

UNDERSTANDING THE RESEARCH PROCESS FOR NEW HIV PREVENTION TECHNOLOGIES

Introduction

In recent years, there have been promising results from both HIV vaccine and microbicide clinical trials. In the next few years, results are anticipated from a number of other microbicide, vaccine and pre-exposure prophylaxis (PrEP) trials. As the results of new HIV prevention technology (NPT) trials are released and discussions emerge about the implications of the results, it is important that a range of stakeholders understand what the results mean, and the process that led to their discovery. Understanding the research process will help advocates, policy makers and service providers to prepare for the outcomes of prevention trials and communicate about trial results. This fact sheet outlines the basic steps in the research process and the roll-out of NPTs; where research is taking place and why; the role and experience of study volunteers; and the roles of other players in NPT research.

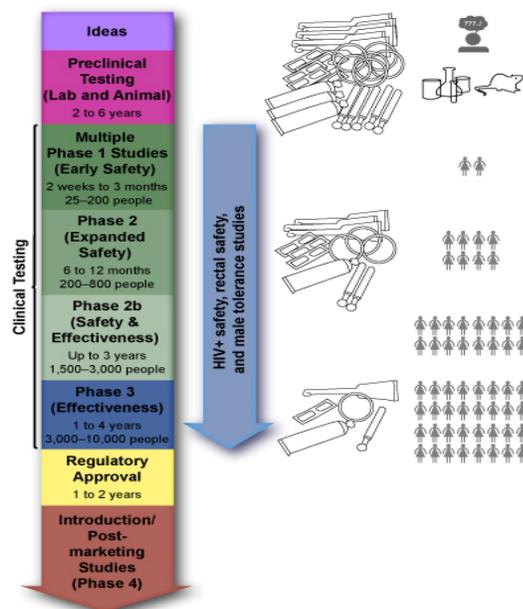
The Phases of Research

It takes more than a decade to develop and test a new product, including pre-clinical testing and clinical trials. Before any new drug candidate can be tested in human beings (also referred to as clinical trials), the developers have to show that (a) it's not likely to be harmful to humans and (b) it may be beneficial. This pre-clinical phase of research is done in laboratory testing and in animals and can take anywhere from 2 to 6 years.

Before a clinical trial can proceed, national and/or local Ethical Review Boards (ERBs) and National Regulatory Authorities ensure that the only trials undertaken are those that are both scientifically valid and ethically conducted.

If a product is approved for human trials, it goes first through a series of Phase 1 safety trials, where small numbers of people who are at low risk of infection use the product and are carefully monitored for signs of problems. Next come one or more Phase 2 trials to gather extended safety data and establish safety among different groups of people—for example, those

The Microbicide Development Process



Global Campaign for Microbicides 2010

who may already be HIV positive or have another sexually transmitted infection.

If a product is shown to be safe in these first two phases, it can then be tested for effectiveness. Generally, the next step is to conduct Phase 3 trials which can take several years because researchers need to enrol thousands of participants who use the product for many months up to several years to see if it reduces their risk of HIV infection. More than one Phase 3 trial may be needed before a product can be licensed for use.

Effectiveness vs. Efficacy

Efficacy is the ability of a candidate NPT product to produce a desired clinical effect, such as protection against a specific infection, at the optimal dosage and schedule in a given population. In other words, how well an intervention works under controlled situations (such as in a trial).

Effectiveness refers to how well an intervention works in practice, taking into account likeliness of people to adhere to it, use it properly, the tolerability or ease of use.

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A Data and Safety Monitoring Board (DSMB) oversees the trial to monitor results at regular intervals. The DSMB has the authority to stop a trial if:

1. The test product is definitely effective
2. The test product may be causing harm
3. The trial can no longer answer the original questions it was designed to answer

Roll-out and Implementation

Of the many products that begin the research process, very few will be proven to be safe and to show that they work to reduce risk of HIV infection. For the few products that make it this far, it will still take some time before the product is licensed and ready for use.

Licensing refers to the steps that a country takes to legally allow a vaccine, medication or other health product to be marketed or distributed within its borders.

