub-Saharan Africa, 67% of those infected with HIV are women.

This trend is not exclusive to Africa. In the United States, women initially composed less than 10% of those living with HIV, but currently make up about a quarter of all those infected. In the US, over half (56%) of all adolescent HIV infections have occurred among young women and HIV/AIDS is the leading cause of death among African American women between 25-54. In Russia and Asia, where HIV prevalence is increasing, a third of all new infections are occurring in women.
HIV is becoming a “women’s epidemic”

HIV prevalence (%) by gender and urban/rural residence, selected sub-Saharan African countries, 2001–2005

15–49 years old, by gender

15–24 years old, by gender

15–49 years old, by urban/rural residence


Supplementary notes on next slide
• This shift in demographics, towards an epidemic that will be dominated by women infected with HIV, is fuelled by many causes, which we will investigate here.

• The increasing incidence of HIV infection in women is fueled by poverty and inequality. Millions of women lack the social and economic power to insist on HIV prevention measures such as condoms, abstinence or mutual monogamy. Male and female condom use requires the tacit cooperation, if not outright participation, of a woman's male partner. The above graph demonstrates the increased HIV prevalence among women in select countries, and is a reflection of the challenges outlined here.

• HIV risk escalates among adolescent girls because of their physical vulnerability and their susceptibility to rape, forced marriage, trafficking, economic dependence and coercion. This violence, coercion, and economic dependency renders millions of women of all ages unable to “negotiate” condom use or to abandon partners who put them at risk. Millions live in societies that permit them no role in sexual decision-making, condone male infidelity and assign to women the burden of shame and stigma associated with infectious disease. Increasing economic inequality and eroding social support networks drive many women to sell or trade sex to support their families. The use of the sex trade as a means of achieving enough economic support to feed their families and survive to the next day is in part reflected in the increased prevalence of HIV among women living in urban centres, as shown in the above graph, where there are few other options for poor women.

Source: UNAIDS and World Health Organization
Why do we need user-controlled HIV prevention?

Women’s Risk is…

• Biological
  – Cervical vulnerability
  – Untreated STIs

• Social & Cultural
  – Gender norms about sexuality
  – Gender-based violence/rape
  – Sanctioned polygamy

Supplementary notes on next slide
In addition to the economic and social disparities that drive the HIV epidemic, as discussed on the last slide, there are also biological and cultural factors that influence the high prevalence among women. Women are at least twice as likely as men to contract HIV from unprotected intercourse.

From a biological perspective, vaginal membranes are exposed to infectious fluids for hours after sexual intercourse. Younger women are at greatest risk because the immature cervix is more vulnerable to viral penetration and subsequent infection. Sexually Transmitted Infections (STIs) often go undetected, and therefore untreated, in women, and this can lead to an increase in women's vulnerability to HIV. In addition, untreated STIs can lead to infertility, ectopic (tubal) pregnancy, infant mortality, and cervical cancer, other illnesses that carry significant morbidity.

Many women want to get pregnant -- for personal reasons and/or to achieve the status and security that, in many societies, they can only attain through motherhood. Since condoms are contraceptive, women now have to choose between childbearing and HIV prevention, and thus, choosing to try to become pregnant can increase their risk of contracting HIV.

In many cultures, girls are discouraged from learning about their bodies and sex and are taught to regard their bodies as the property of men (fathers, boyfriends or husbands). Under culturally enforced ignorance, powerlessness and the threat of violence, women experience little or no control over when and how sex happens in their lives and may see sexual decision-making - including condom use - as the domain of men.
Why do we need user-controlled HIV prevention?

Current Prevention Options for Women...

• Abstinence
• Trusting Partner to be Uninfected and Monogamous
• Persuading Partners to Use Male Condoms
• Female Condoms
Women need education, economic opportunity, and social support. They need gender equality in order to protect their health and rights, and they need HIV and STI prevention tools they can control.

The current prevention options that are available for women do not take into account many of the vulnerabilities - economic, biological, cultural - that were outlined in the previous slides. These current prevention options are outlined above: abstinence, mutual monogamy, use of male condoms and female condoms.

In many instances, remaining abstinent is not an option: because girls will get married at a young age to much older men, because women enter commercial sex work to alleviate immediate threats to their children’s or their own health, such as starvation, or because women are unable to refuse sexual relations with their partners. Similarly, women worldwide may not be able to trust that their partner is uninfected, nor be able to request that the partner obtain an HIV test. If the partner is HIV negative, there is still a concern that HIV will be contracted if the relationship is not mutually monogamous.
Why do we need user-controlled HIV prevention?

The need for non-condom prevention...

- Existing methods -- condoms and mutual monogamy -- depend upon cooperation of a partner.
- Violence, coercion, and economic dependency in relationships make it hard to “negotiate” condom use or leave a partnership that puts a woman at risk.
- Condoms interfere with conception
Most of the time, women are at greater risk of STIs or HIV infection as a result of their partners’ sexual and drug-using behavior than they are as a result of their own. In many countries, the primary risk factor shared by most HIV-infected women is marriage. Women may influence -- but they certainly can’t control -- their partner’s sexual or drug-using behavior.

In many parts of the world, women also don’t have control over when and how they have sex. Asking her partner to use a condom may result in a woman being beaten, threatened, or abandoned by her partner. The possibility of a violent response is especially high if a man believes that a condom means

1) a lessening of male pleasure,
2) that promiscuity or infidelity is occurring or
3) that the woman has “inappropriate” knowledge of sexual practices.

In studies done all over the world, women report that even suggesting condom use can put them in danger-- because it raises the question of whether one partner or the other has been unfaithful.
Why do we need user-controlled HIV prevention?

Men at risk…

- High condom use among men who have sex with men is difficult to maintain as new HIV infection rate shows

- New data reveals reasons for concern:
  - UK: 48.8% unprotected anal intercourse in past year
  - US: 30% unprotected anal intercourse in past year among HIV - men

- STI rates confirm unprotected anal intercourse prevalence
Supplementary notes

• Access to antiretroviral therapies have dramatically reduced the number of AIDS-related deaths occurring in the US, Canada and Europe over the last decade. But these drugs have not stopped – or even slowed down -- the rate of new infections. People continue to have unprotected sex in many populations. The rates of unprotected anal sex among men who have sex with men (MSM), for example, is well documented.

• In the United Kingdom, the Gay Men’s Sex Survey of 16,000 men who have sex with men showed in 2002 that almost half (48.8%) of all respondents had engaged in unprotected anal intercourse in the last year. Even more alarming is that nearly 15% (14.59%) of the 7500 respondents who were HIV negative or hadn’t been tested for HIV said they had definitely, or probably, had unprotected anal sex with a man they thought was HIV+ in the last year.

• In a 5 city study of HIV negative MSM (called the EXPLORE study), HIV negative men report 70% condom use during anal intercourse in the past year – in other words, 30% of these HIV negative MSM had unprotected anal intercourse in the past year.

• Finally, reports from several countries around the world showed increases in unprotected anal intercourse, sexually transmitted infections, and HIV incidence among MSM.

• These studies tell us that we need better prevention education and condom use promotion. They also tell us that we need more prevention alternatives to help men who simply aren’t using condoms consistently reduce their risk of infection.

