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AIDS
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A synopsis of the eleven presentations

International AIDS
Vaccine Initiative

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Presentation One:

Vaccines and the Global Response to HIV and AIDS

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The global response to HIV and AIDS

"Treatment will slow, but not eliminate the carnage...If we're five to ten years away from microbicides or vaccines, there's a desperate human toll to be faced between now and then. At least let the world rally to the prospect of bringing this cataclysm to an end sooner than later. And that means working on every front…care, prevention, treatment, microbicides, vaccines."

- Stephen Lewis, former UN Secretary General's Special Envoy on HIV/AIDS in Africa, Co-director of AIDS-Free World, 8 February 2004

New technologies: microbicides, vaccines, PrEP

- Under development
- Clinical trials planned and ongoing worldwide
- Could be female-initiated or controlled
- All must be incorporated into a comprehensive response to the epidemic

A comprehensive prevention-to-care continuum

- Microbicides, vaccines, PrEP will NOT eliminate the need for other prevention strategies
- Partial effectiveness
- End-users must be taught to maximise benefits by continuing other prevention methods
- Comprehensive prevention-to-care continuum

Key messages

- AIDS represents one of the worst pandemics the world has ever seen. An AIDS vaccine, once developed, will play a major role in halting it.
- Behavioural prevention strategies have slowed the epidemic in some areas of the world, but have not stopped it; a preventive AIDS vaccine is urgently needed.
- An AIDS vaccine will never be the only answer. The response to HIV and AIDS must be comprehensive and should include existing behavioural prevention strategies, new technologies once they are available, and treatment and care for those already infected.

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Presentation Two:

Building a Supportive Environment for AIDS Vaccine Development

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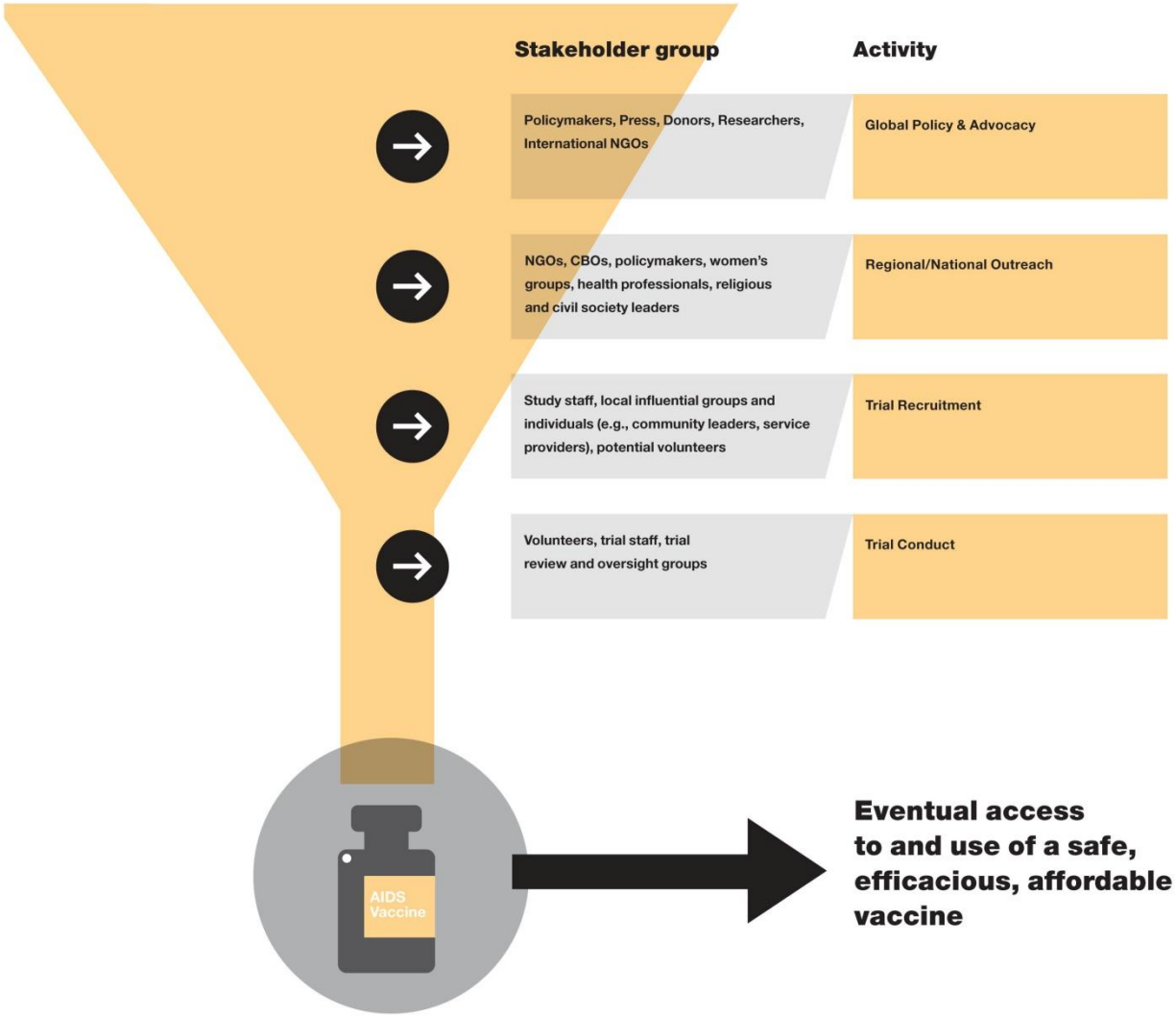
AIDS vaccine trials in developing countries

