MUWRP/AVAC: Biomedical HIV Prevention Research Stakeholder Training Resource

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Introduction

AVAC: The Global Advocacy for the HIV prevention and Makerere University Walter Reed Project (MUWRP) have implemented a one year fellowship project funded by AVAC and supported by MUWRP as host. It is through this fellowship that Jauhara Nanyondo developed this media training manual.

This resource is intended to build capacity for media as primary audience to report accurately on biomedical HIV prevention research in Uganda with a view to setting a conducive policy environment.

Biomedical HIV prevention is not only a scientific affair, but it is important to involve and engage other stakeholders at all levels including policy makers, regulators, the media, civil society and the larger community to build support for scientific research.

The development of this resource has involved review of literature, key informants interviews, and training needs assessment.

AVAC is an international, non-profit organization that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and eventual global delivery of AIDS vaccines and other new HIV prevention options as part of a comprehensive response to the pandemic

MUWRP is a non- governmental, not for profit partnership between Makerere University and the Henry M. Jackson Foundation for the Advancement of Military medicine inc.USA (HJF). Its mission is to develop, evaluate and provide interventions to mitigate communicable disease threats of public health importance to Uganda.

Overall goal

To support Ugandan Media to be able to report accurately on HIV prevention research options to community, and to create a base for ongoing media training.

This manual is not meant to be exhaustive but an overview to encourage media interest and build understanding of key issues in HIV prevention research. Therefore the users are encouraged to seek out more detailed information to have a broader understanding of HIV prevention research, beyond specific trials.

Purpose of the resource

The media plays a central role in raising public awareness and setting a conducive policy environment for the conduct of HIV prevention research in Uganda. It is important to enlighten media about their roles and responsibilities so that they have a strong voice before, during, and after the research process.

This resource is aimed at providing basic information on HIV prevention research options to facilitate a standard ongoing training for media practitioners especially with the high health reporter turnover rate. This will ensure that a cadre of skilled and informed journalists is developed and maintained.

The manual is meant for use by individuals and organizations that provide training to media and other stakeholders to help them understand biomedical HIV prevention research in Uganda.

The manual will also act as a guide that provides journalists direction on key issues concerning research and development of biomedical HIV prevention options, in addition to a range of other issues including HIV transmission and progression.

Intended audience

The manual is targeting both print and broad cast media who report on biomedical HIV prevention research related work. However other stakeholders interested in acquiring information on biomedical HIV prevention research options in Uganda can use the same resource. Using this manual, journalists and other stakeholders will be informed about the issues around biomedical HIV prevention research options and become a more informed voice for the community.

How to use the training manual

This manual has two sections; a resource section with five modules that cover issues ranging from HIV transmission and disease progression; research and development process; through to ethical procedures of conducting biomedical HIV prevention research. The other piece of the booklet will contain a facilitator's guide yet to be developed early 2011.

Module 1: HIV Transmission and Disease Progression

In order to understand HIV prevention methods – both current and those undergoing research – it is important to understand how HIV is transmitted and how HIV infection occurs and progresses to AIDS in the human body.

To understand the need for HIV prevention and new HIV prevention methods, it is also important to keep in mind the severity of the HIV/AIDS pandemic. Globally, the pandemic continues its spread at a rate of over 15,000 new infections every day. In developing and transitional countries, 9.5 million people are in immediate need of life-saving AIDS drugs; of these, only 4 million (42%) are receiving the drugs.

Current global statistics and Uganda-specific information can be accessed on the following websites;

http://www.unaids.org/en/knowledge centre/hivdata/ epiupdate/epiupdarchive/2009/default.asp
http://www.aidsuganda.org

Module 1 contains

Session 1: HIV Transmission
Session 2: HIV/AIDS Disease Progression
Session 3: Status of the HIV Pandemic

Session 1: HIV Transmission

This session contains key information on HIV transmission and provides references for further reading.

----- Core Information ----

Introduction

The core information section discusses

- What HIV is.
- Structure of the HIV virus
- Definition of key terms
- The various ways HIV can be transmitted from one person to another.
- How HIV enters human cells to cause infection.
- What might put an individual at risk of HIV infection

Key Concepts

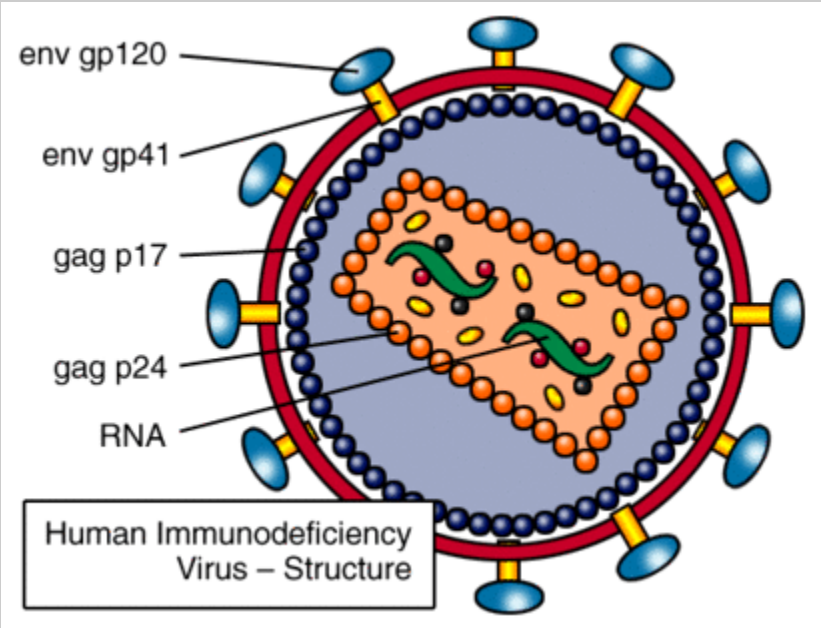
What is HIV?

HIV stands for Human Immunodeficiency Virus, the virus that causes AIDS.
AIDS stands for Acquired Immune Deficiency Syndrome, which is discussed further in Session 2.

HIV is a virus, which is one type of pathogen. A pathogen is a foreign harmful organism that can cause disease in the human body. The most common pathogens are viruses, bacteria, and parasites (worms).

HIV transmission and infection are further discussed in this module.

Structure of the HIV virus



Definition of terms

env gp 120 and env gp 41 These are glycoproteins that are composed of the carbohydrate(s) and protein(s) that make up the structure and defining characteristics of HIV.
Both proteins and glycoproteins act as antigens in human body.

gag p17 and gag p24 These are compounds that make up the structure and defining characteristics of HIV.

RNA is the genetic material contained in HIV

What is HIV transmission?

HIV transmission is where one of the persons involved in the exposure situation is infected with HIV. Blood contains the highest concentration of the virus, followed by semen, then virginal fluids, and then breast milk.

How does HIV infection occur?

It occurs at a point when the HIV virus gains entry into the target cells of the host (human being)
In this process the HIV virus instructs the host cells to make its viral parts, which are later used to propagate the virus in the host body to fuel the infection of other cells in the body.

What are the different ways in which HIV transmission occurs?

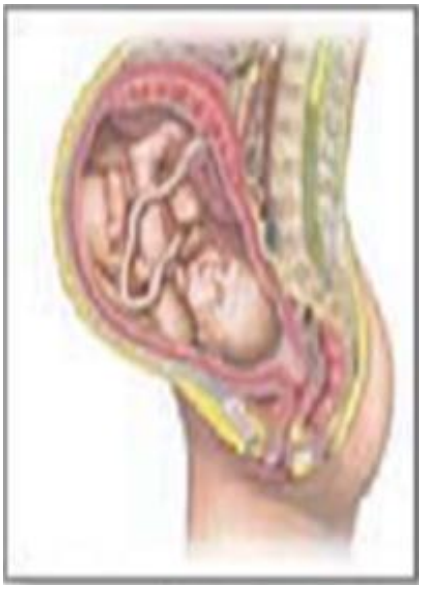
HIV can be transmitted through unprotected sex with an infected person. This is either through vaginal sex or anal sex.

During vaginal sex, HIV is found in sexual fluids of an infected person. HIV can be found in the blood, semen, or vaginal fluid of a person infected with the virus. The lining of the vagina can tear and allow HIV to enter the body. Direct absorption of the HIV through the mucous membrane that line the vagina is also a possibility for transmission.
However during vaginal sex the male is at less risk for HIV transmission than is the female. The virus enters the male body through his urethra (the opening at the tip of the penis) or through small cuts or open sores on the penis making infection with HIV possible.
Much of the world's infections are caused by sexual transmission.

While in anal sex, the risk of infection is greater than that with vaginal intercourse. The lining of the anus is more delicate than the lining of the vagina, so it is more likely to be damaged during intercourse and any contact with blood during sex increases the risk of infection.

Other ways of transmission include the following.

1. Mother to child transmission during Pregnancy



2. Mother to Child transmission during breast feeding

3. Sharing of unsterilized instruments like needles or syringes

4. Unsafe blood transfusion

What factors might put someone at risk of HIV infection?

- Infection with a sexually transmitted disease increases one's susceptibility to HIV infection (genital ulcer diseases like herpes simplex, syphilis, Chlamydial infection, Gonorrhea, Bacterial vaginosis etc).
- Living in HIV Discordant relationship, most couples are unaware of their HIV status.
- Practicing unprotected form sex (heterosexual, anal, and oral sex)
- Injecting drug users who share needles
- Mother to infant infection, this can happen at different stages. These may include; when the mother is still pregnant, at child birth and during breast feeding.

Why are women more at risk of HIV infection?

As seen earlier, sexual intercourse is one of the common ways of HIV transmission. However, the rate of HIV transmission through sexual intercourse is higher in women than in men because of the following factors:

- In the case of vaginal sex, women retain the secretions within the body after sex, whereas men are generally exposed only during the sex act. Semen that is left inside the vagina does not dry up as is with the vaginal secretions coating around the penis. Therefore the amount of time a woman is exposed to HIV is longer that of a man.
- The Vaginal lining is a larger surface so HIV spreads out and comes in contact with lots of cells.
- HIV infects particular target cells and large numbers of these live under the vaginal lining. For men, most of these cells live on the foreskin another reason that circumcision helps to protect men from HIV infection. It is easier for HIV to find cells to infect inside a woman than on a man.
- Having sexually transmitted infections (STI) which cause abrasions, ulcers and sores in the vagina making it susceptible to HIV infection.

- Women whose vaginas are not lubricated during sex, either by their own secretions or by using a lubricant product, because tearing and inflammation only increase the ability for them to contract HIV.
- Additionally, women might have infections within their reproductive system that may not be detected for treatment which might increase a woman's susceptibility to HIV infection.

Social and economic inequities also contribute to women's risk:

- The vast majority of women with HIV were infected during heterosexual sex-many by their husbands or boyfriends.
- Women may influence but do not control the sexual and/or drug-using behavior of their male partners.
- Violence, coercion, and economic dependency in many women's relationships make it difficult to "negotiate" condom use or to leave a partnership that puts them at risk.
- In many societies, women and girls are discouraged from learning about their bodies and about sex in general.
- Often, women are socialized to leave sexual decision-making to men.
- Gender-based social norms often encourage men to seek multiple partners, while women bear the burden of shame and stigma associated with disease.
- Growing economic inequality and eroding social support have driven many women into commercial sex work to support their families.