Source 1: Out and about. Findings from the United Kingdom, Gay Men’s Sex Survey 2002. Sigma Research
Why do we need user-controlled HIV prevention?

Women at risk…

- In large U.S. survey, 35% of women age 25-44 report having had anal intercourse at some time in their life
- 32% of high-risk women reported anal intercourse in past 6 months
Some people think the issue of rectal microbicides is only relevant to a small segment of the population -- men who have sex with men. But that's not true! Anal intercourse is practiced by both heterosexuals and homosexuals for many reasons – including pleasure, a way to be intimate without losing 'vaginal virginity' and as a way of having intercourse without risk of pregnancy.

In a U.S. sample of 12,571 men and women between 25 and 44, 97% of men and 98% of women said they had experienced vaginal intercourse. 90% of men and 88% of women had experienced oral sex with an opposite-sex partner; **and 40% of men and 35% of women had experienced anal sex with an opposite-sex partner.**

In another federally-funded study in the US, 32% of the high-risk women participants reported having had anal sex in the past six months. The small amount of international data available on the topic show that anal intercourse is also practiced in various populations all over the world.

In a U.S. study of 18 to 24 year old women in a neighborhood with widespread injection of drugs and HIV, 14% reported unprotected anal sex with men in the past year.

Receptive sex partners (whether women or men) are at higher risk of HIV and STI infection than insertive partners during unprotected intercourse. So the issue of how people protect themselves during anal intercourse is very much a women's -- as well as a men's --- issue, and a straight -- as well as a gay -- issue.


Why do we need user-controlled HIV prevention?

HIV+ individuals at risk...

- Could reduce risk of co-infection with other HIV strains
- May help protect both partners
- Could reduce risk of other STIs, yeast and bladder infections
- May allow conception while protecting partner

Supplementary notes on next slide
• Microbicides are not something just for HIV negative people, as they may benefit those living with HIV as well.

• Some microbicides may be able to neutralize pathogens in both semen and vaginal secretions. This could give HIV positive people a way of reducing their partners’ risk of HIV exposure during sex, as well as a way of reducing their own risk of infection with other HIV strains. This is what is known as the “bi-directional” effect – when a product can reduce risk in both directions, for both partners.

• Some products may also be able to reduce a woman’s risk of getting other STIs, bladder infection or yeast infections. For people with compromised immune systems, this could be an important advantage. In addition, some microbicides may not be contraceptive, and may allow HIV positive women to get pregnant. Using a non-contraceptive microbicide could help a positive woman to conceive without endangering her partner if he is HIV negative.
Mid-Module Knowledge Quiz

1. What factors contribute to the increasing number of women that are HIV positive worldwide?

2. What are current prevention options for sexually transmitted HIV, and what are their limitations?

3. How could microbicide development benefit those that have anal intercourse? Are these benefits limited to men? Women?
1. What factors contribute to the increasing number of women that are HIV positive worldwide?

There are several factors that contribute to the increasing number of women that are being infected worldwide. In a general sense, the lack of economic, social and political rights contributes to an inability of women to have sexual and reproductive rights. This prevents women from having the ability to negotiate condom use.

More specifically, you can list several factors that contribute to the increase in women that are being infected with HIV, including biological and cultural factors. From a biological perspective, vaginal membranes are exposed to infectious fluids for hours after sexual intercourse. Younger women are at greatest risk because the immature cervix is more vulnerable to viral penetration and subsequent infection. Sexually Transmitted Infections (STIs) often go undetected, and therefore untreated, in women, and this can lead to an increase in women's vulnerability to HIV. From a cultural perspective, many women want to get pregnant --for personal reasons and/or to achieve the status and security that, in many societies, they can only attain through motherhood. Since condoms are contraceptive, women now have to choose between childbearing and HIV prevention, and thus, choosing to try to become pregnant can increase their risk of contracting HIV.
2. What are current prevention options for sexually transmitted HIV, and what are their limitations?

Abstinence - In many instances, remaining abstinent is not an option: because girls will get married at a young age to much older men, because women enter commercial sex work to alleviate immediate threats to their children’s or their own health, such as starvation, or because women are unable to refuse sexual relations with their partners. The greatest risk factor for women contracting HIV in many settings is to be married. Many women in the setting of an established relationship or marriage are unable to say no to sex.

Mutual monogamy - Similarly, women worldwide may not be able to trust that their partner is uninfected, nor be able to request that the partner obtain an HIV test. If the partner is HIV negative, there is still a concern that HIV will be contracted if the relationship is not mutually monogamous.

Condom use - In many parts of the world, women also don’t have control over when and how they have sex. Asking her partner to use a condom may result in a woman being beaten, threatened, or abandoned by her partner. The possibility of a violent response is especially high if a man believes that a condom means

1) a lessening of male pleasure,
2) that promiscuity or infidelity is going on or
3) that the woman has “inappropriate” knowledge of sexual practices.

3. How could microbicide development benefit those that have anal intercourse? Are these benefits limited to men? Women?

In surveys from several countries, there are many people, men and women that have anal intercourse. Often, sex occurs without the use of a condom, either for reasons described in question number 2, or because anal intercourse eliminates the risk of pregnancy, and thus many individuals don’t feel that a condom is needed. Therefore the development of a microbicidal product that is safe and effective in the rectum could lead to increased protection from HIV infection for both men and women.
What is a microbicide?

Microbicides are substances that can reduce the transmission of HIV and other STI pathogens when applied vaginally and, possibly, rectally.

They are not yet available.

Currently, they are formulated as lubricants, gels or creams applied with an applicator like those shown here.
• Having explained the need for user-controlled HIV prevention methods, we will now explore microbicides.

• Microbicides are substances that can reduce the transmission of HIV and other STI pathogens when applied vaginally and possibly, rectally.

• The first generation of microbicides could be available on the market in as little as five to seven years. They will probably look a lot like the over-the-counter yeast infection treatments and birth control products -- the gel, foam, cream and suppository-type products that have been on the shelves for years. These microbicides won’t contain the same chemicals as these birth control products but they will come in some of the same formulations.

• For example, they’re working to make formulations that women can use several hours or even days before intercourse, if necessary. One possibility is a vaginal ring or sponge -- something that could slowly release the protective substance over time, providing around the clock protection. Another possibility is combining a physical barrier -- such as a diaphragm or cervical cap -- with a microbicide. Since the cervix is more vulnerable to infection than the vaginal walls, this combination might provide highly effective protection.

• It must be made clear that at the writing of this module, there are no microbicides currently on the market.
What is a microbicide?

Microbicid​es Must Be…

• Safe for all potential users:
  – Sexually active women and men
  – Pregnant women
  – HIV positive women
  – Adolescents
• Compatible with condoms and other barriers

Microbicid​es Must Work…

• In normal situations
• In the presence of inflammatory and ulcerative STIs
• In the face of micro trauma due to intercourse.
• Vaginally and rectally

Supplementary notes on next slide
There are some characteristics that must be considered to have a safe and usable microbicide beyond just efficacy and preventing sexual HIV transmission.