- Conducting a randomised controlled trial (clinical trial) is the best way to know if a vaccine will be safe and efficacious in a particular population
- Country stakeholders are critical — they must be made partners early on in the process
- Community and country where trial takes place stand to benefit through partnerships with stakeholders
- Immediate needs of communities can be addressed in context of vaccine research

Stakeholder scopes of influence



Key messages

- Involving community representatives and key stakeholder groups in meaningful dialogue early on can contribute to the success of AIDS vaccine research. These individuals often have important insights that can improve clinical trials.
- Trust must be built with communities and in-country stakeholders so that they become allies. It is their right to know about the research and to be involved. Failing to involve them could result in misunderstandings, negative perceptions of trials and delays in progress.

Key messages (2)

- Communities in which trials are conducted should experience benefits beyond their contribution to the trial. Such benefits might include improved services for HIV prevention and care.
- There are very important reasons to conduct AIDS vaccine research in the developing world, even though some may question the motivations for doing so. We must know that the vaccines work where they are needed most, and conducting trials in those countries will help make them available more quickly.

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Presentation Three:

The Immune System and HIV and AIDS

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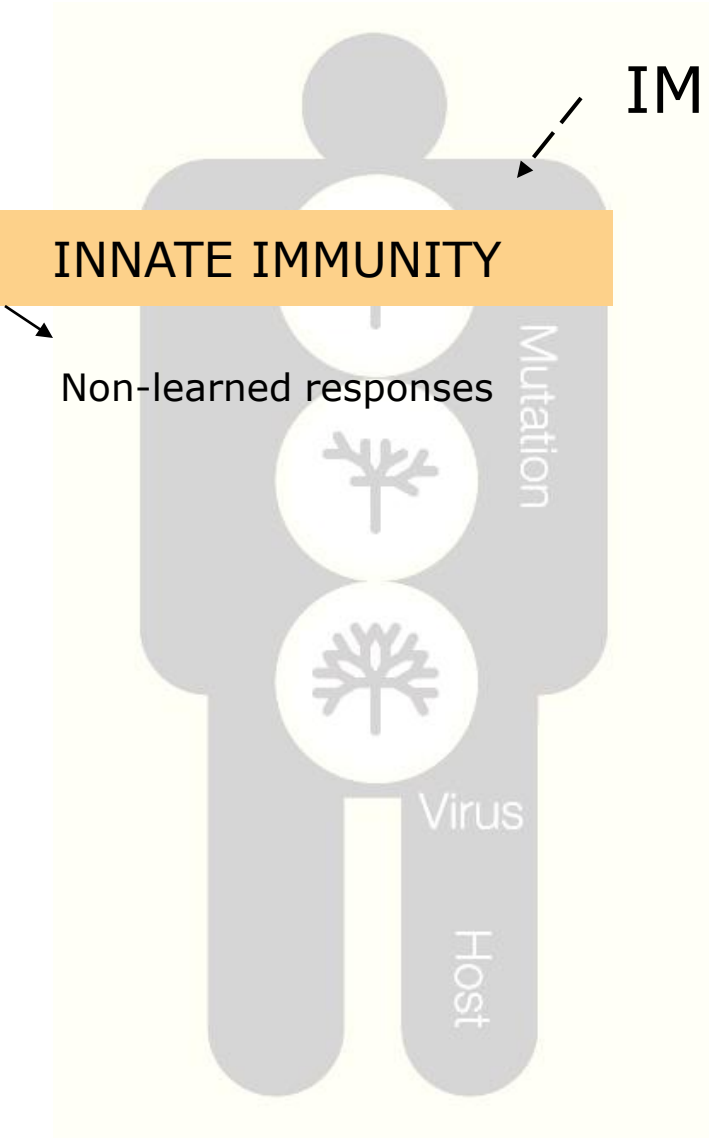
Types of immunity