---- References for Further Information ----

http://www. The body.com/content/treat.html
http://www.aidsuganda.org
http://www.unaids.org/en/knowledge centre/hivdata/epiupdate/epiupdarchive/2009/default.asp
http://www.mnaidsproject.org/learn/basics.htm
http://www.aidshotline.org
http://www.global-compaign.org/womenHIV.htm

Session 2: Disease progression

This session contains key information on HIV progression in the human body and AIDS disease, and provides references for further reading on the topic, and a participatory activity for basic training on the information.

----- Core Information ----

Introduction

The core information section discusses;

- What is HIV infection?
- What is AIDS?
- How does HIV infection progress to AIDS disease?
- The difference between HIV infection and AIDS
- The stages of disease progression in the body

Key Concepts

What is HIV infection?

In disease progression context, HIV infection is a condition caused by the human immunodeficiency virus. The condition gradually destroys the immune system, which makes it hard for the body to fight infections.

What is AIDS?

AIDS stands for Acquired Immune Deficiency Syndrome. Acquired means you can get infected with it.
Immune Deficiency means a weakness in the body's system that fights diseases.
Syndrome means a group of health problems that make up a disease.

How does HIV infection progress to AIDS disease?

After one has acquired the HIV virus into their body cells, then they are capable of transmitting it to another.

More definitions related to HIV/AIDS progression

Window period is the period between a person's infection with HIV and appearance of the detectable HIV antibodies. HIV antibodies take some time to be formed in the body therefore the HIV antibody test will not be positive immediately after a person is infected. Most people develop detectable antibodies within two to six weeks.

Sero-conversion is a stage where the body has formed enough antibodies against HIV and therefore will test HIV antibody test positive but may still look healthy. This stage of infection lasts for a few weeks and is often accompanied by a short flu-like illness. In up to about 20% of people the HIV symptoms are serious enough to consult a doctor, but the diagnosis of HIV infection is frequently missed.

During this stage there is a large amount of HIV in the blood and the immune system begins to respond to the virus by producing HIV antibodies.

This process is known as sero-conversion. If an HIV antibody test is done before sero-conversion is complete then it may not be positive. This is the most infectious period due to the high viral load in the blood.

Asymptomatic sero positive phase is stage where the blood will test positive although the person may look healthy and has no signs and symptoms of the disease. This period can be prolonged by positive living. This is the second stage of HIV disease progression and can last for many years after infection. On average in sub-Saharan Africa it is estimated to be 10years.During this period, the HIV antibodies are detectable in the blood.

Symptomatic sero positive phase is where a person has intermittent bouts of certain illnesses. These illnesses are light and when treated, the person recovers. However, it should be noted that illnesses are not conclusive for a diagnosis of AIDS.

This is the stage where HIV infection progresses into AIDS.

A person suffers several life threatening illnesses; the attacks of illnesses are frequent, severe and complicated and the patient may take long to respond to treatment. At this stage, a clinician is able to diagnose AIDS.

AIDS stage

Over time, infection with HIV can weaken the immune system to the point that the system has difficulty fighting off certain infections. These types of infections are known as *opportunistic infections*. These infections are usually controlled by a healthy immune system, but they can cause problems or even be life-threatening in someone with AIDS. The immune system of a person with AIDS has weakened to the point that medical intervention may be necessary to prevent or treat serious illness.

It is at this stage that Anti-Retroviral therapy is introduced to such a person to boost his or her immunity. Currently WHO recommends that one who's CD4 have lowered to 350 should be started on Anti Retroviral drugs (ARVs).

---- References for Further Information ----

The body, the complete HIV/AIDS resource, http://www.thebody.com/content/treat.html
http://www.avert.org/stages-hiv-aids.htm
www.healthhype.com/stages-of-hivaids-first-to-final-phase-signs-and-symptoms.html
www.sfaf.org/hiv-info/basic
http://www.nlm.nih.gov/medlineplus.htm

Session 3: Status of the HIV Pandemic

This session contains information on the statistics of the HIV/AIDS epidemic, and references to updated statistics.

-----Core information-----

Introduction

The core information highlights

- The statistics of HIV/AIDS globally, nationally

Key Concepts

Globally, the HIV/AIDS pandemic continues its spread at a rate of over 15,000 new infections every day. Sexual transmission of HIV-1 is the dominant mode of this pandemic spread. For the first time since the disease emerged in the early 1980s, about half the 42 million people now living with HIV/AIDS worldwide are women. Worldwide, more than 90 percent of all adolescent and adult HIV infections have resulted from heterosexual intercourse.

- More than 25 million people have died of AIDS since the HIV virus was isolated.
- Africa has over 14 million AIDS orphans.
- At the end of 2009, women accounted for 50% of all adults living with HIV worldwide
- In developing and transitional countries, 9.5 million people are in immediate need of life-saving AIDS drugs; of these, only 4 million (42%) are receiving the drugs.

Table showing the global status of the HIV epidemic

Category	Range
People living with HIV/AIDS in 2009	31.1-35.8 million
Adults living with HIV/AIDS in 2009	29.2-33.7 million
Women living with HIV/AIDS in 2009	14.2-17.2 million
Children living with HIV/AIDS in 2009	1.2-2.9 million
People newly infected with HIV in 2009	2.4-3.0 million
Children newly infected with HIV in 2009	0.24-0.61 million
AIDS deaths in 2009	1.7-2.4 million
Child AIDS deaths in 2009	0.15-0.41 million

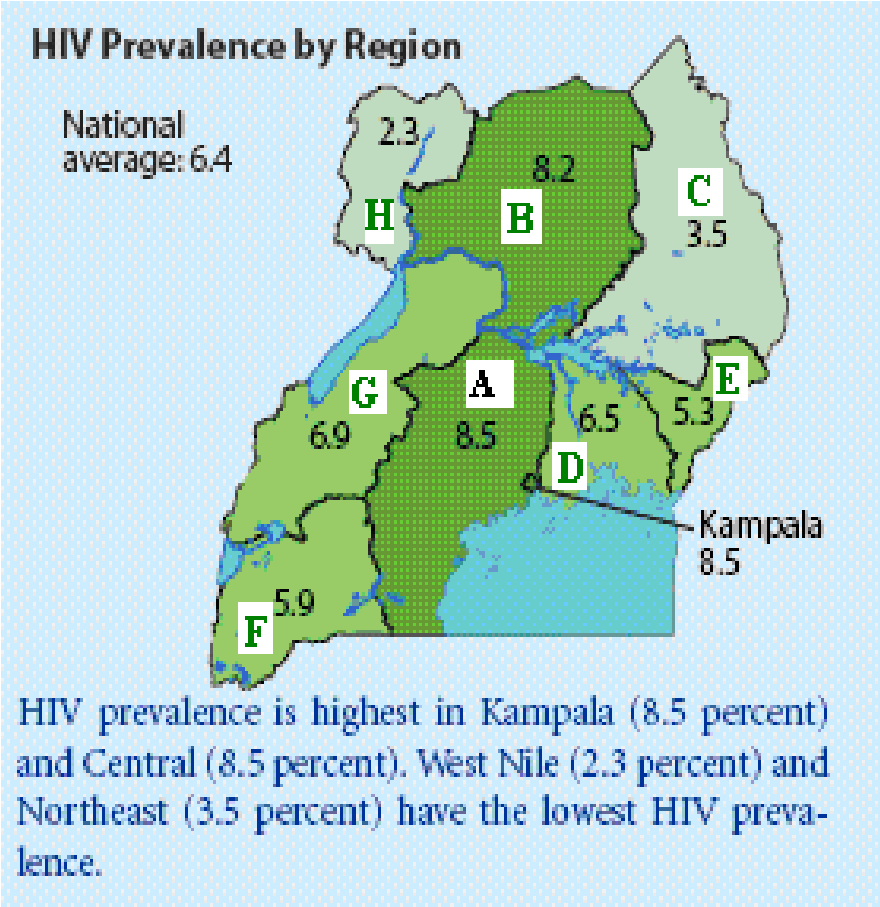
Adapted from UNAIDS report-2009

Sub-Saharan Africa

Sub-Saharan Africa remains the region most heavily affected by HIV. In 2008, sub-Saharan Africa accounted for 67% of HIV infections worldwide, 68% of new HIV infections among adults and 91% of new HIV infections among children. The region also accounted for 72% of the world's AIDS-related deaths in 2008.

The epidemic continues to have an enormous impact on households, communities, businesses, public services and national economies in the region. In 2008, more than 14.1 million children in sub-Saharan Africa were estimated to have lost one or both parents to AIDS.

HIV prevalence by region in Uganda



Key

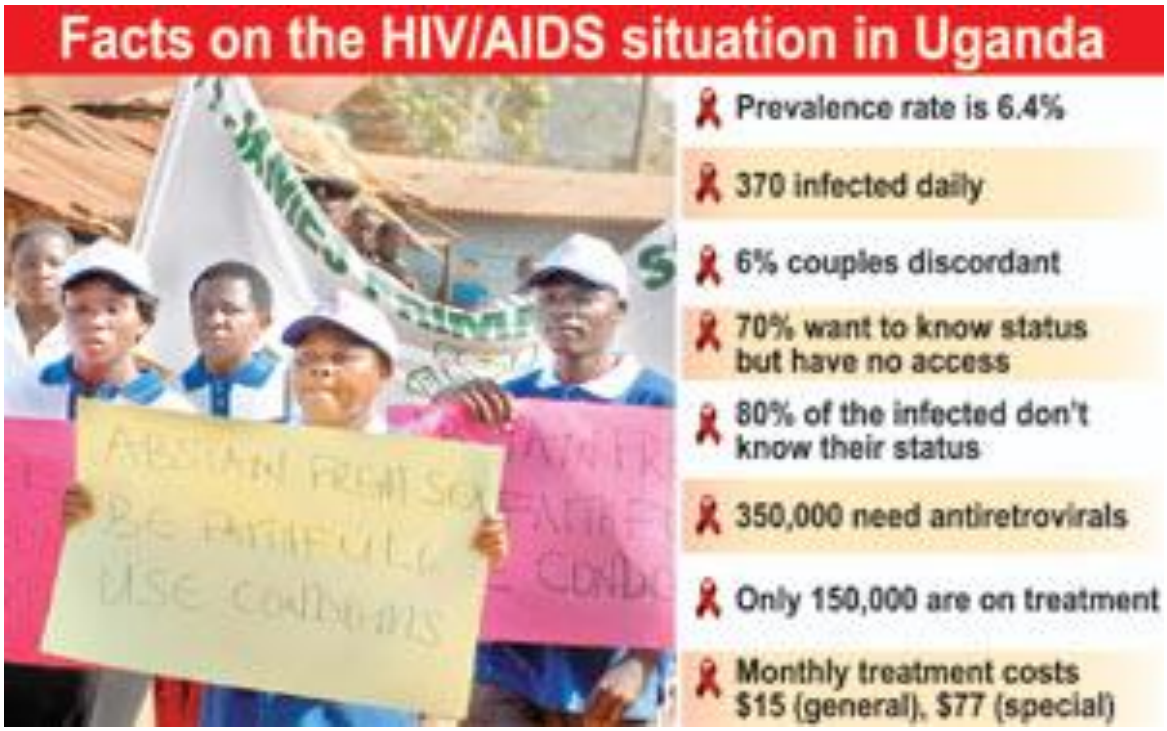
Areas with the highest prevalence (above 8%)

With prevalence between 7%-5%

Areas with lower prevalence

Uganda AIDS Commission report says that;

- Approximately 650,000 individuals in Uganda are living in discordant relationships
- Approximately 85,000 new infections per year
- About 57% of HIV infected individuals have a negative partner
- The Ministry of Health estimates up to 350 infections per year.