Microbicicides must be safe and acceptable for both sexually active women and men. If a product causes irritation, burning or discomfort in men or women, then there is little hope that the product would be used willingly or regularly. In addition, the microbicide must be tested for safety in pregnant women to ensure that sexually active pregnant women are able to reduce their risk of contracting HIV, thus protecting themselves and their child. In addition, as mentioned earlier in the module, the microbicide should be safe for HIV+ women, thus allowing them to protect themselves from re-infection with other HIV strains, to reduce the risk of HIV transmission to their partners, and to decrease their chances of contracting other sexually transmitted infections.

In addition, because condoms will likely remain a more efficacious method of HIV prevention, at least in the short term, the microbicide should be compatible with condoms and other barrier methods of contraception and HIV prevention. If microbicicides decreased the stability or safety of condoms, then they would not be an acceptable means of decreasing a person’s risk of HIV.

There are also setting in which the microbicide must work, beyond the setting of healthy sexually active individuals. A microbicide must provide sufficient protection from HIV infection in the presence of both ulcerative and non-ulcerative STIs, as both can increase the risk of HIV transmission. Another concern is the development of micro trauma due to repetitive motion of sexual intercourse. A microbicide must be sufficiently robust as to prevent transmission, in both the vagina and rectum, in a setting of increased blood to semen or vaginal fluid contact.
What is a microbicide?

The ideal microbicide …

- Bi-directional, i.e., protect both partners
- Available over the counter
- Active against a range of sexually-transmitted pathogens
- Long duration of effect
- Available in spermicidal & non-spermicidal formulations
- Sustain or enhance normal vaginal ecology
Supplementary notes

• There are other characteristics that would lead to enhanced acceptability of microbicides, an thus enhanced usage and reduced HIV risk.

• Bi-directionality of protection, or the ability to reduce the risk of HIV transmission to both partners will increase the acceptability of use. Similarly, if there is activity against a range of other sexually transmitted infections, use of the product will serve an even greater public health purpose by reducing the spread of diseases such as human papilloma virus (HPV), herpes simplex virus (HSV) and others. This may lead to decreased morbidity and mortality from STIs or cervical cancer. Because infection with these other STIs also leads to an increased risk of HIV transmission, decreased incidence of these STIs will also indirectly lead to decreased HIV transmission.

• In addition, the product must be easily accessible in resource poor settings, which includes making the product over the counter, stable under a variety of environmental conditions, and it must be amenable to shipping and storage. The longer the duration of action, the less frequently the product will need to be applied.

• In many settings, a woman may want to become pregnant and have children, but there exists no option to conceive while still protecting oneself from HIV infection. Research is being conducted to develop some microbicides that would allow for conception yet protect against HIV. In the setting where religion or culture prohibits the use of contraception, these microbicides would fill an important niche. However, some microbicides would serve the dual purpose of contraception and HIV prevention. This may enhance the use of such a product, because the woman would be able to justify using the product for its pregnancy preventing effects.

• The vaginal mucosa is normally inhabited by a delicate balance of microbes. The ideal microbicide would not alter this micro-environment in such a way as to make a woman more susceptible to yeast infections, bacterial infections, etc.
How Effective Will Microbicides Be?

• **First** microbicides may be 40-60% protective

• **Second** generation products may be 60-80%

• Should be promoted as an adjunct or “back-up” to condoms, **not** as a replacement

• Use them with **harm reduction** messages, such as:
  
  – “Use a male or female condom every time you have sex; if you absolutely can’t use a condom, use a microbicide”
  
  – “Use a microbicide with your condom for added pleasure and protection”
Supplementary notes

• Microbicides will help people reduce risk of infection -- but they aren’t going to eliminate risk. Microbicides will probably never be as effective as condoms. It’s safer to keep a virus out of your body than it is to try to kill or disable it once it’s there.

• Obviously no one can predict exactly how effective microbicides will be when they become available. However, based on preliminary basic and clinical evaluations, the first microbicides are likely to be 40-60% protective against HIV. That doesn’t sound very good compared to a condom effectiveness, but it’s more protection than people get when they’re using nothing.

• The second generation microbicides are likely to be 60-80% effective against HIV and, by the third generation, they may be as high as 90% effective. But for now, we are talking about microbicides as part of a harm reduction approach. We need to encourage people to continue to use condoms if they possibly can, because when used consistently and correctly a condom is the most effective way to prevent sexually transmitted HIV infection.

• Microbicides will a health care provider something to suggest when a woman says “I just can’t make him use a condom. Isn’t there something else I can do to protect myself?” Once microbicides become available, we’ll be able to answer by explaining clearly that these new products aren’t as effective as condoms -- but they’re way better than nothing. And, as we all know, a lot of women are getting infected because “nothing” is all they have.

• The overall impact of microbicides is primarily influenced by the extent to which microbicides can be made widely available and used. At 10% coverage microbicides could avert 1.4 million HIV infections (44% less than at 20% coverage). At 30% coverage, a microbicide with 60% HIV efficacy could potentially avert up to 3.7 million HIV infections – 46% greater than at 20% coverage. Even assuming that a microbicide is only 40% HIV efficacious, at 20% coverage 1.7 million HIV infections could be averted, illustrating how the widespread use of even a relatively low efficacy microbicide could have an important impact on HIV transmission.

### Where do Microbicides Fit?

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<thead>
<tr>
<th>Prior to exposure</th>
<th>Point of transmission</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Rights-focused behaviour change</td>
<td>Male and female condoms and lube</td>
<td>Improved antiretroviral therapy</td>
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<tr>
<td>Voluntary counselling and testing</td>
<td>ART to prevent perinatal transmission</td>
<td>Treatment for opportunistic infections</td>
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<tr>
<td>STI screening and treatment</td>
<td>Clean injecting equipment</td>
<td>Basic care/nutrition</td>
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<tr>
<td>Preventative Vaccines</td>
<td>Vaginal and rectal microbicides</td>
<td>Prevention for positives</td>
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<tr>
<td>Pre-exposure prophylaxis (PREP)</td>
<td>Cervical barriers</td>
<td>Education and behavior change</td>
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<tr>
<td>Male circumcision</td>
<td>Post-exposure prophylaxis (PEP)</td>
<td>Therapeutic vaccines</td>
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Supplementary notes on next slide
Supplementary notes

• As you are learning about what a microbicide will be, it is important to put it into context with currently available HIV prevention strategies as well as compare and contrast microbicides with other methods of prevention under development. There is an ever expanding toolkit of HIV prevention and treatment.

• At this point, we have many tools that people can use before exposure, right at the point of HIV transmission, and also after being infected. To be sure, we must work to improve people’s access to these existing tools—we need to make sure that male and female condoms are available to those who need them at an affordable price, and that women can access prevention of mother to child transmission services when they need them.

• For more information on these topics, please see module “HIV/AIDS”. Microbicides would also fall under the category of decreasing HIV transmission at the point of contact. There are other methods under investigation, including cervical barriers to help prevent HIV infection of the delicate cervical tissue, as well as post-exposure prophylaxis. Currently there is post-exposure prophylaxis in the setting of occupational exposures. However, the use of this in broader settings is being evaluated.

• The tools that are currently available are in black text, while the tools that are under development are in blue text.