IMMUNE SYSTEM

INNATE IMMUNITY

Non-learned responses

ACQUIRED IMMUNITY

Learned responses

HUMORAL IMMUNITY

Antibody responses

CELLULAR IMMUNITY

Cell-mediated responses

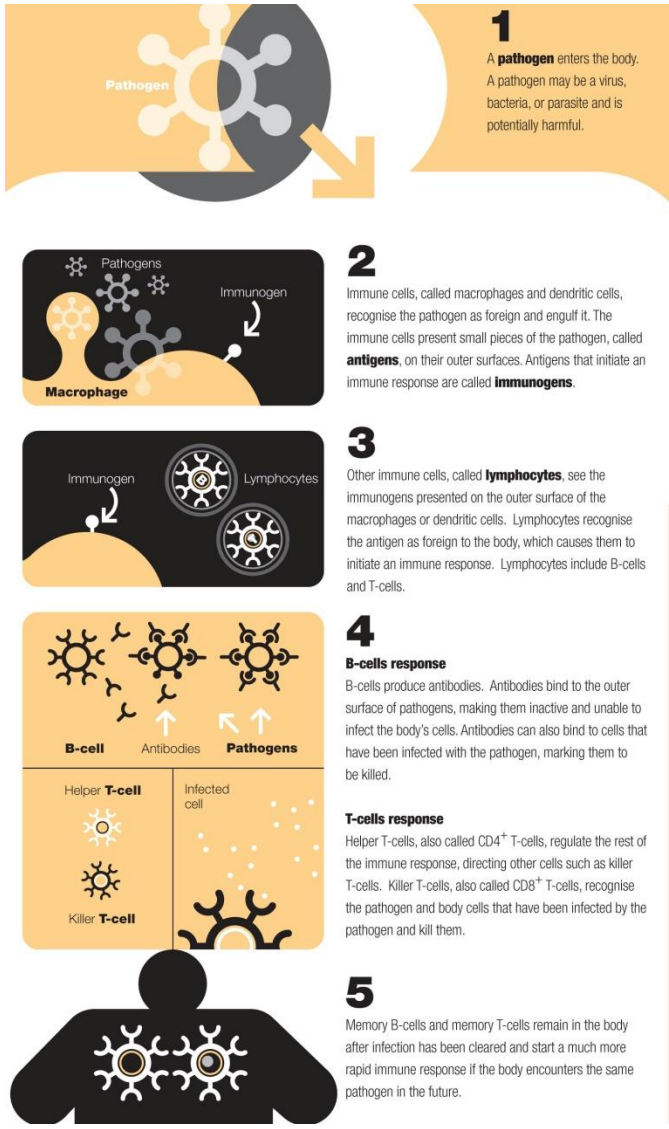
Immune response

Explanation:

- Pathogen enters body
- Parts of immune system 'pick up' the pathogen
- Certain pieces of the pathogen are presented to other components of immune system
- Immune system responds to the pathogen

How this concept relates to HIV:

- HIV can avoid the immune response
- HIV makes many copies of itself and mutates, making itself unrecognisable to the immune system
- HIV kills immune cells important in defending the body against HIV
- Presents challenges to AIDS vaccine development



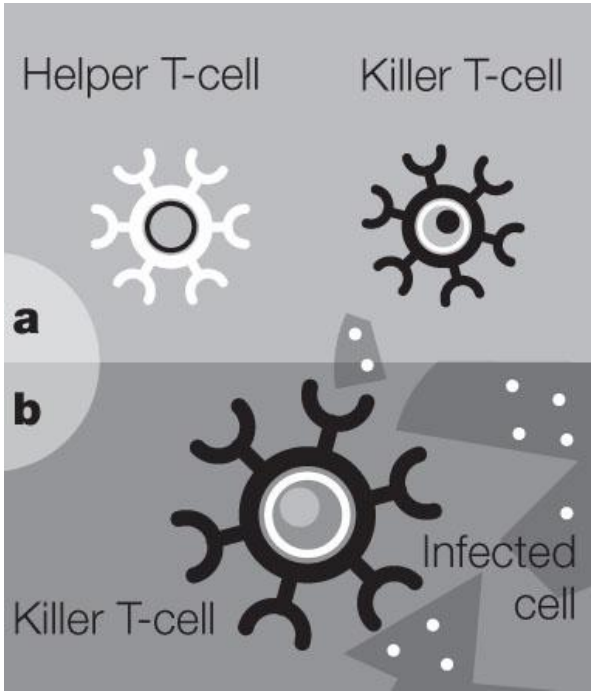
T cells

Explanation:

- Recognise a pathogen or a virus-infected cell
- Can kill abnormal or virus-infected cells through several different methods
- Two types of T cells: $CD4^+$ cells and $CD8^+$ cells

How this concept relates to HIV:

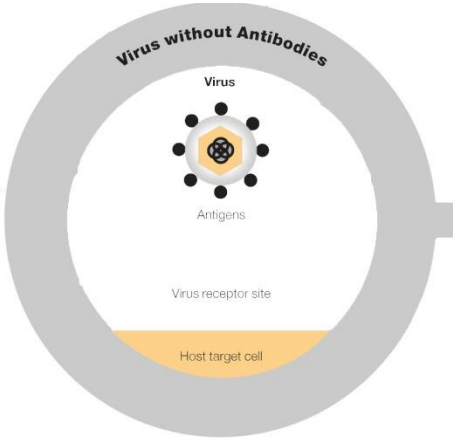
- $CD4^+$ cells recognise cells infected with HIV
- $CD4^+$ cells are targets of HIV — they become infected themselves

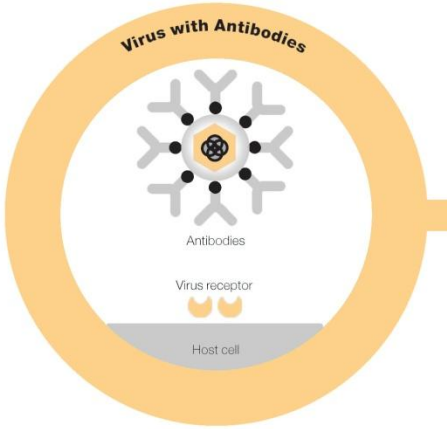


Antibody

Explanation:

- Proteins specifically shaped to attach to an antigen
- Lock or bind to antigens on the surface of the pathogen
- Coat the pathogen
- Make pathogen inactive and mark it so other immune cells can easily kill it
- Prevent viruses from entering host cells





How this concept relates to HIV:

- HIV can change its coating to avoid the effects of antibodies
- A common way to test for infection is by testing for HIV antibodies

Key messages

- The immune system is a powerful tool for fighting infections and keeping us well; it even helps control HIV in the early stages of infection.
- HIV is particularly harmful because it directly attacks the parts of the immune system that would normally fight off other infections and it makes the immune system incapable of fighting HIV itself.
- An effective AIDS vaccine will 'teach' the immune system to fight HIV; this may prevent initial infection and/or lessen disease after infection.

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Presentation Four:

Vaccines

Definition of “vaccine”

- A substance that is introduced into the body to prevent infection and/or to control disease due to a pathogen
- ‘Teaches’ the body how to defend itself against a pathogen by creating an immune response
- Every vaccine protects only against one particular disease, and it will not protect against other diseases
- Examples of existing vaccines: polio, tetanus, measles

How a preventive vaccine works

- Vaccine introduces safe forms, fragments, or copies of fragments of the pathogen into the body
- Fragments cause cells of immune system to generate a protective response:
    - B cells – produce antibodies
    - T cells – activate 'killer cells'
- Memory cells remember a pathogen, will quickly recognise it in case of future exposure, and will initiate strong immune responses to avoid or lessen infection

Vaccine types (4)

DNA vaccines

- Use copies of single or multiple genes from pathogen
- Gene produces particular protein, causing immune system to develop a response
- Common strategy being used for AIDS vaccine development

Vector vaccines

- Same strategy as DNA vaccines, adding ‘vector’ for better delivery
- Vector usually harmless virus
- Common strategy being used for AIDS vaccine development

Key messages

- Vaccines are made to prevent healthy people from getting infection or disease; this is also the goal in developing a preventive AIDS vaccine
- No existing vaccine works on all people 100% of the time; it is likely that a future AIDS vaccine will be less effective than some vaccines used for other diseases and will not eliminate the risk of HIV infection. Even after people receive the vaccine, they will still need to take other prevention precautions (such as using condoms)
- Traditional approaches for developing vaccines have either not worked well or would be unsafe when applied to AIDS vaccine development, so scientists are using newer techniques. Using these techniques, there is no chance that an AIDS vaccine will cause HIV infection

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Presentation Five:

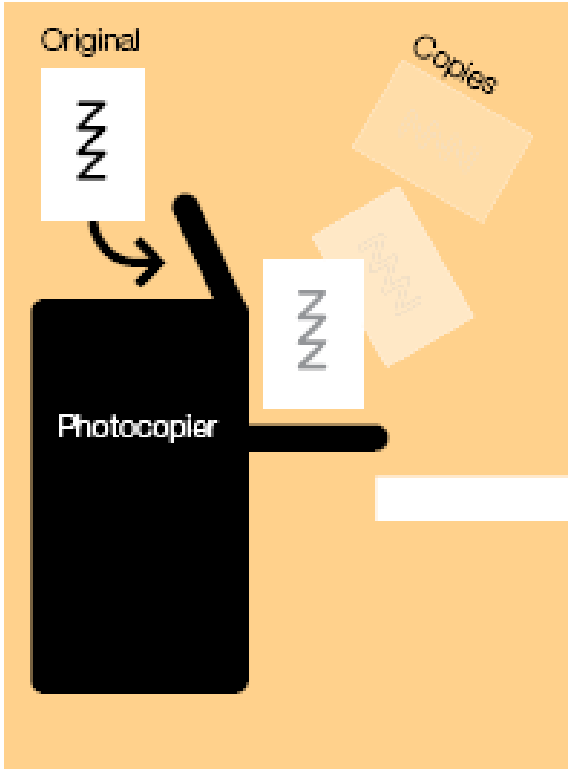
AIDS Vaccine Development

AIDS vaccine research and development

- Presently no AIDS vaccine available
- Research ongoing since late 1980s
- Preventive and therapeutic vaccines being researched; most effort around preventive
- Preventive vaccines are developed for HIV-uninfected individuals
- Preventive vaccines may slow progression from HIV infection to AIDS
- No AIDS vaccine candidates can cause HIV infection — no part of HIV used, only artificial copies of small non-harmful portions

“Copies” of genes

- Genes that are included in vaccines do not come directly from HIV.
- Scientists make artificial copies of these genes in the lab and use the copies in the vaccine.
- Like a photocopy of a famous painting



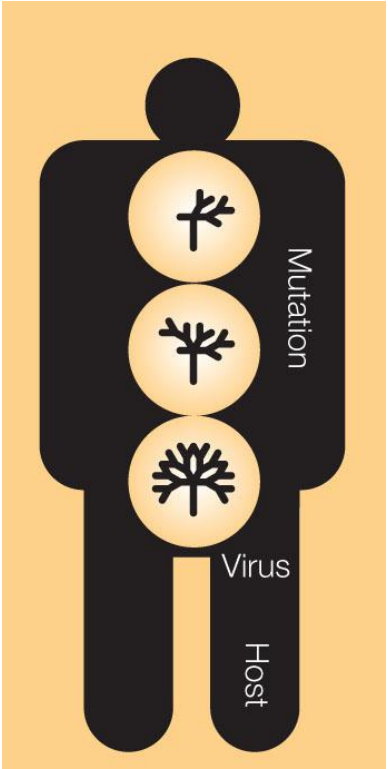
Major points in AIDS vaccine research history

Date	Event
1987	First clinical trial begun by US Government
1996	International AIDS Vaccine Initiative (IAVI) formed
1997	US President Clinton announces 10-year goal for development of an AIDS vaccine
1998	First Phase III trial begins of gp-120 VaxGen vaccine
1999	First AIDS vaccine trial in Africa begins in Uganda
2000	First AIDS vaccine trial for *clade*/subtype A begins in UK
2001	Same trial begins in Kenya
2003	Phase III trials completed of gp-120 VaxGen – results indicate no vaccine efficacy
2007	Phase IIb trials of Adeno-5 vector vaccine prematurely halted due to lack of efficacy

Challenges (4)

Mutation and Subtype:

- HIV mutation leads to different forms –
  - Different forms of HIV within an individual
  - Different forms of HIV throughout the world
- 9 major subtypes throughout the world
- Scientists do not know significance of subtype in vaccine development
- Ideal vaccine would protect against all subtypes



key messages

- Currently, no AIDS vaccine has been proven to be safe and effective. As of 2008, it may take many more years of research to identify one.
- There is no chance that any of the AIDS vaccine candidates could cause HIV infection.

Developing an AIDS vaccine is very difficult for many scientific reasons:

- The virus is extremely effective at evading the immune system because it can mutate within an individual, meaning that HIV can learn how to avoid the effects of a vaccine.
- Mutation leads to different subtypes of the virus throughout the world, each subtype reacts differently to different vaccine candidates hence testing in many countries is necessary

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Presentation Six:

The Clinical Vaccine Trials

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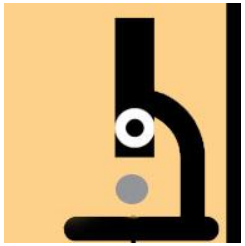
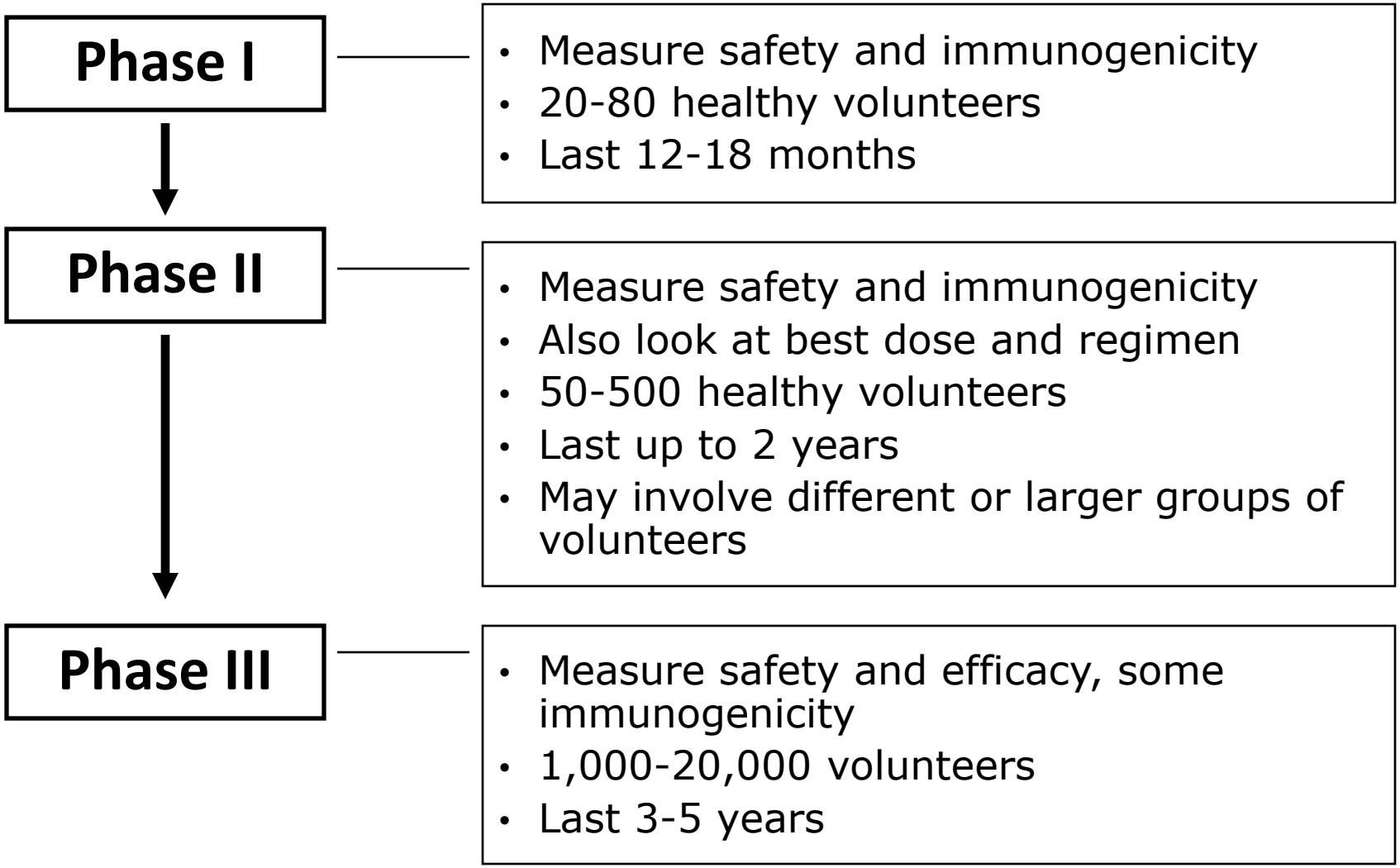
What is a clinical trial?

- Study conducted in humans
- Answers specific research questions about a new vaccine or drug
- Tests ‘candidate’ vaccines or drugs
- All candidate vaccines or drugs go through a series of trials
- Pre-clinical trials = non-human/animal studies



Typical phases of clinical trials



Additional studies

Phase IIb/test-of-concept

- Smaller than a Phase III trial
- Trial in smaller number of people at higher risk for infection, measuring efficacy
- Gives researchers indication of whether vaccine will show efficacy and should be moved to larger Phase III trials

Screening test-of-concept

- Same as Phase II, but conducted with population at higher risk for infection
- Gives researchers initial sign if a candidate vaccine will protect and should be moved to larger trials

Placebo

- Harmless, inactive substance
- Looks like vaccine
- Placebo group = control group
- A control must be used for comparison of data
- Alternatives to using a placebo
- Placebo must be used in AIDS vaccine trials