KEY MESSAGES TO STAKEHOLDERS

- The status of HIV epidemic is updated annually by WHO
- Women have the highest rates of infection and account for over 50% it therefore important to find efforts of having a prevention strategy that is controlled by women.

-----References for further information-----

For updated statistics visit ;
http://www.aidsuganda.org;
http://www.unaids.org/en/knowledge
UNAIDS (2009, November), 'AIDS epidemic update'

Module 2: Current HIV Prevention Options

This module provides information on the existing prevention options against HIV and later explains why we need new prevention options at this moment.

The module has three session, they include;

Session 1: Available HIV prevention package and the need for new options.
Session 2: Safe male Circumcision as a proven strategy

Session 1: Available HIV Prevention package and the need for new prevention Options

This session contains key information on current HIV prevention options, provides references for further reading on the topic.

----- Core Information ----

Introduction

The core information section discusses

- When can HIV be prevented?
- What are the existing HIV prevention/treatment options
- Factors supporting the need for new prevention research
- The prevention research strategies done in Uganda
- Gender related issues affecting new HIV prevention approaches

Key Concepts

When can HIV infection be prevented?

HIV can be prevented prior to exposure, at the point of exposure and after one has been infected by the virus to slow the progression of the infection as shown in the table below.

Table showing prevention options available

Before Exposure	**During Exposure**	**After Exposure**
Abstinence	Male and female condoms	Anti Retroviral Therapy (ART)
Being faithful to your partner	Sterilized injecting needles	Opportunistic infection(OI) treatment
Education	Prevention of Mother To Child Transmission (PMTCT)	Basic care and nutrition
Voluntary counseling and testing		Education and behavioral change
Treatment of Sexually Transmitted Infections		Post Exposure Prophylaxis (PEP)
Medical Male Circumcision (MMC)		

During Exposure, there a number of options that can help one prevent themselves from catching HIV as shown in the table above. However, let us have a deeper explanation of prevention of mother to child transmission (PMTCT) and post Exposure Prophylaxis (PEP).

What is prevention of mother to child transmission (PMTCT)?

Prevention of Mother-to-child transmission (PMTCT) is an intervention that provides drugs, counseling, and psychological support to help HIV positive mothers safe guard their infants from the virus.

An HIV-infected woman passes the virus to her baby during pregnancy, labor and delivery, or breastfeeding. Without treatment, around 15-30% of babies born to HIV positive women will become infected with HIV during pregnancy and delivery as sighted by UNICEF on www.unicef.org/aids.

An intervention provides drugs, counseling and psychological support to help mothers safeguard their infants against the virus.

Women who have reached the advanced stages of HIV disease require a combination of antiretroviral drugs for their own health. This treatment, which must be taken every day for the rest of a woman's life, is also highly effective at preventing mother-to-child transmission (PMTCT). Women who require treatment will usually be advised to take it, beginning either immediately or after the first trimester. Their newborn babies will usually be given a course of treatment for the first few days or weeks of life, to lower the risk even further.

The simplest of all PMTCT drug regimens was tested in the HIVNET 012 trial, which took place in Uganda between 1997 and 1999.The study was conducted by Makerere University John-Hopkins Collaboration (MUJHU). This study found that a single dose of nevirapine given to the mother at the onset of labour and to the baby after delivery roughly halved the rate of HIV transmission. As it is given only once to the mother and baby, single dose nevirapine is relatively cheap and easy to administer. Since 2000, many thousands of babies in resource-poor countries have benefited from this simple intervention.

Pregnant women who do not yet need treatment for their own HIV infection can take a short course of drugs to help protect their unborn babies.

What is Post Exposure Prophylaxis (PEP)?

An emergency medical response used to protect individuals exposed to HIV. PEP consists of HIV antiretroviral medication, laboratory tests and counseling.

Post-exposure prophylaxis (PEP) is short-term antiretroviral treatment to reduce the likelihood of HIV infection after potential exposure, either occupationally or through sexual intercourse. Within the health sector, PEP should be provided as part of a comprehensive universal precautions package that reduces staff exposure to infectious hazards at work.

This is usually provided to health workers and people who have been sexually assaulted or those that have had isolated or episodic injecting drug use and consensual sexual exposure.

What options are available to treat HIV?

Currently there is no treatment to cure HIV infection, ARVs significantly delay the progression of HIV infection to AIDS and allow people living with HIV to live relatively normal health lives.
The treatment consists of drugs that have to be taken every day for the rest of a person's life.
The aim of antiretroviral treatment is to keep the amount of HIV in the body at a low level. This stops any weakening of the immune system and allows it to recover from any damage that HIV might have caused already.
For more information on ARVs please visit; http://www.avert.org/treatment.htm

Why do we need new prevention research options?

No one option will end the AIDS pandemic. We need existing prevention strategies -- such as behavior change, voluntary counseling and testing, access to clean needles and syringes, STI diagnosis and treatment, broad access to male and female condoms, and anti-retroviral drugs -- and new tools such as microbicides and vaccines. Once developed, these new technologies will meet specific needs.For example microbicides are a strategy that women could use without explicit negotiation with their partners.
There is need for new HIV prevention research so that questions that are still existing related to HIV Prevention are addressed. The following issues still exist and therefore need attention.

- There is increased infection rates and complacency towards HIV
- There are deaths still related to HIV infection
- Treatment challenges (cost, infrastructure, resistant strains, treatment complexities, adherence, etc)
- There is need to protect those that have not yet got infected with the virus (Uganda: 93%)
- Prevention is cheaper than treatment
- Need to protect future generations

For this manual however, discussion will focus on vaccines, Microbicides, and Pre- Exposure Prophylaxis which are discussed in Module three.

What is the role of gender in the development of new HIV prevention options?

Gender is a term used to mean socially constructed nature of males and female identities. Gender refers to the characteristics that society defines as masculine and feminine.
Gender roles are socially and culturally determined attitudes, behaviors and responsibilities for men and women.

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 cooperation, if not outright participation, of a woman's male partner.

HIV risk escalates among adolescent girls because of their physical vulnerability and their susceptibility to rape, forced marriage, trafficking, economic dependence and coercion.

Violence, coercion, and economic dependency render 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.
Many women want to get pregnant for their own 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.

-----References for further reading-----

http://www.unicef.org/aids
http://www.avert.org/hiv-breastfeeding.htm
http://www.aids-sida.com/en/aids-hiv-glossary-2.php
http://www.who.int/hiv/topicsprophylaxis/en/
http://www.avert.org/treatment.htm
AIDS VAX literacy toolkit Core Content
http://www.womenandaids.net

Session 2: Safe Male Circumcision

This session discusses key information on Safe Male Circumcision (SMC) and provides references for further reading on the topic.

-----Core information-----

Introduction

The core information section discusses:

- Definition of SMC
- Benefits of SMC
- SMC 's role in preventing HIV
- Scientific evidence FOR SMC
- Need for SMC as prevention strategy
- Myths and misconceptions around SMC
- Status of SMC in Uganda

Key Concepts

What is safe male circumcision?

Circumcision is the act of removing the fore skin, the free fold of the skin that covers the head of the penis. Circumcision is an old practice that is performed for various purposes such as religious, cultural, hygiene and medical.

Safe Male Circumcision (SMC) is the surgical removal of the fore skin of the penis by a trained health care professional in a health care setting. In this case recommended surgical methods are utilized to achieve safe outcomes.

SMC is offered as a package which includes:

- Health education
- Pre and post SMC counseling
- Routine HIV counseling and testing
- Reproductive health services for men

As discussed below, SMC has been scientifically proven to reduce the risk of HIV infection for men. Additional benefits of SMC include:

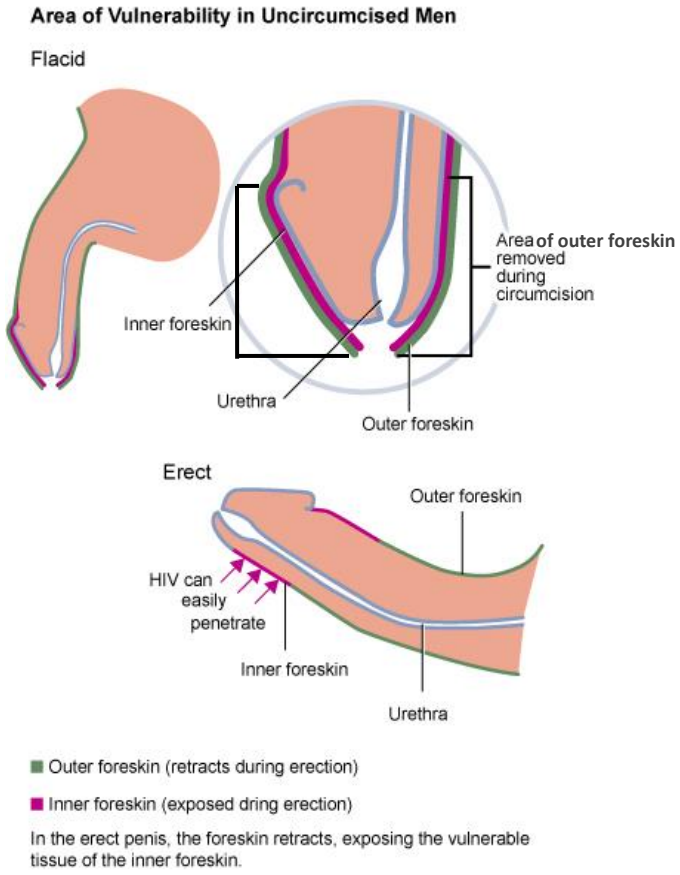
- Improved genital hygiene, a circumcised man penis is much easier to clean as opposed to the uncircumcised penis with a foreskin.
- Reduced risk of genital ulcerative sexually transmitted diseases such as Chancroid and syphilis.
- There is reduced risk of penile cancer
- Reduced risk of phimosis (inability to retract the fore skin)and paraphimosis (swelling of the retracted foreskin resulting in the inability to return the foreskin to its normal position)

- Prevents several medical problems of the penis and foreskin such as inflammation of the glands and that of the foreskin.
- Among children there is reduced risk of urinary tract infections

How does SMC prevent HIV?

During SMC, a significant portion of the man's foreskin is removed. This helps prevent HIV infection because:

- The foreskin is largely made up of types of cells that are known to be easily infected by HIV. These types of cells are sometimes referred to as HIV target cells.
- When the penis becomes erect, the inner surface of the foreskin is exposed. This exposes the tissue that is vulnerable to HIV infection.
- The inner layer of the foreskin is delicate and is easily injured during sex. Injury may make the area even more vulnerable to HIV infection.
- There is increased risk of sexually transmitted infections that cause ulcers among the non-circumcised men. This increases the risk of contracting HIV during sexual intercourse.



How do we know SMC is effective in preventing HIV?

Initial interest in male circumcision as an HIV prevention strategy stemmed from observational studies that showed that countries and regions with high rates of male circumcision had lower rates of HIV infection. This observation was subsequently confirmed by three randomized controlled clinical trials of male circumcision for HIV infection. These trials showed that circumcision reduced men's risk of HIV infection by 60%. These trials were conducted in Uganda (Rakai), Kenya (Kisumu) and South Africa, ending in 2006.