  VCT is voluntary counseling and testing for HIV
  PREP is pre-exposure prophylaxis
  PMTCT is prevention of mother to child transmission
  PEP is post-exposure prophylaxis
Microbicide Mechanisms of Action

1. boosts vagina’s natural defenses
   - Gel/cream: Physical barrier, Lubrication
   - Maintenance of normal microflora
   - Prevention of other STDs
   - Viral disruption

2. surfactants
   - Inhibition of HIV uptake by dendritic cells (e.g. anti-DC-SIGN)
   - Inhibition of reverse transcriptase
   - Fusion/absorption inhibition (e.g. polyanions, co-receptor antagonists)

3. entry inhibitors
4. antiretroviral


Supplementary notes on next slide 34
Knowing the need for a microbicide is great worldwide, and now understanding some of the properties that microbicides must possess to be acceptable and usable, we will now explore the mechanisms of action of those products currently under development.

The products now in the research pipeline have four general mechanisms of action. This slide is a picture of the vaginal wall and illustrates the different ways that candidate products might work to reduce infection.

1. The first approach is to build or improve upon the innate immune system. For example a healthy vagina normally has an acidic pH, which makes it inhospitable to invading pathogens like HIV. But semen, which is alkaline, neutralizes the acidity of the vagina and creates an environment where HIV can survive. Some candidate microbicides build on the simple principle of maintaining the vagina’s natural acidic environment even in the presence of semen.

2. Surfactants disable the virus by disrupting the envelope. They can also disable sperm in the same way so they are also effective contraceptives. The challenge is to make sure that surfactants are strong enough to disrupt the invading pathogen, but without damaging the healthy cells that line the vagina’s walls. If the candidate product disrupts the surface mucosa, it may actually increase the transmission of HIV.

3. Entry inhibitors work by interfering with the virus getting into the body’s CD4+ cells—the target cells of HIV. There are two categories of entry inhibitors: *attachment* inhibitors that prevent interactions between the virus (gp120/gp41) and the CD4+ white blood cell, while *fusion* inhibitors prevent the conformational change in gp120, thus preventing the fusion of the HIV envelope with the cell, and therefore preventing HIV entry into the cell.

4. Finally, some microbicides are being created by reformulating the same anti-retroviral drugs developed to treat HIV infection. These drugs are designed to stop HIV from replicating. The goal is to determine if topically applied antiretroviral drugs (ARVs) will stop viral replication rapidly enough to prevent HIV infection from spreading beyond the vaginal and cervical mucosa.

The first microbicides to become available will contain single active agents and as such each will most likely exhibit only one of the mechanisms of action listed above.

It is very likely, however, that later generation microbicides will be combination products -- using two or more mechanisms of action to enhance their effectiveness.

Formulation Innovation

• Products being developed on the basis of:
  – Stability
  – Absorption
  – Local environment (rectum vs..... vagina)
  – Acceptability

• Broader range of delivery systems
  – Gels, foams, films, suppositories, and rings
• Knowing the mechanisms of action of potential microbicides, you can now begin to predict some of the formulations that are being considered for microbicide delivery.

• Factors that are being taken into consideration include the stability of the product, or how long a product will provide protection after it is applied. In some cases, delivery systems are being researched that would allow for a long duration of action, likely in the form of a vaginal ring that would supply active microbicidal product over the course of weeks to months.

• Another factor to evaluate is that of absorption. If a microbicide that is really a vaginally or rectally applied anti-retroviral drug is absorbed into the blood stream of someone that is HIV positive, would that contribute to the development of resistant HIV strains? Would selection pressure in the vaginal environment when topical antiretroviral are applied select for infection with drug-resistant HIV strains? These are factors being considered.

• In addition, the acceptability of the products is being tested. This encompasses the way a product feels, smells, tastes and looks, as well as factors like the mode of application, such as a suppository, ring, gel, cream, douche or enema. In addition, the volume of product required to prevent HIV infection also is evaluated in the context of delivery systems and acceptability.
Differences Between Vaginal and Rectal Microbicides: The Anatomy
Differences Between Vaginal and Rectal Microbicides: The Physiology

<table>
<thead>
<tr>
<th>Vagina</th>
<th>Rectum</th>
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<tr>
<td>Most of the epithelium is 40 cell layers thick</td>
<td>Very fragile epithelium, 1 cell layer thick.</td>
</tr>
<tr>
<td>Fewer CD4 cells than rectum</td>
<td>More inflammatory cells under surface (CD4 receptors)</td>
</tr>
<tr>
<td>Acidic pH</td>
<td>Alkaline, rather than acidic pH</td>
</tr>
<tr>
<td>Enclosed pouch</td>
<td>Open-ended tube</td>
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</table>
• Formulating a microbicide for rectal use is more challenging than making one for vaginal use just because the rectum is a very different environment.

• In terms of histology, the vaginal epithelium is significantly thicker than that of the rectum. This provides additional protection against abrasions and shearing forces produced during sexual intercourse, and thus decreases the chances that there will be direct exposure of semen to broken blood vessels. In addition, the vaginal mucosa has fewer CD4+ cells than the rectum, thus decreasing that chances that a localized exposure to HIV will result in cells becoming infected.

• There are differences in the pH of the vagina as compared to the rectum. The vagina is normally an acidic environment. Semen counteracts this acidic milieu, and creates a more alkaline environment, which is needed for the survival of sperm. If a microbicide were able to maintain the acidic environment, it could potentially serve as a spermacide and an anti-HIV product. But contrast this with the rectal pH, which is alkaline. A product that encourages an acidic environment may lead to irritation and disruption of the normal pH in the rectum. Thus, products designed for one environment may not be safe and effective in the other.

• An obvious feature of the rectum is that it is an open ended tube. The vagina is a closed pouch. You can coat the inside of the vagina with about 3-5 ml. of product. Since the rectal cavity isn’t closed, it could require significantly more product to protect the rectal walls where they need protection. It has been demonstrated that semen can travel up to two feet in the colon upon ejaculation. One of the key questions to answer now is exactly what quantity of product it will take and what areas have to be covered to get a good protective effect.

• Research has begun to develop rectal microbicides. They are urgently needed by men and by women who engage in anal intercourse. The next slide will describe some of the additional research questions that have been raised in the course of rectal microbicide research.

• But until we have an effective rectal microbicide, we have to insist that all vaginal microbicides be tested for rectal safety and be labeled appropriately to let the public know that they are not designed for rectal use and should not be used that way.
Rectal Microbicides
Research questions…

- Infection – Basic science of infection and micro-trauma in anal intercourse
- Testing - What assay to measure infection and tissue response?
- Distribution – How would microbicide spread over epithelium?
- Application Methods?
- Dosing – What volume is acceptable and tolerable?
- How does rectal shedding of HIV impact risk?

Supplementary notes on next slide
• Because of the unique environments within the vagina and rectum, it is crucial to fully understand the different physiology and mechanisms of HIV transmission. However, in the setting of rectal tissue researchers have more questions than answers.

• **Testing / Assays:** How do we design tests that will give us information about the course of infection? For example, how do we measure how well the product coats the epithelium, how much of it is absorbed into the bloodstream and how it gets displaced around during sex? MRI scans have been shown to be an effective tool for assaying how products distribute in both the vagina and the rectum.