Key messages

- Before a Phase III clinical trial is completed and the data are analysed, no one knows whether an experimental AIDS vaccine is protective. Volunteers in an AIDS vaccine trial cannot assume that they are protected against HIV
- In any clinical trial, including AIDS vaccine trials, there are benefits and risks for volunteers; however, there is no risk that the vaccine itself will cause HIV infection and no volunteer is ever intentionally exposed to HIV
- All clinical trials are held to the same high ethical and scientific standards, no matter where in the world they are conducted

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Presentation Seven:

Participation In AIDS Vaccine Trials

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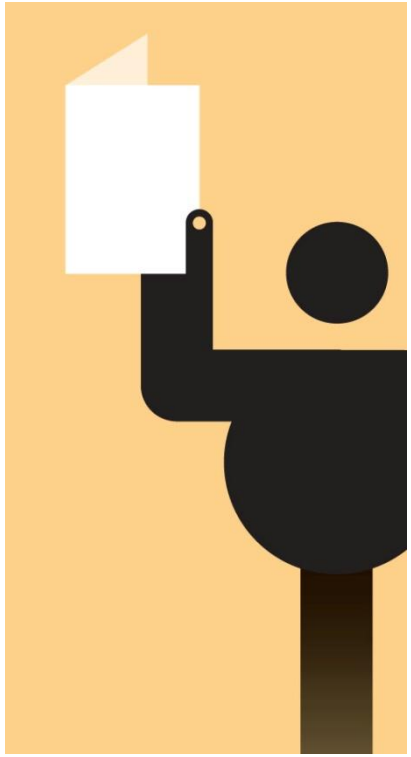
Basic trial process

1. Education and info to make the decision to participate
2. Informed consent
3. Screening w/HIV test
4. Entry into trial
5. Assignment to vaccine or placebo group
6. Repeated injections and monitoring of health, including HIV status
7. Follow-up and completion of enrollment

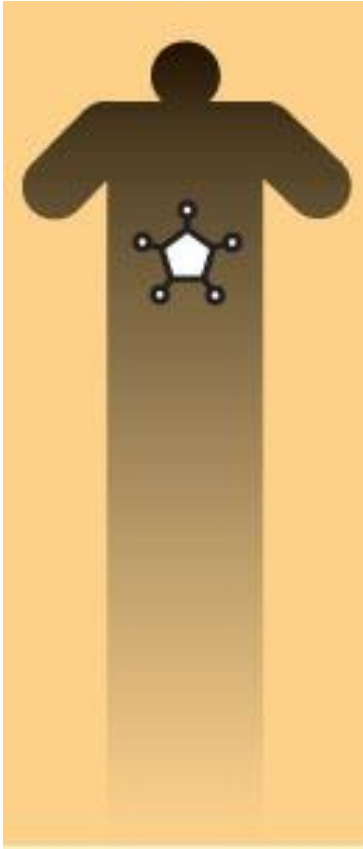
Screening and HIV testing

- Screening may involve a complete medical history, physical exam, questionnaire
- Screening involves HIV test with pre- and post-test counselling
- HIV testing and counselling occurs before each trial injection
- Volunteer needs to remain uninfected to continue receiving injections



Falsely testing antibody - positive

- Volunteer's body may produce antibodies to HIV, if reacting to vaccine
- Most standard HIV tests look for antibodies
- Important to distinguish between testing for antibodies vs. testing for actual virus
- "Antibody positive" = volunteer is producing antibodies against HIV due to vaccine response
- "Antibody positive" → volunteer is NOT actually HIV infected



Key messages

- Most experimental AIDS vaccines have been designed to prevent HIV infection. This is why most trials only enrol volunteers who are not infected with HIV.
- All volunteers should continue to use condoms and practice other forms of risk-reduction, as they cannot count on the experimental AIDS vaccine to protect them against HIV infection and because they may receive a placebo.

Key messages (2)

- The decision about whether to participate in a trial should be made by the individual volunteer; it is unethical for anyone (family members, trial staff, etc.) to pressure someone into participating
- During the trial, a volunteer who becomes infected with HIV through sexual or blood exposure is provided with or linked to available health care; he or she continues to be monitored to find out if the vaccine affects HIV

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Presentation Eight:

Gender

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Concept of gender

- 'Gender' not necessarily the same as 'sex'
- Sex = biological characteristics
- Gender = socially constructed identity
- Gender roles = attitudes, behaviours, responsibilities, expectations
- Roles vary from culture to culture