It is important to remember that the trials evaluated SMC procedures conducted by trained professionals in medical settings. In addition, the trials show that SMC is not 100% effective in preventing HIV infection among men. Men who are circumcised can still become infected with HIV. This is the reason SMC should be implemented as part of the comprehensive HIV prevention package for men in addition to the already existing HIV prevention package.

Challenges involved in SMC

- SMC requires professionals to provide care and information before, during and after the surgery as well as specific supplies and an opportunity setting for the surgery. These are additional costs for policy makers and government s to absorb.
- Messages around SMC are complex and must be communicated accurately to ensure the benefit from the procedure is optimized. Key messages include:
    - The need to abstain from sex for six weeks following surgery
    - The partial protection provided by the surgery, the lack of information about SMC as a strategy for reducing transmission risk from HIV positive men to their female partners.

What are the common myths and misconceptions?

There are different myths and misconceptions on male circumcision raging from the intensions of the practice to wound healing process. For effective Safe male circumcision implementation, it is important to recognize and address the different myths and misconceptions that are related to it. They include;

Misconception: For wound healing people believe cow dung, traditional herbs, and vaginal secretions to facilitate wound healing process.
Reality: The wound healing process after circumcision should be guided by information from a health worker, In addition these substances can even cause wound infections that can prolong the normal healing process.
Misconception: After circumcision a man has to have sex with another woman other than his official wife or girl friend to cleanse him or wash away the bad omens
Reality: The above believe is not true and this kind of practice can lead on to causing himself more complications related to wound healing and infection to the fresh wound.
This practice can lead one to also getting infected with the HIV virus since one exposes a fresh wound to sexual secretions.
Misconception: When one gets circumcised, his penis enlarges or shortens, and one becomes infertile or impotent.

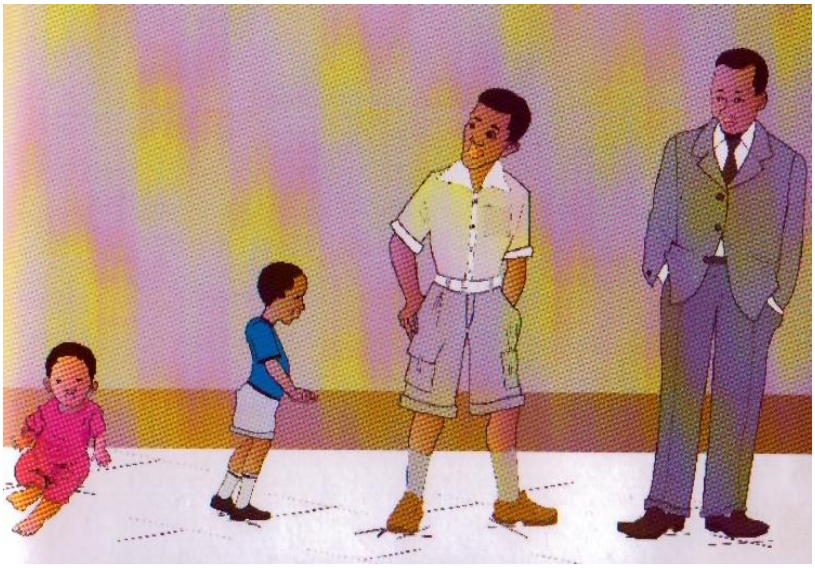
Reality: Circumcision is a scientifically researched on option that does not bring about any of the above stated issues. During the circumcision trials, none of the above was highlighted as a side effect of one's under taking circumcision.
Misconception: Circumcision helps the man perform better during sexual intercourse, delays ejaculation during sex, more pleasurable for women, and increasing the man's libido and makes his promiscuous.
Reality: Sex is an activity that is developed from the mind. Therefore circumcision as a practice has nothing related to sex performance.

Status of SMC in Uganda as of 2010

The World Health Organization has recommended safe male circumcision for countries which have high HIV prevalence and low circumcision rates.
In September 2010, the Uganda Ministry of Health launched the national policy for national implementation of SMC.
The policy stipulates that in Uganda, a standard service of SMC is conducted by a Trained Clinical Officer or above, supported by a nurse or theatre assistant as well as a professional to serve as a counselor.
SMC is carried out under safe conditions at a health center four facility or above, or any health facility accredited by the MOH.
The following steps are involved for the conduct of SMC:

- Client health education and counseling should precede the operation in order to enable client understand all benefits, limitations and to make informed decision.
- A physical examination is done to rule out any contra-indication to surgery
- Give a local anesthesia to kill pain during circumcision. This takes effect on the penis alone and the rest of the body remains alert.
- The health worker will clean the penis, cut off the fore skin, tie off the bleeding vessels and close the wound by stitching the skin edges together.
- A dressing is applied to cover the wound. After this step the client can put on his pants and trousers, ready to go home after a short observation of about 30 minutes.
- Clients are given post SMC counseling regarding wound care, pain medication, sex resumption, danger signs, and contacts in case of a problem.
- Clients are given a date of appointment for review.

The policy encourages that SMC be accessed at any age.



Infants Children Adolescents Adults

Note: World Health Organization has recommended safe male circumcision for countries which have high HIV prevalence and low circumcision rates.

-----References for further information-----

WHO/UNAIDS (2008) manual for male circumcision under local anesthesia.

UNAIDS 2008, safe voluntary, informed male circumcision and comprehensive HIV prevention programming: guidance for decision makers on human rights, ethical and legal considerations.

Health communication partnership resources

AVAC*2007 A new way to protect against HIV, understanding the results of male circumcision studies for HIV prevention

http://www.womenandaids.net/resource-centre

www.malecircumcision.org

http://www.circumcisioninfo.com

http://www.circumcision.com.au

Module 3: Ongoing Research on HIV Prevention Options

This module focuses on communication around the need for new prevention strategies in addition to existing tools. No one option will end the AIDS pandemic. Current tools such as behavior change, voluntary counseling and testing, access to clean needles and syringes, STI diagnosis and treatment, broad access to male and female condoms and male circumcision for HIV prevention are important. But there is also room for new strategies. Some of the interventions being tested presently include microbicides, Pre- Exposure Prophylaxis and vaccines.

The module will discuss three experimental HIV prevention options which are currently under research. These include;

- Microbicides
- Vaccines
- Pre-Exposure Prophylaxis

Session 1: MICROBIDES FOR HIV PREVENTION

This session contains core information on the HIV prevention strategies undergoing research in Uganda and elsewhere in the world and provides references for further reading

-----Core information-----

Introduction

The core information section discusses,

- What a microbicide is
- How Microbicides work
- Need for microbicides in HIV prevention
- How microbicides are delivered
- Types of microbicides
- Global status of microbicides trials
- Ongoing trials in Uganda as of 2010

Key Concepts

What are Microbicides?

The term microbicide refers to a product such as a cream, gel or suppository that could be used vaginally or rectally to reduce the risk of HIV during sex. Currently, there is no proven microbicides for HIV prevention.

How do microbicides work?

The strategy behind all microbicides is to deliver a protective substance to the site of sexual exposure to HIV. Many different types of microbicides have been investigated. So far, one experimental product

called 1% tenofovir gel has shown initial signs of efficacy. This product contains tenofovir, an antiretroviral also used to treat HIV infection. When used in HIV negative people, tenofovir appears to block HIV's ability to establish infection (see also PrEP)

Why Microbicides for HIV prevention?

Today's prevention options like condoms, mutual monogamy, and STI treatment-- are not feasible for millions of people around the world, especially women. Many women do not have the social or economic power necessary to insist on condom use and fidelity or to abandon partnerships that put them at risk. Globally, women account for half of all HIV infections, and in sub-Saharan Africa, women comprise 60 percent of all infected adults. Young women are especially vulnerable. In southern Africa women aged 15 to 24 are at least three times more likely than their male peers to be infected with HIV (Reasons to support this paragraph please refer to Session one of Module one.)

Microbicides would not necessarily require a partner's co-operation, which would put the power of individual protection in the hands of the disadvantaged women.

To date, the majority of microbicides research has focused on vaginal microbicides used for the prevention of HIV in women. Yet, receptive anal intercourse is common among men who have sex with men and there is increasing evidence that heterosexual women in both the developed and developing world practice receptive anal intercourse. So the availability of a microbicide that does not require a partner's involvement, this would put the power of protection into their hands.

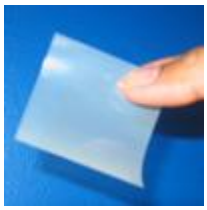
How are microbicides delivered?

The microbicides that have been tested to date have been in the form of gels inserted into the vagina or rectum via plastic applicators. Different dosing strategies have been tested including daily gel use, gel use just before sex and gel use within 12 hours before and after sex. There is ongoing research on other delivery systems including a ring that could be inserted into the vagina and provide continuous protection over longer periods of time.

What are some of the types of microbicides?

- **Vaginal Rings** inserted into the vagina near the cervix, these flexible plastic rings allow gradual release of the active ingredient

- **Films** are small, thin sheets that are inserted into the vaginal near the cervix, where they would release the microbicide as they dissolve.



- **Sponges** are inserted into the vagina, and would release microbicides over time. Currently available as contraceptives

- **Diaphragms/cervical caps** are soft silicone or latex cups, inserted to cover the cervix that would be used with a microbicide

- **Vaginal gels are substances inserted in the vigina to prevent the transmission of HIV.**

Global Status of Microbicide trials

Previous Trials:

Name	Date	Trial Phase	Status
HPTN 035 using PRO 2000		Phase11b	30% effective, results released in 2009
Carraguard	2004-2007	Phase 111	The product was safe and acceptable, but did not reduce the risk of acquiring HIV. Results released in 2008
Savvy (C-31G)	2005-2006	Phase111	Two trials of Savvy closed, one in 2005, another in 2006 No evidence that Savvy protected against HIV
MDP 301,Pro 2000		Phase 111	Results released in Dec.2009, found it safe but not protective.

Ongoing Microbicides trials

Name	Date	Trial phase	Status
Voice (MTN-003)	Started enrolling 2009	Phase 11b	On-going
IPM-009		Phase 111	On-going

-----References for further reading-----

Alliance for Microbicide Development website at http://www.microbicide.org/

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

International Rectal Microbicide Advocacy http://www.rectalmicrobicides.org/

http://www.mtnstopshiv.org/news/studies/mtn003

AVAC: Global Advocacy for HIV prevention website at www.avac.org

Session 3: Pre-Exposure Prophylaxis (PrEP) for HIV Prevention

This session discusses key information on Pre-Exposure Prophylaxis, provides references for further reading on the topic, and a participatory activity for learning will be provided.

-----Core information-----

Introduction

The core information section discusses,

- What is Pre- Exposure Prophylaxis (PrEP)?
- How does Pre Exposure Prophylaxis work to prevent HIV?
- Ongoing Pre-Exposure Prophylaxis studies
- PrEP sites in Uganda

Key Concepts

What is Pre-exposure Prophylaxis (PrEP)?

Pre-Exposure Prophylaxis is an experimental approach that involves the use antiretroviral medications to reduce the risk of HIV infection in HIV-negative people. Antiretrovirals (ARVs) are used to treat people living with HIV.

With this option, two ARVs are currently being evaluated in effectiveness trials. These are: Tenofovir disoproxyl fumarate (TDF) marketed as Viread, and the other as a combination of TDF and Emitricitabine (FTC) marketed as Truvaada.

Scientists have focused on these drugs because they are taken once a day, have relatively low rates of side effects, and there is significant data on their long term safety and resistance profile in HIV positive people.