• **Distribution or dilution:** What concentration of product can give the most protection against HIV and other STIs without causing damage to rectal tissue? What happens to the microbicide once it is inside the rectum? How long can it dissolve and spread out before it becomes ineffective?

• **Application methods:** How a product is applied will influence both its acceptability and level of protection. Will people be willing to use gels inserted with applicators, anal douches, suppositories that dissolve over time, lubes or other products applied to the penis?

• **Dosing:** How do various products feel and how much can one apply before causing rectal “fullness” and discomfort? Different formulations will cause different sensations and will coat the rectal walls differently. Dosage acceptability and coverage issues have to be studied.

• **Bi-Directional Partner Protection:** What impact would a microbicide have on HIV that is already in the rectum of an HIV positive partner. And how will that affect the insertive partner's risk of becoming infected or re-infected by the receptive partner during intercourse? There needs to be study of bi-directional protection in the setting of vaginal and rectal HIV transmission.
Mid-Module Knowledge Quiz:

1. Define ‘microbicide’ and list several features of an ideal microbicide.

2. What are some of the ways the microbicides could potentially work?

3. Compare and contrast the vaginal and rectal environments as they relate to developing a microbicide for each setting.

Supplementary notes on next slide
1. Define ‘microbicide’ and list several features of an ideal microbicide.

Microbicides are substances that can reduce the transmission of HIV and other STI pathogens when applied vaginally and, possibly, rectally. Ideally they would be safe for all potential users, such as men, women, pregnant women, adolescents and those that are HIV positive. In addition, they need to be safe both vaginally or rectally, or they need to be clearly labeled as to their safety in either setting. The microbicide would also need to be affordable and accessible to those that need them.

2. What are some ways that the microbicides could potentially work?

They could coat the vaginal or rectal mucosa and prevent HIV from coming into contact with CD4+ cells. The microbicide could disrupt or disable HIV and render it non-infectious. Products could prevent the binding of HIV to target cells, or if HIV did gain entry into the CD4+ cell, products derived from anti-retroviral medications could halt replication early in infection.

3. Compare and contrast the vaginal and rectal environments as they relate to developing a microbicide for each setting.

In the vagina, maintenance of an acidic pH is critical to preventing both pregnancy and to disabling HIV and preventing infection. In addition, the multi-layered epithelium in the vagina provides a robust layer of protection against infection, and preservation of that lining is an important consideration. Similarly, protection of the vaginal mucosa from other sexually transmitted infections is an important step in HIV prevention. Lastly, the vagina is essentially a closed ended pouch, and therefore requires a limited volume to coat all surface area.

In the rectum, the pH is normally more alkaline, and it is unclear what effect this will have on potential microbicides. The mucosal lining of the rectum and anus consists of only one cell layer, making preservation of this barrier of utmost importance, which reflects the need for a microbicide that is not irritating to the mucosa. In addition, the rectum/colon is a hollow tube, not a closed cavity like the vagina, and therefore any microbicide designed to protect in this environment would need to be applied in such a way that it protected sufficient surface area. However, the method of application and the actual length of colon that needs protection is not yet clear.
Timeline for Microbicides Research and Clinical Trials

- **Laboratory Testing**: 2-6 Years
  - Phase 1 (safety): 1 to 6 Months
  - Phase 2 (safety): Up to 2 Years
  - Phase 3 (efficacy): 2 to 4 Years
  - **Simultaneous studies**: HIV+, penile & rectal
  - **People involved**: 25 – 40 people
    - 200-400 people
    - 3,000-10,000 people

- **10 or more years**

Supplementary notes on next slide
Supplementary notes

- We will now begin to describe the timeline and challenges for microbicides research and clinical trials.

- As you see, microbicides research is not quick to do. **Because microbicides are being marketed as a preventative medicine for healthy people, extreme caution must be taken to do no harm and it is therefore extremely difficult to shorten the timeline presented here.** The whole process often takes about a decade. Before anything can be tested in humans, the developers have to show that (a) it's not likely to be harmful to humans and (b) it may be beneficial. The research is done in the laboratory and can take from 2-6 years.

- If a product is approved for human trials, it goes first through a series of Phase I safety trials, each taking between 1-6 months. Next comes one or more Phase 2 trials to gather extended safety data and that can take up to two years. If it's shown to be safe, they test to see if it is effective. The Phase 3 effectiveness trials can take 2-4 years because a large number of participants are enrolled and they get a year or two of follow up services, to see if the product has any effects after extended use. It may be necessary to do two Phase 3 trials before a product is proven effective.

- While clinical trials are going on, researchers also undertake separate trials to look at whether the product is irritating to the penis, how the body will react if the product is inserted rectally, and whether it is as safe for HIV positive people to use as it is for HIV negative people.

- When you consider this whole timeline, it's makes sense that the soonest we could have a microbicide on the market is in five to seven years. If one of the products now in Phase 3 is effective, we should see proof of its effectiveness in the next 3-4 years. It will then take another year or two for the product to be considered by regulatory authorities and, if approved, go to market.

- But this is a “best case” scenario. If none of products now going into Phase 3 proves to be effective, we will wait longer. How long it takes depends, in part, on how fast we can keep new products advancing in the pipeline.
Experience of a Phase III Participant

**Recruitment:** Participant receives information about the trial

**Screening Visit 1:** Education about the trial, HIV and pregnancy test, STD tests and treatment, baseline data collected

**Screening Visit 2:** Results of tests, counseling, reinforce education about trial

**Randomization:** Participant assigned by chance to a group.

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Microbicide trials: The process

Informed consent for screening

Informed consent to enroll.

Condoms + placebo

Condoms + experimental gel

Family Planning

Supplementary notes on next slide
The experience of those participating in phase III effectiveness trials is important to consider, and we will explore that before we delve into the scientific and ethical challenges in undertaking microbicides trials.

Every woman who is recruited for an effectiveness trial goes through a careful informed consent process and is tested for HIV and other STIs. Women who test positive for HIV can’t enroll in these first effectiveness trials because women have to be negative at the start of the trial to see how well the product helps them to remain negative. Women who test positive are connected to local providers of HIV-related care, treatment and support. They are also advised of other trials that are enrolling HIV positive women, if any are going on in their area.

Everyone in a phase III trial receives state-of-the-art HIV prevention services. Right now, this means participants receive intensive risk reduction counseling, including condom counseling, large supplies of condoms and treatment for sexually transmitted infections if needed. All the women are encouraged to use condoms, whether they are given the active microbicide or not.

In order to actually find out if the experimental microbicide works, the trial participants are randomly divided into two groups:

1. Those who receive the condoms and prevention services plus the experimental microbicide gel.
2. Those who receive the condoms and prevention services plus a placebo gel that looks just like the drug being studied but does not contain the active ingredient.

At the end of the trial researchers compare the two groups to see if the HIV rate is lower among those who received the microbicide versus those who received the placebo. If it is, that difference is the measure of the microbicide’s effectiveness.