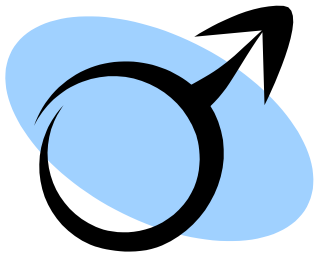
Role of vaccines

- Vaccines may significantly reduce women's vulnerability to HIV
- Current prevention options are not feasible for many women
- Partners' behaviour can make women more vulnerable
- Vaccines not associated with sexual act
- Have potential to be used without partner's knowledge if necessary

Women in vaccine trials

Both men and women must be included in clinical AIDS vaccine trials:

- To detect differences in effect of vaccine
- For licensure purposes
- Both sexes can benefit



Key messages

- Although the AIDS pandemic is affecting women at greater rates than men in many places, current prevention options are not feasible for many women. There is an urgent need for new prevention options that are more easily used and initiated by women.
- Once available, an AIDS vaccine will be an important tool for reducing women's vulnerability to infection; it is a method that women will be able to use easily without men's cooperation, if necessary, as it is separate from the sexual act.

Key messages (2)

- It is important that women participate in vaccine trials to determine whether a vaccine works for them, but they often find it difficult to participate for social, cultural and logistical reasons. Efforts should be made to support involvement of women in trials and to ensure that they make voluntary and independent decisions to participate.

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Presentation Nine:

Ethical Issues

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Primary principles of ethical research

- Value – provide useful knowledge
- Validity – appropriate and practical
- Fair participant selection
- Favourable risk/benefit ratio
- Independent review
- Informed consent
- Respect for participants

Informed consent process

- Informed consent is NOT just a document
- Signed agreement between researcher and volunteer
- Volunteer must have complete understanding through process of education and dialogue
- Involves outreach to broader community and to the individual
- Must avoid coercion to participate

UNAIDS guidance document

Updated version issued 2007

Topics addressed:

- Community participation
- Capacity building
- Control groups
- Involving populations at higher risk
- Available online: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf

Key messages

- All AIDS vaccine trials follow the same set of international ethical guidelines to ensure that each volunteer's health, dignity and well-being are protected
- National and international authorities that are independent of trial researchers and sponsors conduct ongoing monitoring of research projects to ensure that they meet ethical standards
- Obtaining each volunteer's informed consent to participate in a trial is essential to ethical research; the purpose is to ensure that participants fully understand essential information about the trial and that they are not unfairly influenced to participate

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Presentation Ten:

Review and Approval for AIDS Vaccine Trials

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Review groups

- Every trial protocol and product to be tested must be reviewed by committees
- In general, review committees include regulatory, scientific, and ethics, and include both international bodies and country-specific committees
- Some community groups provide feedback on protocol – this is *not* considered official review, but is important

Review example: Brazil

Any trial in Brazil must be reviewed by:

- IRB of the university or research institution
- National Ethics in Research Committee
- National Technical Committee on bio-safety (for genetically engineered products)
- National Agency for Sanitary Surveillance
- National AIDS Programme (plays an advisory role in some cases; not required)

Good clinical practice (GCP)

- Established by US, in agreement with ICH
- Establishes standards for design, conduct, recording, and reporting of clinical trials
- Include requirements for review and approval of trials

Key messages

- All clinical trials, including AIDS vaccine trials, are carefully reviewed before they receive approval to begin, to make sure that they are scientifically and ethically sound and safe for volunteers.
- Review committees and regulatory authorities are completely independent of the people who sponsor and conduct the trial; these authorities conduct additional reviews as a trial is carried out and have the power to stop a trial at any time
- Clinical trials must be reviewed and approved by appropriate committees in each country and institution where the trial is to be conducted

Access to an AIDS vaccine, once licensed, must happen quickly in developing countries

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Presentation Eleven:

Preparing for Future Access and Use of an AIDS Vaccine

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Why must they be *tested* in developing countries?

- Vaccines should be tested in various areas where they are likely to be used
- Vaccines must be safe and effective for the population
- Trial conduct may help put delivery systems in place
- In-country testing facilitates national approval
- In-country testing raises awareness and empowerment of communities

Preparing now for access

Lessons to be learned now about future access:

- Vaccine pricing for developing countries
  - Understand potential mechanisms
- Approval processes
  - Better understand and streamline system
- Current introduction of a new vaccine
  - Study experience of HPV vaccines

Key messages

- Historically, vaccines have taken up to 20 years after approval and licensure to become available to people in countries where they are most needed. This delay must not happen in the case of an AIDS vaccine
- There are concerns about how soon to address access issues for a product that is not yet licensed, but it is necessary to focus on the issues at an early stage, given the history of delayed access to important public health interventions
- Working on eventual access to a vaccine can go hand-in-hand with clinical trials for AIDS vaccines. This may be a very efficient way to address some of the barriers to access