In November, researchers from the iPrEx trial of once-daily TDF/FTC announced evidence of benefit from a study of nearly 2500 gay men and other men who have sex with men. In that trial, the men who were prescribed TDF/FTC for daily use had approximately 44% lower risk of infection compared to men who received placebo. All participants received a standard prevention package.

Other trials are ongoing to evaluate PrEP in heterosexual and injection drug using populations.

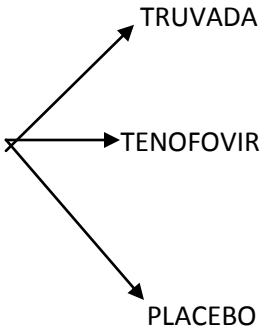
Why Pre-Exposure Prophylaxis for preventive of HIV?

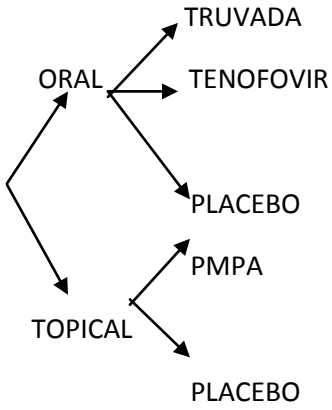
- The scientific basis for testing Pre-Exposure Prophylaxis in humans comes from laboratory studies and other fields of HIV prevention. Studies of Pre-Exposure Prophylaxis strategies in monkeys have shown that dosing with ARVs prior to exposure reduces risk of infection among animals challenged with strains of SHIV (a family of HIV-like viruses that can cause disease in monkeys).
- There are also relevant data from humans. ARVs are given to HIV-negative infants born to HIV-positive pregnant women as part of effective strategies to reduce the risk of vertical transmission. The ARVs taken by the HIV-negative infants may contribute to their reduced risk to infection.
- Additionally, the concept of prophylaxis has worked for other diseases like malaria; scientists believe that it might work for HIV as well. Taking medicine to **prevent** rather than to **treat** a disease or condition, for example; taking pills to prevent malaria when you travel, Using hormonal contraceptives (injections or pills) to prevent pregnancy, Taking pills to avoid pneumonia, if you are at risk.

Ongoing Pre-Exposure Prophylaxis studies

Type of study/ Name	Product under study	Population	Where being conducted	Who's sponsoring and conducting the study	Status
Phase III	Tenofovir	2,000 injecting drug users	Thailand	U.S. Centers for Disease Control and Prevention (CDC)	Fully enrolled; results due 2010
Phase III	Truvada *Switched from tenofovir*	1,200 heterosexual men & women	Botswana	CDC	Enrolling; expects to finish 2011
Phase III (iPrEX Study)	Truvada	3,000 men who have sex with men	Peru, Ecuador, Brazil, United States, South Africa, Thailand	U.S. National Institutes of Health (NIH)	Results released recently,shown 44% efficacy
Phase III (Partners PrEP Study)	Truvada, Tenofovir	3,900 serodiscordant heterosexual couples	Kenya, Uganda	Bill and Melinda Gates Foundation University of Washington	Enrolling; expects to finish 2011
Phase III (FEMPrEP)	Truvada	3,900 high-risk women	Kenya, South Africa, Tanzania, Zambia	USAID Family Health International	Expects start 2009; finish 2012
Phase IIb (VOICE)	Truvada, Tenofovir	4,200 heterosexual women	Uganda, South Africa, Zambia, Zimbabwe	NIH Microbicide Trials Network	Expects start 2009; finish 2012

PrEP sites in Uganda

Location	Sponsor	Population	Design
Kampala (IDI), Kabwohe KCRC Mbale TASO Tororo CDC Jinja (IDI)	UW (Gates)	3900 HIV discordant couples	 **Using them orally**

Location	Sponsor	Population	Design
VOICE STUDY MU-JHU	MTN (NIH)	4200 high risk women	

-----References for further reading-----

Reports on PrEP visit the AVAC website on http://www.avac.org/prep

Session 1: HIV VACCINES

This session discusses key information about provide reference for further reading, and a participatory activity for learning.

-----Core information-----

Introduction

The core information section discusses,

- Definition of Vaccines other key terms for this session
- How do vaccines work to prevent HIV?
- Why do we need vaccines for HIV prevention?
- What are the types of vaccines?
- Myths and misconceptions around vaccines
- Ongoing vaccine studies

Key Concepts

What is a Vaccine?

This is a substance that teaches the body to recognize and defend its self against bacteria and viruses that cause disease.
Scientists developing AIDS vaccines are pursuing candidates that would either reduce the risk of infection or reduce the viral load in those who get the vaccine and later become infected.

All the candidates being studied are experimental; there are no effective HIV/AIDS vaccines available today.

Sample of vaccine above

Why do we need vaccines for HIV prevention?

Vaccines are one of the world's most effective public health tools. Effective vaccines against polio, measles, mumps, and other diseases have significantly reduced rates of these illnesses in many parts of the world.
Today, many scientists, clinical trial teams, and communities are working together on the search for an HIV vaccine. Viral diseases have always been had to treat.

What are the types of HIV Vaccines?

- Scientists are looking to develop various kinds of AIDS vaccines. These include preventive vaccines that aim to block infection in people who are HIV negative;preventive vaccines that would lower viral load and improve clinical health in people who receive the vaccine when HIV negative and go on to become HIV positive; and therapeutic vaccines that could be used as an immune-based therapy in people who are already infected with HIV at the time that they receive the vaccine.

Note: For purposes of this manual, we will focus on Preventive vaccines for HIV.

There various ways to design Preventive vaccine, each of which uses a different approach to produce a response from the immune system.

Note:
The vaccines now being developed and tested in humans cannot cause HIV infection for the following reasons:

- Vaccines being tested in clinical trials do not contain any virus
- The vaccines contain either a protein that resembles the outer coat or the other part of the HIV, or they contain manufactured copies of small segments of the genetic material resembling that of the HIV; which no single gene or protein could cause HIV infection.
- The genes contained in the vaccines are copies of HIV genes, meaning that scientists have produces them in laboratories, so the final genes put into the vaccines have never been part of an actual virus.

Common myths and misconceptions about HIV prevention vaccines

Myth: An AIDS vaccine exists, but it is only available in place where people can afford it.

Reality: Currently no AIDS vaccine exists anywhere in the world. However, scientists are studying possible vaccines and testing several in human clinical trials.

Myth: Western scientists are unfairly using people in developing countries to test AIDS vaccines.

Reality: To make sure that a vaccine will be safe and effective in nations hardest hit by the epidemic, it is necessary to test them there. Volunteer's protection no matter where the trial is conducted is utmost concern. Trial sponsors work to ensure trials are conducted in a locally relevant and ethical way.

These trials follow strict international guidelines to ensure ethical conduct. Trials in developing countries are often led by in-country researchers working in collaboration with researchers and trial sponsors from other countries.

Vaccines need to be tested in countries where they will be used, and trials should be conducted in close partnership with in-country scientists and other groups.

Myth: The experimental AIDS vaccine might cause HIV infection in trial volunteers.

Reality: There is no chance of a candidate AIDS vaccine causing infection in trial volunteers. Many other vaccines, such as the measles vaccine, use weakened (also known as live-attenuated) versions of the virus the vaccine is meant to protect against. However, researchers have not used this approach to develop AIDS vaccines to avoid the possibility that such vaccines could cause infection.

To develop AIDS vaccines, researchers use only copies of pieces of genetic material from HIV. Candidate vaccines developed in this way cannot cause HIV infection but can create immune responses against HIV in humans.

There is no chance that candidate AIDS vaccines cause HIV infection, because they do not contain the virus.

Myth: While participating in the trial, volunteers will be exposed to HIV to see if the vaccine really works.

Reality: No volunteer is ever intentionally exposed to HIV. Exposure to HIV would be highly unethical. Volunteers receive HIV education and risk-reduction counseling to reduce their risk of infection. Behavioral protection is not perfect; however, it is possible that some volunteers will become infected through such means as sexual transmission or injecting drug use. To find out whether the vaccine is effective, researchers monitor a large number of volunteers over a long period of time to see how many become infected through such means. The researchers compare the infection rate in the group of volunteers who received the vaccine to the infection rate in the group who did not receive it to determine if the vaccine has efficacy.

For the vaccine trials done elsewhere in the world, please visit the AVAC website at http://www.avac.org

-----References for further information-----

Understanding Vaccines, US Department of Health and Human services, National Institute of Allergy and Infectious Diseases, January 1998
Vaccine concepts and designs, NIAID Division of HIV Vaccine site
http://www.niaid.nih.gov/daids/vaccine/concepts.htm>
Core content, AIDS Vaccine Literacy tool kit
http://www.iavi.org/vaxlit

Module 4: Biomedical HIV prevention research and development

Any new drug, vaccine, or other intervention must go through a rigorous process of lab, animal, and human testing before it can be licensed and distributed to intended populations. This is the process of research and development. . This module will explain the stages of HIV prevention research and development, with in-depth information about the clinical trials process.

Module 4 contains

Session 1: The research and development process
Session 2: Preclinical research
Session 3: Clinical research

Session 1: The research and development process

This session provides an introduction to the research and development process and references for further reading.

-----Core information-----

Introduction

The core information section contains

- Definition of research
- Definition of basic research
- Definition of applied research
- Pre-clinical research
- Clinical research
- HIV prevention research and development (R&D) process

KEY CONCEPTS

What is research?

Research is an organized process of testing a hypothesis or educated guess based on observation or other data. Through the process of testing a hypothesis, data is produced and collected, and then analyzed and used as evidence to evaluate whether the original hypothesis is true or false.

What is basic research?

The research and development process begins with basic and applied research. Basic research refers to experimental work focused on understanding how and why different processes happen. In the case of HIV, basic research explores topics such as how HIV infection happens,

the life cycle of the virus, and how the virus affects the immune system. Basic research isn't aimed at developing a product, but its discoveries can lead to future directions for HIV research.

What is applied research?

Applied research refers to original investigation undertaken in order to acquire new knowledge and is directed towards a specific practical aim or objective.

What is preclinical research?

Preclinical research is a broad term referring to any studies conducted before an investigational product is tested in humans. The preclinical stage involves development of the concept, basic and applied research in a laboratory, and animal testing.

The main goal of preclinical research is to determine a product's ultimate safety profile so that it can be tested in humans.
(See Session 2 for further information).

What is clinical research?

Clinical research refers to any trials conducted in humans. Generally this is a process of moving from small-scale to large-scale trials to prove an intervention is safe and effective. This stage is sometimes referred to as the development stage of a new product. Session 3 contains full details on the conduct of HIV prevention clinical research.

How does the HIV prevention research and development process work?

Once a product is found to be promising, it is moved to the animal testing stage which starts in small animals such as mice, and eventually moves to larger animals such as non-human primates that more closely resemble humans.