Trials can also bring increased health care, prevention services and treatment access into highly-impacted communities. How those services are provided and how well they are continued after the trial is a subject of intense ethical debate among researchers and communities, and we will explore some of these concerns shortly.
Microbicide trials: The process

THE AMERICAS:
- United States: Phase I, II, IIB
- Brazil: Phase II

WEST AFRICA:
- Benin: Phase III
- Nigeria: Phase III
- Cameroon: Phase I, II

SUB-SAHARAN AFRICA:
- Botswana:
- Kenya: planned
- Madagascar: Phase
- Malawi: Phase II, IIB
- Rwanda: Phase I/II
- South Africa: Phase I, IIB, III
- Tanzania: Phase III
- Uganda: Phase III
- Zambia: Phase IIB, III
- Zimbabwe: Phase I, II, IIB

EUROPE
- Belgium: Phase I/II

ASIA
- India: Phase II, III
- Thailand: Phase I

AUSTRALIA
- Phase 1

Source: Alliance for Microbicide Development

Supplementary notes on next slide
• This slide is to give you a sense of where these trials are taking place. As you see, phase I and II safety trials are going on all over the world, but especially concentrated in the U.S., Africa, and India.

• To study effectiveness, a microbicide has to be tested by large numbers of women at high risk of sexually transmitted HIV. This means that the countries in which Phase 3 trials are carried out must have:
  
  • A high incidence of HIV
  • A stable population so that participants can be followed up easily
  • Almost no injecting drug use or other sources of HIV risk among women

• These conditions are found across sub-Saharan Africa and in India and parts of Southeast Asia. Places where HIV is prevalent among women in the North America and Europe also tend to have high rates of injecting drug use. This factor could confuse the trial results by introducing other sources of HIV risk. In part due to this reason, the majority of effectiveness trials are taking place in Africa and India as indicated here.
Microbicide trials: The challenges

- Lack of surrogate marker(s) of protection
- Efficacy vs. effectiveness trials
- Adherence to product use during trial
- Product use during pregnancy
- Ethical issues
- Community Involvement
- Legacy of nonoxyl-9

And even more challenges need attention
Microbicide trials: The challenges

Lack of surrogate markers or correlates of protection...

- Absence of:
  - lab assays
  - clinical parameter
  - animal model
- No measure of biological activity of product
- The only meaningful effectiveness studies are those with HIV infection as the endpoint
One of the clear challenges of conducting microbicides trials revolves around the issue of prevention. A successful microbicide will prevent a certain outcome, specifically, the seroconversion from HIV negative to HIV positive.

At this point, there is no other method of determining if a microbicide will be effective. In vitro, meaning in the laboratory, the primary measure of microbicide’s effectiveness is the ability of a compound to disable HIV, and render it non-infectious. This, however, does not necessarily correlate to the complex setting of the vaginal or rectal mucosa, where there are multiple cell types, differing epithelial linings, and micro-trauma from sexual intercourse.

In the human setting, there are not currently any lab tests or clinical indicators that show that a microbicide has the potential to work. In both the human setting and in animal models (which use primates) there is a reliance on the end point of seroconversion as a measure of effectiveness. This forces a reliance on large clinical trials in communities with a high HIV prevalence and a high incidence of HIV seroconversion. One cannot use the presence or absence of particular antibodies, enzyme activity or markers in the blood to predict microbicide effectiveness.
Microbicide trials: The challenges

Effectiveness vs.... Efficacy

• Real world constraints
• Poor adherence - suboptimal product usage
• RESULT: lower levels of product use - lowers effect size

The effectiveness of a candidate microbicide refers to its theoretical ability to prevent sexually transmitted HIV infection with perfect and consistent use in every act of intercourse. Laboratory studies can predict the effectiveness of a product. However, efficacy refers to the reality of the preventative effect seen with a microbicide. Real world constraints, such as inconsistent use of condoms, inconsistent use of microbicide candidate, imperfect application, and inaccurate recall and reporting of usage all can lead to an apparent decreased efficacy of the microbicide.

To put it more formally, in a randomized trial of a candidate microbicide and a placebo, nonuse of the microbicide will result in underestimation of microbicide efficacy, with the magnitude of this difference between effectiveness and efficacy increasing directly with the level of microbicide nonuse.
Microbicide trials: The challenges

Product use during pregnancy

- Lack of reproductive toxicity data means products have to be withheld during pregnancy
- High pregnancy rates in current microbicide trials
- A pregnancy rate of 40 per 100 women years (mean = 6 months pregnant) means that 20% of women-years on study are without product
- RESULT: Lower usage of product leading to lowering of the effect size
Because there is always real and warranted concern for the health and development of the fetus in a pregnant woman, if a woman becomes pregnant during the course of her participation in a microbicides clinical trial, the candidate microbicide is withheld. Because a large percentage of women are becoming pregnant during the course of the microbicides trial, this means that these women are not considered in the trial data when evaluating efficacy of the candidate product. This leads to a lower number of actual participants than the total number that was enrolled.

This means that larger numbers of participants need to be enrolled in a trial from the start to end up with a significant number of participants to evaluate at the endpoint of the trial.

However, this also means that there is no way to evaluate the safety of these products on the developing fetus. Pregnant women worldwide have sexual intercourse, either vaginally or rectally. It is unclear how this lack of reproductive toxicity data will impact how microbicides are marketed for pregnant women.
Principles of Research Ethics

• Research ethics rests on a set of fundamental ethical principles. The primary ones are:
  – Beneficence
  – Justice
  – Respect for persons

• Different ethical principles can be in conflict

• Ethics is not a formula, but a process of reflection and weighing of choices
Ethics is a branch of philosophy that assists us in deciding what is right and wrong in human conduct. Ethical reasoning takes place when you need to provide moral reflection on a specific action or behavior, such as a research project or a procedure.

Human research ethics rests on a number of basic principles that are considered the foundation of all guidelines or rules governing bio-medical research. An ethical principle is considered the most fundamental unit of ethical reasoning. All norms, guidelines and higher-order principles derive from these. It is important to remember, however, that ethics is not a formula or a “cook book.” At times, different ethical principles can be in conflict or tension with each other, and resolution can only be achieved through thoughtful reflection and debate.

The first principle – beneficence – creates the obligation to protect research participants from harm and to maximize possible benefits. This principle is often interpreted to mean that, on balance, the research must due more good than harm. For example, the Belmont Report, an American articulation of research ethics, states that “the risks to subjects should be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society.” The report notes, however, that “in balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight.” The principle also leads to the notion that the risks imposed by research must be commensurate with the expected benefits. In other words, risks considered acceptable in testing a new cancer therapy may be more severe than risks considered acceptable in studying treatments for a less serious disease.
The second major principle of biomedical ethics is justice. In research, the complex principle of justice is usually interpreted as “distributive justice” – meaning that there should be a fair distribution of both the risks and benefits of research. This principle is used to argue, for example, that the benefits of research should be made available to the persons and populations being researched. This becomes of particular interest in microbicides trials. Community advisory boards in locations where current microbicides trials are being conducted are advocating for any microbicide product that becomes approved to be accessible in the community in which it was tested. This principle also gives rise to the requirement that research participants and sites be selected fairly – both in terms of who stands to benefit from the research as well as who bears its burdens. The principle of justice, for example, argues that all who stand to benefit from the research should contribute to its risks and discomforts. In other words, research that may benefit both the rich and the poor should be conducted with both groups, not only with the poor. In thinking through the setting of HIV prevention trials, recall that the majority of phase I and phase II trials are occurring in the developed world, while the majority of phase III trials occur in the developing world. Please review the epidemiologic reasons from the previous slide describing why this is so.

They third principle, respect for persons recognizes the capacity and rights of all individuals to make their own choices and decisions. It refers to the autonomy and self determination of all human beings; acknowledging their dignity and freedom. An important component of this principle is the need to provide special protections to those who may be vulnerable. Can you think of one or more conditions that might render someone in need of special protection? In addition, can you think of circumstances where the reward of participating in a trial would coerce and individual into participating? To acknowledge the respect for persons and the autonomy of those enrolled in microbicides trials, we often use the term research participant rather than subject. “Participant” is thought to be more respectful whereas “subject” implies a subordinate relationship between the researcher and the volunteer.
Microbicide trials: The challenges

Ethical challenges

• Ethical challenges in conducting microbicides trials:
  • Adequate communication of risk and benefits
  • Therapeutic misconception
  • Intensive counseling on risk reduction
  • Condom promotion
  • STI treatment
Supplementary notes

There are a number of ethical considerations in undertaking microbicides trials.

Because the trials are enrolling healthy, young individuals who are at high risk for HIV infection but are not currently infected, the process of ‘informed consent’ is critical. There is a tendency in some quarters to equate “informed consent” with the signing of an “informed consent document.” While a signature on a consent form may hold legal weight, it does not hold moral weight. There must be an adequate communication of risk/benefit.

For consent to be ethically valid, a prospective participant must:

1. Be **appropriately informed** about the nature of the research
2. **Adequately understand** this information and its implications
3. **Voluntarily decide** to participate, without coercion or “undue inducement”
4. **Explicitly consent** to participate, either orally or in writing

Another consideration in ‘informed consent’ involves the notion of therapeutic misconception. “Therapeutic misconception” is a term applied to the tendency of some research participants to steadfastly believe that an intervention or drug offered to them in research study is going to work-- or benefit them personally -- even though they have been advised otherwise. In research, because of randomization, not all participants may receive the experimental intervention, and it is not clear going in, whether the experimental product even works. Despite every effort to emphasize this fact, some participants persist in the belief (or hope) that they are getting a drug or intervention that works. The misperception generally occurs when there is a **blurring in the mind of a participant between the boundaries of research and therapeutic care**. In research, the goal is to generate new knowledge that can be helpful to future patients or individuals not necessarily to the research participants themselves.
Supplementary notes

But individuals are accustomed to trusting their physicians to recommend or prescribe the best possible intervention for them. So it is easy for participants to assume (wrongly) that an investigator would not be suggesting that they use a drug, such as an experimental microbicide, unless they knew it worked. This confusion is especially likely to occur when the investigator is indeed a physician, as is the case in many drug trials. Especially in settings where people are unfamiliar with the conduct of research, it is VERY important that every effort is made to clarify and reinforce that people are invited to participate in a clinical trial precisely because we do not know whether the study product works. Informed consent requires that people fully comprehend that they are participating in an “experiment.”

There can also be ethical conflicts in the setting of research collaborations between higher-resourced and lower-resourced countries. There may be a perceived conflict of interest when there is a pressure to publish research findings or when there is funding from commercial, private or independent sources.

In addition, there must be intensive counseling on risk reduction as one enrolls participants in the trial. Please review the slide on the challenges in undertaking microbicides trials for more information on counseling for risk reduction and condom promotion.

One must also consider the standard of treating STIs during the course of enrollment in a microbicides trial. Does the opportunity to be tested and treated for these infections constitute coercion?
Microbicide trials: The challenges

Community involvement …

Activities and mechanisms that promote partnership between communities, civil society, and research teams in decision-making, problem-solving and program implementation
• Community involvement represents on-the-ground implementation of science’s accountability to society, at the local as well as global level. Engaging a wide range of stakeholders as active and informed partners in decision-making about the research and its implementation enhances both the scientific validity and ethical integrity of clinical trials. This has been widely recognized in the field of AIDS research, and almost all publicly-funded research networks require a community involvement component. Generally, this has been done by forming a community advisory board (CAB) or similar structure, a model developed in the US in the early days of activist involvement in HIV treatment trials.

• Recently, however, research networks are questioning whether the CAB model is the best or only approach to developing partnership with communities. The community liaison teams at various trial sites are exploring a variety of strategies to engage with communities as partners in the research enterprise. Key considerations in developing community participation include:

  • Build trust between community members, researchers, and health authorities
  • Develop partnership in decision-making, setting research agenda
  • Ensure exchange of relevant information
  • Protect the rights of trial participants
  • Provide tangible benefits to the community as well as participants
  • Reduce vulnerabilities of participating communities
  • Prepare stakeholders to advocate for policy change, prepare for access
Legacy of Nonoxyl-9

- Phase 2/3 trial in 892 sex workers from 4 countries

- 32% women used >3.5 applicators per working day

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<thead>
<tr>
<th></th>
<th>N-9</th>
<th>Placebo</th>
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<tr>
<td>N (women years)</td>
<td>376 (403)</td>
<td>389 (435)</td>
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<tr>
<td>cumulative incidence</td>
<td>59/376 (16%)</td>
<td>45/389 (12%)</td>
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<tr>
<td>Incidence rate</td>
<td>14.7</td>
<td>10.3</td>
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Lessons:
- Potential for harm
- Obligations of researchers
- Lack of a true placebo
- Effectiveness trial possible with <1000 women
N-9 products are sold over the counter as contraceptive spermicides, not for the prevention of HIV or other infections. Since N-9 kills HIV in a test tube, research was undertaken in the 1980s and 90s to see if these products would also work for HIV prevention. The 2000 study data showed that a 52.5 mg. N-9 gel (the lowest dose product on the market) did not protect women from HIV infection. In fact, when used more than once a day, N-9 contraceptive products may actually increase HIV risk slightly by irritating the vaginal membranes and causing disruptions that make it easier for the virus to enter the blood stream. Other studies show that N-9 is are even more irritating to rectal tissue than to vaginal tissue. 

In 2002, World Health Organization (WHO) experts came to the following conclusions: N-9 is not effective at preventing the transmission of HIV or other sexually transmitted infections (STI). It shouldn't be used or promoted for disease prevention. N-9 contraceptive products (used alone or with a diaphragm or cervical cap) offer an important option for women who chose not to use hormonal birth control methods. But N-9 may also increase a woman's chances of getting infected, if exposed to HIV. So women at risk of HIV, especially those having sex more than once a day, shouldn't use N-9 for birth control.

Women who are at low risk of HIV can continue to use N-9 for birth control purposes safely. Condoms with N-9 provide no more protection against pregnancy or infection than plain lubricated condoms. Since N-9 condoms may cause irritation, they should not be promoted. Instead, lubricated condoms without N-9 should be used. Products with N-9 -- including condoms, lubes and birth control products -- should never be used for anal sex. The rectum is more fragile than the vagina. Even the small amount of N-9 on condoms can damage the rectum, raising HIV risk.