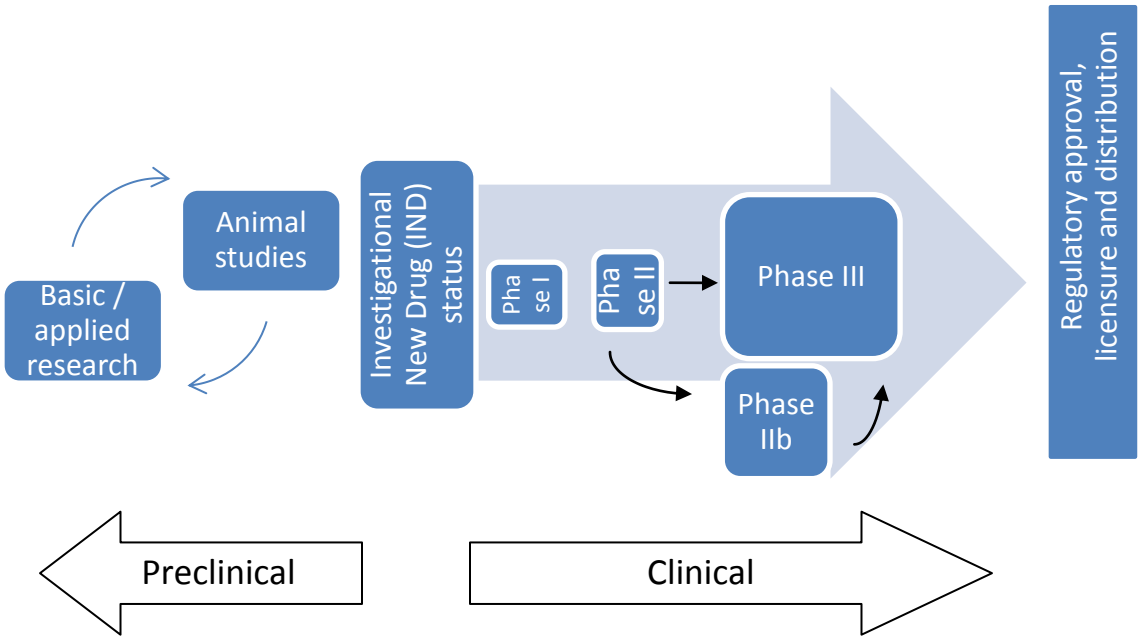
These animal studies provide initial data on safety and can provide preliminary indications of effectiveness. However the animal model cannot tell for certain whether a product will reduce HIV risk in humans. Products move from preclinical to clinical trials when there is extensive animal safety data. At this stage, researchers may seek regulatory permission to test the product in humans. One component of this is an application for Investigational New Drug (IND) status for the product. This status indicates that the product can be tested in humans.

Clinical HIV prevention trials move from Phase I through Phase III to ultimately prove the product's safety and efficacy for general use in the target population. Details of each phase and of clinical trials are further discussed in Session 3.

Once enough data is gathered about the product's safety and efficacy, it gains appropriate regulatory approval and licensure for distribution to the intended population. The types of approval will vary based on where the product will be used.

Phase IV trials are carried out after general distribution of the product. These studies continue to look at the safety and other characteristics of the product as it is being distributed among an uncontrolled population outside of a clinical trial setting.

The diagram below outlines the stages of research and development.



As indicated in the diagram, the R&D process is generally cyclical. Rarely does one experimental product go straight through the entire process from beginning to end. Typically developing a new product involves a great deal of back and forth between various stages of both preclinical and clinical research, depending on results at any given point.

-----References for further information-----

National Institutes of Health general information on research and development .Available at www.clinicaltrials.gov/rd/info/resources

National Science Foundation. SRS Definitions of Research and Development: An Annotated Compilation of Official Sources. Accessed 20 November 2010. http://www.nsf.gov/statistics/randdef/fedgov.cfm

www.arc.gov.au/general/glossary.htm

www.avac.org

Session 3: Clinical Research

This session will discuss key information on clinical research and provide references for further reading on the topic.

-----Core information-----

INTRODUCTION

The core information contains,

- The definition of clinical trials and other related terms
- The phases of clinical trials
- Concepts related to clinical research conduct
- Licensure and introduction of the product
- Conducting further studies after roll out of the product

Key Concepts

What is Clinical trials/ Research?

This is a study done in humans to answer specific questions about a new product undergoing testing. This process helps scientists to evaluate the safety, and effectiveness of the product. Research plays a more active role in improving health care, by leading to new research treatments.

What is the meaning of the following in terms of clinical trials?

Safety: It is used in clinical trials to mean that researchers are testing to make sure that the prevention option undergoing research does not cause side effects in a significant number of people to a severe degree in any person. Clinical trials have an important role in examining safety.

Tolerability: It is used to indicate how well a particular investigational product is tolerated when taken by people for the provided dosage. Good tolerability means that drug side effects do not cause people to stop using the product.

Efficacy: The ability of an investigational product to protect against infection or disease. For example in an HIV microbicide trial, the microbicide should protect HIV infection or disease progression to AIDS in volunteers who received the microbicide in contrast to those who received the inactive product (placebo).

Note:
Clinical research is also referred to as clinical trials and these words will be used interchangeably.

What are the phases of clinical trials?

Phase 1: The primary objective of a phase1 is to test for safety and tolerability of the experimental product. This is the first time the experimental product is being tested in humans. These trials involve

small numbers of volunteers usually not more than 100 individuals who are at low risk of becoming infected.
Phase 1 trial generally last 12-18 months. Once the experimental product has shown to be safe and tolerable, it moves into phase 2 for testing.

Phase 2*:* Primarily this phase evaluates safety and tolerability of the product in the body.

In vaccine trials, immunogenicity (*the products ability to stimulate an immune response*) is also evaluated at this stage. The trial involves hundreds of volunteers and lasts up to 2 years.

They also look at other parameters like dosing, short term side effects and risks associated with the candidate. If the experimental product is shown to be immunogenic, and is still safe and tolerable, it may move into phase 3 testing.

Phase 2B*:* This phase is also known as the proof of concept efficacy trial. Phase 11B trials give preliminary information about the product's potential to prevent HIV infection and /or lower HIV levels in those who may become infected. Highly efficacious products are recommended for the next stage.

This stage involves hundreds of HIV negative participants at high risk of infection.

Phase 3*:* At this phase, scientists are testing for safety, tolerability and efficacy (the product's ability to prevent infection, transmission or disease progression).This is a large trial-generally involving thousand or tens of thousands of trial volunteers from the general community. This phase takes 3 to 5 years. If the experimental product is shown to have efficacy, it's licensed, manufactured, purchased and distributed for general use. Access plans should be formulated as part of the research and development process.

However, the product is continued to be evaluated for effectiveness and if there any other new side effects recorded, then they are added on the safety profile list of the product.

Phase 4*:* At this stage, if the product proves to be safe and protective, then it is introduced for general use.

Groups of people who were not included in earlier trials such as babies, elderly and people with health complications may be included in this phase to ensure that the product is adequate in these groups.

During this period other studies are conducted among product users to acquire more information on the effectiveness and safety outside trials. This helps to identify other side effects that were not recorded in the other phases.

This phase also helps to continue monitoring the candidate's risks, benefits and its optimal use.

Effectiveness in this context means how well the product that has got to this stage is able to reduce disease when it is used in the overall population.

Summary of phases of clinical trials

Phase	No. of Volunteers	Length	Objective
1	Not more than 100	12-18 months	Safety for
11	Hundreds (100-500)	2 years	Vaccines: Immunogenicity Microbicides: PrEP: Safety and tolerability
11B	Smaller than those in phase three	2- 3 years	Safety, tolerability, and efficacy (Proof of efficacy concept phase)
111	Thousands (2000-10000)	3-4 years	Safety, tolerability, and efficacy
1V	General population	On going	Safety and effectiveness

Additional key concepts involved in clinical trials

- **Site selection** refers to the process of identifying and evaluating sites for a planned biomedical HIV prevention trial to conduct a trial. At this stage the sponsors assess the epidemiology, infrastructure, human resource capacity and site capacity for and experience with community engagement.
- **Site development** is a preparatory phase for clinical trials which may include training laboratory technicians, validating standard operating procedures, and expanding infrastructure to meet the needs of the proposed HIV prevention trial. At this stage, strengthening and deepening the relationship between the research team and the surrounding community is paramount before the start of the study protocol. Activities at this stage may include; formative research, community engagement plan, communications plan, and the establishment of the community Advisory mechanisms.
- **Protocol** is a study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. It describes the type of people required to participate in the trial, the schedule of tests, procedures, medications, dosages, and the length of the study.
- **Protocol initiation** is a stage where recruitment activities of the study begin. The activities include launching of the pre-screening, screening, and enrolment all of which continue as the protocol suggests. At this stage, the research team has developed materials to be used for recruitment depending on the varying target audience. Outreach strategies should be in place to reach out to potential study participants. Site staff is dedicated to mobilize and educate community about research in their community. This is geared to helping community members make an informed decision to joining the research.

What are some concepts common to the conduct of clinical trials?

- **Informed consent** is the process of providing research information to potential participants to facilitate informed consent decision.

In this process, the study participants learn about the rationale for the study, nature of the experimental product, the kinds of procedure and tests that the volunteers will undergo, risks and the benefits of study participation, so that they can decide whether to or not to participate voluntarily. Potential participants should be given enough time to ask questions related to the information they have received about the study.
Each participant is asked to sign/thumb print as evidence that he or she received the information and agreed to participant in the study. Efforts should be made throughout the trial to ensure that volunteers continue to understand and to participate freely as the trial progresses

- **Placebo** is a harmless, inactive substance that looks like the investigational product. When the placebo is used in a group of volunteers, it is only through the evaluation of these groups that the researchers can evaluate the safety and efficacy of the investigational product.
- **Blinding** is a situation where the participants do not know whether they have received the investigational product or the placebo. Sometimes it is called "masking" This is done in way to avoid bias.
- **Randomization** Participants in a trial are assigned to the investigational product and control groups by chance or by random selection, sometimes using a computer.
  Neither the researcher nor the participant can decide which study group each participant will go into.
- **Study closure** the trials run until their scheduled completion dates, may be prolonged or may be stopped early. There varying reasons for the later to happen. For example if there is evidence of harm or futility. Researchers are encouraged to be prepared for any such eventualities in trial conduct.
- **Data analysis and validation**, at this stage it is important for the research team to clearly understand their involvement in data analysis and validation. Once results have been analyzed and interpreted then researchers are obliged to disseminate to the different stakeholders including the participants of the study. They should be given an opportunity to ask questions about the results. It is ethical for researchers to give some indication of when the researchers expect to announce their trial results. Participant should have provided correct contact information so that one can be reached when results are available. Results should be explained in the language most understood by participants.
- **Results dissemination** should be done to trial participants, surrounding communities, medical professionals, policy makers, etc as an obligation. These groups should have published results of the study.

-----References for further reading-----

A guide to understanding ethical issues related to participation in clinical trials for preventive HIV vaccines, July 2005
Good participatory practice, guidelines for biomedical HIV prevention trials, 2007
AIDS Vaccine literacy toolkit core content 2005, www.iavi.org/vaxlit

Module 5: Ethical issues in Biomedical HIV Prevention Research

Ethical issues are the primary concern in conducting studies in humans. These concerns apply to all clinical research and are given special attention by researchers and other authorities involved in biomedical HIV prevention research.
All clinical research must meet the international ethical standards.

It is important to conduct biomedical HIV prevention research that follow ethical standards. It is important to protect human participants over the interest of the researcher in biomedical research.

The module contains

Session 1: History/ landmarks of research ethics
Session 2: Participation issues
Session 3: Review and regulation of clinical research
Session 4: Stakeholder engagement

Session 1: History and landmarks of research ethics

This session contains key information on land marks and history points for ethics in research, provides references for further reading on the topic.