Building demand for microbicides

- Public awareness
- Public demand
- Political support
- Increased resources for R&D ($$$)
- Safe and effective microbicides on the market
- All people know about & have access to affordable microbicides

Supplementary notes on next slide
Supplementary notes

• The presentation thus far has demonstrated a need for user controlled HIV prevention methods. However, how can the development of a safe and effective microbicide come to fruition? Many advocacy groups globally are working towards the goal of accessible and affordable microbicides.

• Before this goal can be achieved, there needs to be safe and effective products on the market – microbicides that have gone through all of the laboratory and clinical testing and gained the approval of the Food and Drug Administration in the United States or a similar regulatory body.

• To have a product on the market requires years of research and development, which requires active funding and support from governmental agencies. This funding will be the result of political support, which will only be realized if there is a perceived public demand. Many of those that have the greatest need for a microbicide don’t have access to those with the power to make decisions on funding, research and innovation in the developed world. Therefore, increased public awareness in the developed world has the potential to represent the needs and realities of those women and men in need of a user-controlled HIV prevention method.
Summary

• Need for user controlled HIV prevention options
• Research and development slow but promising
• Significant challenges in microbicide clinical trials
• Requisite for advocacy and community involvement
• In summary, there is a significant need for user controlled HIV prevention methods. The increasing incidence of HIV infection in women is fueled by poverty and inequality. Millions of women lack the social and economic power to insist on HIV prevention measures such as condoms, abstinence or mutual monogamy. Male and female condom use requires the tacit cooperation, if not outright participation, of a woman's male partner. This cooperation is not a reality for millions of women in every part of the globe. While microbicides do not offer a magic bullet, their development, alongside work to address gender inequality, sexual violence, economic realities and educational opportunities, has the potential to decrease the number of those seroconverting to HIV positive.

• It is true, research and development on microbicides can seem frustratingly slow, especially in the face of millions of new infections every year. It is important to understand the complexity of the vaginal and rectal environments, and the caveats that exist in preventing HIV infection in each setting. The timeline presented here for a candidate microbicide to go from an idea and experiment in the laboratory to the stage where it is possible to seek approval from a drug approval agency extends past a decade. The slow process thus requires that new products are entering the pipeline continuously, and that researchers at every level are supported financially and institutionally.
Once a product makes it through the basic science hurdles in the laboratory, this module should have made it clear that conducting a microbicides trial involves a critical analysis of many challenges, both logistically, statistically, from a community perspective and beyond. These constraints are not all novel to microbicides trials, as the HIV vaccine trials have faced similar roadblocks. However, as you see news articles about microbicides trials globally, you are now in a better position to understand the subtle challenges inherent to HIV prevention trials, and you are well positioned to explain these challenges to your peers and the public.

Lastly, having gained the knowledge contained in this module, you can appreciate the need for advocacy to bring a safe and effective microbicide to market in a way that makes it accessible and affordable to women and men in the developing and developed world in a timely fashion. This is no small feat, but the continued and enhanced financial investment in microbicides research requires that government officials and institutions be aware of the dire need for user controlled HIV prevention options. The materials contained in this module, in conjunction with the most up to date information that can be found in the ‘other resources’ section of this module, will allow you to advocate effectively for microbicides research.
End of Module Knowledge Quiz

1. Describe the two study arms in a microbicides phase III clinical trial.

2. List and explain characteristics needed in a community that participates in a microbicides clinical trial.

3. Propose factors important that a community advisory board (CAB) should take into consideration when a microbicides trial may take place in their community.

Quiz answers on the next slides
1. Describe the two study arms in a microbicides clinical trial.

When a person enrolls as a participant in a microbicides phase III clinical trial they are randomly assigned to either the control arm or the study arm of the trial. Both arms or groups receive comprehensive HIV prevention education, they receive testing and treatment for STIs, and they receive supplies of condoms. The control arm gets a ‘fake’ or control microbicide that looks like the real thing but has no active ingredient. The study arm of the trial gets the ‘real’ microbicide, the one that contains the test, active ingredient.

2. List and explain characteristics that are needed in a community that participates in a microbicides clinical trial.

- A high incidence of HIV: Because there are no surrogate markers that allow one to determine if a microbicide works, the end point of a microbicides clinical trial is the seroconversion to HIV positive of the participants. If the trial was conducted in a community with a low incidence of HIV, then there would be very few seroconversions in the control arm of the study. This would make it nearly impossible to determine if a microbicide candidate product was reducing the risk of HIV transmission because the risk was so low to begin with. However, if the incidence of HIV infection was high in the community, then if a microbicide was able to prevent infection, that decrease would be noticeable against the backdrop of higher HIV seroconversion.

- A stable population so that participants can be followed up easily: Because the time that it takes to conduct a microbicides clinical trial can take years, you need to have a population that does not migrate due to shifts in food supply, famine, drought, war, internal or international conflict, etc. These factors are not entirely predictable, but they must be taken into consideration at the outset of a clinical trial.

- Almost no injecting drug use or other sources of HIV risk among women: Microbicides will only protect against HIV infection that is contracted across the vaginal or rectal mucosa. Microbicides will not be a harm reduction tool for those that contract HIV through intravenous drug use. If the participants are at risk for contracting HIV through injecting drug use, then it would be impossible to know if a person seroconverted to HIV positive because the candidate microbicide didn’t work or because they got the HIV through the injection. Therefore, microbicides trials must be conducted in a setting where prevalence of injecting drug use is low to absent.
3. Hypothesize factors that are important for a community advisory board (CAB) to take into consideration when a microbicides trial may take place in their community.

This is an ever evolving list, but factors to consider include but are not limited to:

- Development of health infrastructure and the ability to maintain it once a trial is completed.
- Training of local individuals as community health workers to assist in trial logistics.
- Care and treatment for those that seroconvert to HIV positive during the course of a trial.
- Managing expectations about the potential harm/benefit of a candidate microbicide.
- Working to ensure that if a microbicide comes to market as the result of that community’s involvement that the community members have access to the product.
- Avoiding undue coercion or incentives for individuals to participate in a microbicides trial - i.e., preventing financial, medical or perceived protective benefits from being the reason that someone joins a clinical trial.
Further Sources

Global Campaign for Microbicides
http://www.global-campaign.org/

Alliance for Microbicide Development
http://www.microbicide.org/
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Global Campaign for Microbicides
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Andrew Branagan
Abbreviations

HIV: Human Immunodeficiency Virus
AIDS: Acquired Immunodeficiency Syndrome
PCP: Pneumocystis carinii pneumonia
STD/STI: Sexually Transmitted Disease/Infection
ARV: Anti-retroviral
MSM: Men who have sex with men
CMV: cytomegalovirus
HPV: Human Papilloma Virus
HSV: Herpes Simplex Virus
FDA: Food and Drug Administration
CDC: Centers for Disease Control and Prevention
HAART: Highly Active Anti-retroviral Therapy
WHO: World Health Organization
VCT: Voluntary Counseling and Testing
PREP: Pre-exposure Prophylaxis
PMTCT: Prevention of Mother to Child Transmission
PEP: Post-exposure Prophylaxis
CAB: Community Advisory Board
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