-----Core information-----

Introduction

The core information section discusses

- Definition of Ethics
- The fundamental principles of research
- Landmarks in ethics and regulations for research involving human participants

Key Concepts

What is the meaning of Ethics?

The term ethics addresses ideas of right and wrong and with moral duty and obligation. Research ethics address "rights" and "wrongs" surrounding research that uses human participants to find answers to scientific questions. The primary focus of ethics guidelines for research in humans is safeguarding the rights, dignity, and health of the trial participant.

Definitions of what constitutes ethical conduct in research have evolved and continue to change. Today, internationally recognized documents set ethical standards for research involving human participants. These guidelines were written in response to occurrences where humans had their rights violated in experiments. One notorious example is from World War II -- when the Nazi regime experimented on people held in concentration camps. Because of such incidents, a number of guidelines and laws have been put into the place both on international and local levels worldwide to set standards for how research must be conducted when it involves human beings. Some of the guidelines include; The Code

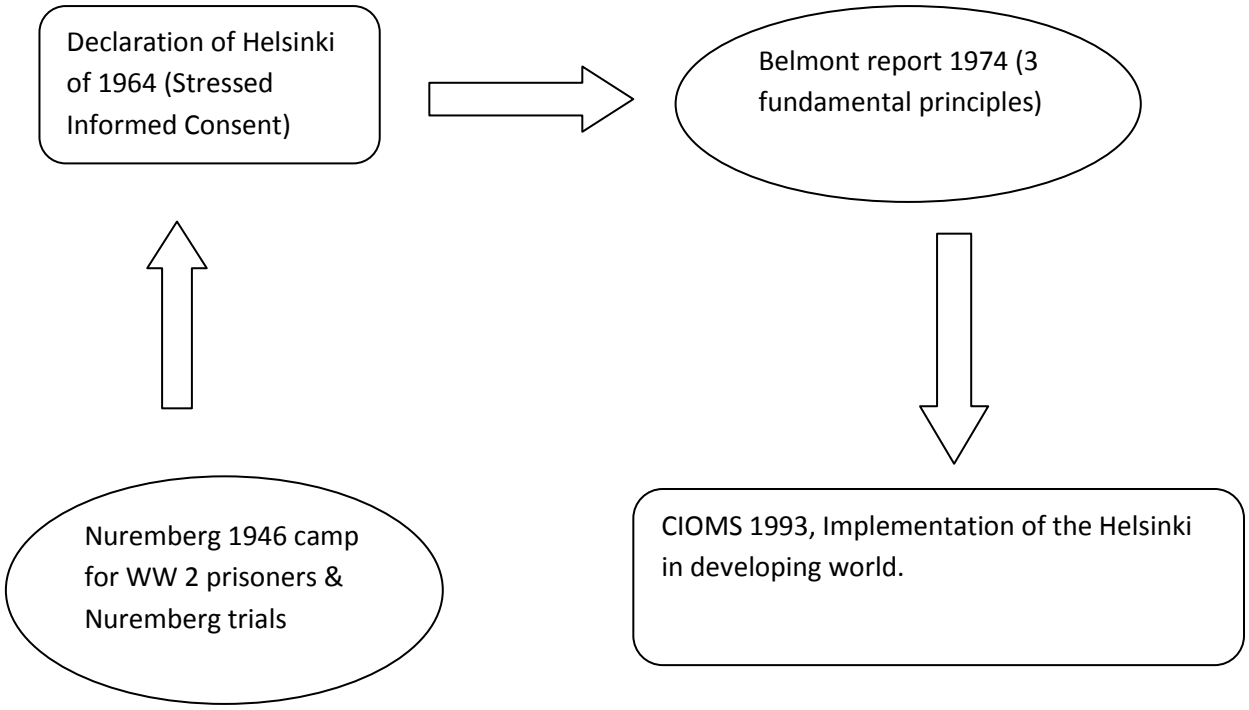
of Federal Regulations (CFR), Nuremberg Code, Declaration of Helsinki, and the Belmont Report, which will be discussed in detail in this module.

The three fundamental ethical principles for using human subjects for research

- Respect for persons: protecting the autonomy of all people and treating them with courtesy and respect and allowing for informed consent; it also provides for extra protection to those with limited autonomy. Participants should be empowered to make free decisions. During the informed consent process, the aspect of voluntarism is emphasized.
- Beneficence: maximizing benefits for the research project while minimizing risks to the research subjects; and
- Justice: ensuring reasonable, non-exploitative and well-considered procedures are administered fairly (the fair distribution of costs and benefits to *potential* research participants.) Justice forbids exposing one group of the people to the risks of research solely for the benefit of another group.

These principles are universal and apply everywhere in the world. These principles should guide the thinking of all individuals involved in planning, conducting, and sponsoring research that involves human participants.

Landmarks in ethics and regulations for research involving human participants



-----References for further reading-----

National guidelines for research involving humans as research participants (Uganda National Council for Science and Technology) March 2007
Council for International Organization of medical Sciences(CIOMS) http://www.cioms.ch
NIH bioethics resources http://www.nih.gov/sigs/bioethics
Research Ethics training curriculum for community representatives, 2004 by Family Health International http://www.fhi.org
British Medical Journal, No 7070 Volume 313, 7 December 1996
http://www.cirp.org/library/ethics/helsinki/
http//www.citiprogram,org/members/learnersII/moduletext,asp

Session 2: Issues related to trial participation

This session discusses key information on volunteer's participation in biomedical HIV prevention research, resources for further reading on the topic and a participatory activity for training on the activity.

-----Core information -----

Introduction

The core information section discusses

- Approaches used to put guidelines and laws into practice
  - Informed consent
  - Study design
  - Ethics committees
- Guidelines and laws followed in research
- Main components of the informed consent process
- Protection of study participants
- Benefits and risks of participating in research

Research Ethics in Action

Various approaches are used to put guidelines and laws into practice. For example:

Informed consent

Informed consent is a process by which a person is provided with enough information about a study to decide whether he or she would like to participate. In this process, trial-site staff educates the prospective participant about the study, including the potential risks or harms, the potential benefits, study procedures, and what is expected of participants. The informed consent process then involves a written document called the informed consent form -- which includes all of this information and more. An individual interested in volunteering for a study provides consent, and this is then documented on the informed consent form. Informed consent should be an ongoing process in which participants may decide to drop out of the trial at any point, even after providing consent to enroll in the study.

Study Design

1. *Risk-benefit ratio*

Researchers are expected to design studies that minimize risks to potential participants and implement every reasonable safeguard to protect participants from harms. Ethics review committees and other regulatory bodies review protocols to determine whether a trial should take place. If its risks seem too great in comparison to the benefits a participant might receive, then the study might not be approved, or it might be considered again once it has been redesigned by the investigators.

2. *Selection of participants and location*

For later-stage trials, participants in studies should be from populations who would benefit from the research findings. Such trials should therefore be conducted in locations where the illness exists and with participants who face or may face the particular health problem.

3. *Full disclosure about alternative ways to treat the illness (for treatment studies) or offering a full package of ways to prevent the illness (for prevention studies)*

When people consider joining a trial, they must be informed about other ways to treat their health problem (or prevent it) so they can decide whether to seek treatment that is already established or to agree to participate in a trial to test an experimental strategy. In the case of biomedical HIV prevention trials, ethical guidelines stipulate that participants be provided with information about how to reduce their risk of getting HIV and be offered other known prevention strategies like condoms, testing for and treatment of STIs, and clean needles. As new treatments or methods of prevention become available, participants should be informed about them.

Ethics Committees

Ethics Committees (ECs) and Institutional Review Boards (IRBs) are committees that sit within different institutions that conduct research, such as hospitals, universities, and government agencies. The role of these committees is to review research protocols and determine if they are ethically and scientifically sound. These committees include people who have expertise in scientific areas and also usually at least one person who is not a scientist but who has experience and expertise in other areas. Ethics committees are also expected to be diverse, with not all members representing one sex, age group, or cultural background.

These committees review protocols and make decisions about whether a research study can be conducted by their institution. Specifically, they might approve the research, require changes to the research, or deny approval of the research. Most research protocols must receive approval from several ECs or IRBs in order to proceed. This is particularly true with large international studies, where research is conducted at multiple sites and countries. In studies such as these, the protocol will have to be approved by the Ethics Committees at the sponsor organization, at the network conducting the study, at the institution receiving funds to conduct the research, at the sites where the research will take place, and by the governments of the countries where the research will take place.

What guidelines and laws have to be followed?

All research is funded by a sponsor -- such as a government, a research organization, or a pharmaceutical company -- and the sponsor of the research determines which regulations or guidelines must be followed, as does the country where the research is being conducted. For example, with research that is sponsored by the US government but conducted in another country, researchers must follow the laws and guidelines specified by both countries. Non-government sponsors of research must also follow the laws of the countries where the research is conducted, but they may specify additional ethical research guidelines to be followed.

Do these guidelines prevent all controversies and ethical breaches?

No. Challenges can still arise despite the many laws, guidelines, policies, and practical applications that have been put into place to help ensure that research conducted on human participants is done ethically. What is considered "ethical" changes over time, and different stakeholders may have varying views about what is "ethical" and what is not. There have been many controversies around clinical research over the years, where stakeholders disagreed about whether a trial was being conducted ethically, even causing trials to be shut down. It is the responsibility of funders to provide enough money to allow researchers to conduct the research ethically, of researchers to follow ethical guidelines and norms, and of community members who want to engage in the process to learn about research so that they can make constructive criticism to the process.

What are the main components of the informed consent process?

Information

A potential volunteer should be provided all relevant information about the research, the experimental product being tested. One must be provided with all study information in order for facilitate making of an informed decision.

Comprehension

Potential volunteers are asked if they understood all the information presented to them. Informed consent requires more than just getting information. It requires one to understand what is being asked of him /her, what risks she/ he might be taking, what benefits, if any, there might be. Potential participants are usually given time to ask questions and a test of understanding is provided to them to facilitate their comprehension of study information.

Freedom/autonomy

It must be established if potential volunteers have the freedom to decide if they want to participate in the study or not. Some people do not have the legal freedom to make such a decision, for example minors. Still others may not have the social freedom to make such decisions, for example some cultures require permission from a family or community leader before making such decisions. It is important to establish on the onset of the trial if a participant decide to participate on their own or someone else made the decision for him/her.

Note: UNAIDS provides for specific recommendations about working with populations that may have limited freedom or capacity to provide informed consent.
Please visit (Insert a link to this effort)

What should be in place to protect and keep the confidentiality and privacy of study participants?

Confidentiality is "respecting a potential or current participant's right to be free from unauthorized release of information that the individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure".

Privacy is respecting an individual's right to be free from unauthorized or unreasonable intrusion (*interference*), including control over the extent (*how much or how far*), timing (*when*) and circumstances (*how*) of obtaining personal information from or about them.

In the context of a research protocol, "confidentiality" refers to the understanding between the participant and investigator (e.g., as set forth in the consent and authorization documents) as to how participant information will be handled, managed, and disseminated (e.g., shared with others) as part of the research

Private Information means individually identifiable information:

- About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place
- Which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Sensitive Information is a subset of "private information" and means private information relating to:

- Sexual attitudes, preferences or practices
- Use or treatment for alcohol, drugs or other addictive products
- Illegal conduct
- Information which if released could reasonably cause stigmatization or discrimination, or result in damage to areas such as financial well-being, employability, or reputation.
- Certain health information, including psychological or mental health.

Personal Information about a participant is collected as part of the research process. It is important for the researchers to keep personal volunteer information confidential. Researchers should explain to participants if there any limitations to confidentiality. Keeping the confidentiality of study participants is done through the following;

- Using codes and not names on participant charts, samples and results
- Storage of participant charts under double lock in a locked cabinet located in a locked room
- Access to participant information granted to authorized persons only
- Publications do not include identifiers

What are benefits and risks involved while participating in research?

Benefits vary depending on a given trial; however the following cut across;

- Mainly contributing to medical information that may be beneficial in the improvement general health care to mankind
- Increased uptake of HIV counseling and testing as a result of increased community health information.
- Medical evaluation during the trial with referral for care and treatment

The risks of participating in clinical trials include;

- Social risks such as stigma or discrimination that may be associated with participating in a trial if the participant chooses to disclose his or her participation.
- Medical risks like side effects after participation such as pain of injection, and during circumcision process.
- In HIV clinical trials, false positive because of the antibodies stimulate by the vaccine.

What efforts have been put in place to protect participants while in the study?

A **Data Monitoring Committee** (DMC) — sometimes called a **Data and Safety Monitoring Board** (DSMB)- is an independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing.

Need for a DMC

Many randomized clinical trials are double blind, i.e. no one involved with the trial knows what treatment was given to the trial participant. This includes the participant, their doctor, and even the study personnel at the company that is sponsoring the trial. There are many extremely good reasons to conduct a trial in this manner and only after the trial database is finalized is the blind broken and the true treatment assignments disclosed.

The DMC is a group (typically 3 to 7 members) who are independent of the company sponsoring the trial. At least one DMC member will be a statistician. Clinicians knowledgeable about the disease indication should be represented, as well as clinicians knowledgeable in the fields of any major suspected safety effects (e.g. nephrology, cardiology). A few long, visible trials may include an ethicist or even a representative from a patient advocacy group. The DMC will convene at predetermined intervals (three to six months typically) and review unblinded results, i.e. results split by experimental and control arms. The DMC has the power to recommend termination of the study based on the evaluation of these results. There are typically three reasons a DMC might recommend termination of the study: safety concerns, outstanding benefit, and futility.

Safety concerns
The primary mandate of the DMC is to protect patient safety. If adverse events of a particularly serious type are more common in the experimental arm compared to the control arm, then the DMC would have to strongly consider termination of the study. This evaluation has to be made in consideration of risk/benefit. In many cases, the experimental arm could cause serious adverse events (chemotherapy, for example), but the resulting improvement in survival outweighs these adverse events.

Overwhelming benefit
In the rare, but fortunate, situation that the experimental arm is shown to be undeniably superior to the control arm the DMC may recommend termination of the trial. This would allow the company sponsoring the trial to get regulatory approval earlier and to allow the superior treatment to get to the patient population earlier. There are cautions here though. The statistical proof needs to be very high indeed. Also, there might be other reasons to continue, such as collecting more long-term safety data.

Futility
Futility is not as widely recognized as safety and benefit, but actually can be the most common reason to stop a trial. As an example, suppose a trial is one-half completed, but the experimental arm and the control arm have nearly identical results. It's likely in no one's interest to have this trial continue. It is extremely unlikely that the trial, should it continue to its normal end, would have the statistical proof needed to convince a regulatory agency to approve the treatment. The company sponsoring the study could save money for other projects by abandoning this trial. Also, current and potential trial participants could be freed to take other treatments, rather than this experimental treatment which is unlikely to benefit them.

-----References for further reading-----

Ethical considerations in HIV Preventive Vaccine Research
http://www.unaids.org/html/pub/publications/IRC-pub02/JC765-Ethicalcons-Repr-en_pdf.htm
Research Ethics Training Curriculum for community Representatives
Robert Rivera, DavidBorasky, Florence Carayon,Robert Rice, Stella Kirkendale, Wayne L. Wilson, and Cynthia Woodsong (2004)
National Institutes of Health,Ethical Frame work for Clinical Research
http://www.bioethics.nih.gov/research/humanres/ethicsframework.pdf>.
http://data.unaids.org/publications/IRC-pub01/jc072-ethicalcons_en.pdf

Session 3: Regulatory and Ethics review of clinical trials

This session discusses key information about the review and regulations when conducting a clinical trial, resources for further reading on the topic and a participatory activity for training on the activity.

-----Core information -----

Introduction

The core information section discusses;

- Regulatory and ethics review process
- Required documents for review at the Institutional level
- Ethical issues considered during protocol review

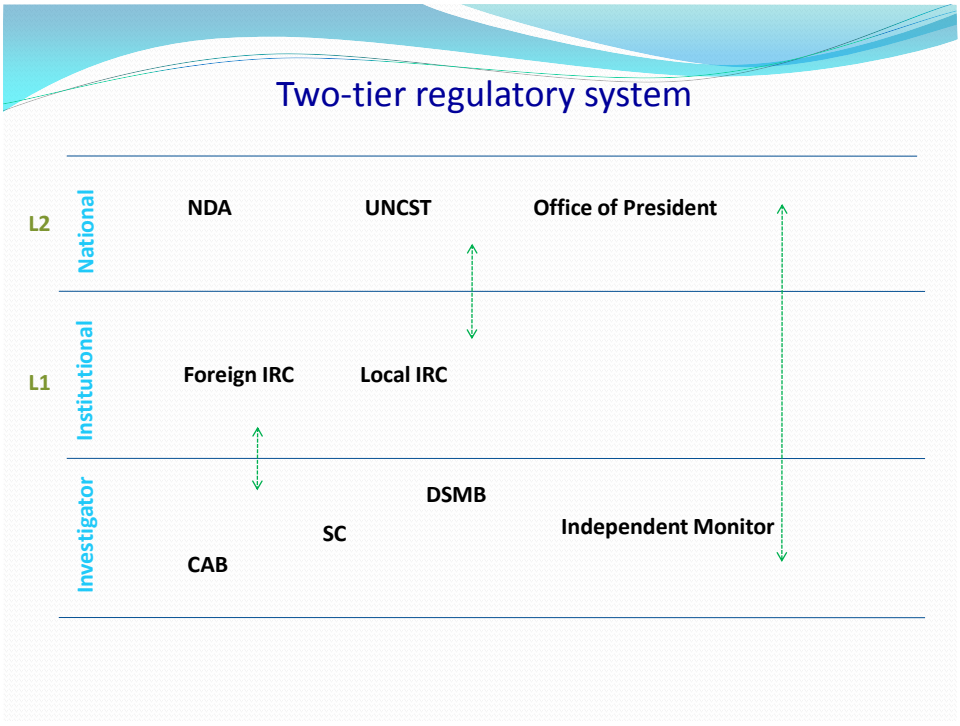
Key Concepts

What is involved during regulatory and ethics review process?

The review process of experimental products and research protocols is conducted by various committees in Uganda. These groups include ethical review committees and regulatory authorities.

The over sight of research in Uganda is presently carried out at two levels, at the institutional level by the Institutional review committees and at the national level by the Uganda National Council for science and Technology. The UNCST liaises with the Research Secretariat in the office of the president, for national security reasons, to clear researchers to undertake their project in Uganda.

The Following Table Shows the Regulatory Review Process in Uganda



At the investigator's Level before regulatory review

The key players include; Community Advisory Boards (CABs), Data Safety Management Boards (DSMBs), Independent monitors and scientific committees. These can have input into the protocol before submission at level 1 (Institutional level) and consequently Level 2 (national level)..

CABs are established by study investigators to facilitate dialogue between community members, study volunteers & researchers. Primary role is to assist investigators understand and incorporate community concerns into their research

Scientific committees (SCs) approve research prior to submission to an IRC; with primary aim of evaluating all scientific aspects of research projects (Suitability, relevance and feasibility of study).

DSMBs are Independent group of experts established by study sponsor to review safety data during a trial. All Clinical Trials, and some community interventional trials, require Data Safety Monitoring Boards Should have at least 3 persons (one of whom should be a clinician and one other a biostatician)

Institutional level

We have the Institutional Review Committees (IRCs) that are local and international.

IRCs are established by institutions whose mandate includes carrying out research.
The Primary function of an IRC is to conduct initial and continuing review and approval of research projects, with an aim of protecting the rights and welfare of human research participants.
IRCs monitor research activities to ensure compliance with scientific and ethical requirements in accordance to national guidelines.
All IRCs operating in Uganda must be accredited by the UNCST. For collaborative studies, approval from a foreign IRC is also required prior to submission to UNCST.

National level

We have Uganda National Council for Science and Technology (UNCST), National Drug Authority (NDA) and Research Secretariat Office of the President

UNCST is a semi-autonomous government agency established in 1990 (CAP 209 of the laws of Uganda.It is mandated to;

- Develop and implement strategies for integrating science & technology into national development process;
- Provide advice to government on policy matters necessary for advancing S & T and Oversee.

Coordinate research and development activities in Uganda, including the following .

- UNCST liaises with Research Secretariat Office of the President to clear researchers to undertake projects in Uganda

NDA regulates the safety, quality, efficacy, handling and use of drugs /drug related products in research. Part IV, section 40 0f the NDA Act (Chapter 206)
With regards to clinical trials, applicant must obtain the National Drug Authority to import and / or use the trial drug/device in Uganda.

Before any trial is started with humans, Institutional Review Committees must review the specific documents and approve the trial. This is all to ensure safety, human rights protection, and the well being of volunteers involved.
What are the documents reviewed at the Institutional level in Uganda?

The following documents must be submitted to an Institutional Review Committee for review and approval of the protocol to be implemented in Uganda.

1. A clear statement of the objectives of the study, provide the current state of knowledge and justification for undertaking the study.
2. A precise description of all proposed procedures and interventions, including the duration of the study.
3. The inclusion and exclusion criteria for the volunteers and the procedures for the withdrawal of individual participation.
4. Description of study population and the number of participants required for the study.
5. The specific procedures to be done at each visit, i.e. the amount of blood at each visit, what samples to be obtained from the participants? What tests to be done on the samples obtained?
6. The statistical analysis plan.
7. Complete details of informed consent process, including the proposed means of obtaining informed consent.
8. Evidence that the investigator is appropriately qualified and experienced and has facilities to enable the study done safely and efficiently.
9. Provisions in place to keep the confidentiality of the participant's information.
10. Study instrument to be used.

What are the ethical issues considered during protocol review?
While reviewing the protocol, Institutional review committees should make sure that the following ethical issues are addressed;

1. The research being carried out should have scientific validity i.e. in terms of methods used, designed using scientific principles, methods and reliable practices; and has clear scientific objectives.
2. The study should have science and social value. It should be able to demonstrate value in terms of new information to be added to the scientific community and there should be foreseeable benefits to the individuals and community where the research is being carried out.
3. The research should have a favorable risk/benefit ratio to the individual participant and to society in terms of knowledge that will be obtained from the study.
4. There has been community involvement in the research process right from the inception to the post research period. Community involvement includes participation and implementation of the research project and dissemination of research findings.
5. There is fair selection of research participants based on the scientific question to be answered but not to by the convenience of getting the participants. In case of exclusion of a specific category of individuals, justification should be provided.
6. The informed consent process should be able to provide accurate information regarding the purpose, methods, risks, benefits, and alternatives to research for them to make an informed decision into the study.

-----References for further reading-----

Ethical Principles and guidelines for the protection of human subjects of research<http;//www.fda.gov/oc/orht/irbs/Belmont.htm>
Uganda national guidelines for research involving Humans as research participants, March 2007