Once a product has demonstrated efficacy, usually in more than one trial, the product developers can apply for licensure. A product is licensed on the basis of the information provided by the developers, including data from preclinical and clinical trials and on the quality of the manufacturing process. Product licensing also considers what the product label will say, including information about what the product does or does not do, any warnings about side effects and information about use in pregnant women. The licensure process is completed by regulatory agencies, such as Health Canada and the US Food and Drug Administration. Many developing countries also have regulatory agencies that consider product information and may also look to guidance from the World Health Organization in making their decisions¹.

Introductory studies might take place at the same time as the regulatory process. These studies will provide information about strategies for delivering or communicating about the product. They may also serve as a means to ensure access to the product while licensure is sought, for participants who took part in the efficacy trials.

After a drug has been licensed and brought to market, post-marketing studies will continue to seek out more information on issues that were not identified through earlier studies, such as rare events, long-term safety issues, or effects on a particular population of users. These studies can also provide information about how

a product is being used in the “real world”, outside of clinical trials.

Where Research is Taking Place

Prevention research has been a global endeavour. There have been safety and effectiveness trials all over the world, and international research partnerships have driven much of the research. Some HIV vaccine research has taken place in Canada, including part of the world’s first Phase 3 HIV vaccine trial.

The majority of Phase 2 and 3 trials are taking place in southern Africa and in Southeast Asia. It is necessary to run prevention efficacy trials in places where there is a high incidence of HIV, and a relatively stable population. In addition, conducting clinical research in countries where NPTs are most needed will help to ensure the acceptability of the products among the populations that are most likely to benefit from them.

In the case of microbicide trials, it is also important to run trials in areas where sex is the primary mode of HIV transmission. Trial results could be confused if participants are becoming infected through injection drug use. For example, communities where HIV incidence is high among women in North America and Europe also tend to have high rates of injecting drug use, which could confuse the results of microbicide trials by introducing other sources of exposure to HIV.

Vaccine trials must take place where target HIV subtypes (clades) are present so that future vaccines will be effective in those areas.

Participating in Clinical Trials

Clinical trials would not be possible without the willingness and dedication of trial volunteers, and it is critical that the rights of trial participants be protected. There are many mechanisms in place to protect participants in clinical trials, including ethics committee reviews, the informed consent process and access to care and treatment for participants who become HIV-positive during the trials. Ethics Review Boards ensure that there is an appropriate informed consent process, including clear information about the trial in the language and format that is suitable to the local community where the trial will be conducted.

Potential volunteers are often required to give informed consent at pre-screening (to see if they are

suitable for the trial), at screening and again at enrolment once they are found to be eligible to participate in a trial. Participants in trials are allowed to leave the study at any time they wish.

Participants in all prevention trials will at minimum receive regular safer sex counseling, condoms, and testing and treatment for sexually transmitted infections (STIs). Despite being offered the standard package of prevention services, some participants will become infected with HIV over the course of the trial. This risk is not because of the trial, rather it is a reality of life for many people and further highlights the importance of developing additional prevention options.

Advocates are working hard to ensure that participants who become infected with HIV during the course of any HIV prevention trial are assured access to HIV care and treatment, including antiretroviral drugs when needed. Since participants who become infected with HIV during the course of a prevention trial are unlikely to need ARVs for a number of years, most trials make arrangements with local health care providers for access to treatment as it becomes needed.

UNAIDS and the WHO recommend that “Participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognised as optimal. Prior to initiation of a trial, all research stakeholders should come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment.”ⁱⁱ

Many trials also try to facilitate access to care for those who test HIV positive at the time of screening, by providing tests and other assessments that can help them qualify for locally-available treatment programs.

A wide range of stakeholders are engaging in ongoing dialogue to address challenging ethical issues surrounding clinical trials. Such issues include ensuring appropriate levels of community engagement throughout in the research process; ensuring a culturally-appropriate and rights-based informed consent process; deciding what additional health care should be offered to trial participants; and what care, if any, is due to people who are screened out of a trial because they are already HIV-positive.

Roles of Various Players

Academic and Non-profit Institutions

Almost all HIV prevention research to date has been conducted by non-profit and academic institutions or small biotech companies. These institutions conduct: basic research—the scientific discovery and development of NPT candidate concepts and products; clinical research—testing the safety and efficacy of candidate NPT products, and; social research—on acceptability, preparedness, access and delivery issues, and working alongside clinical research to understand usability and acceptance of NPTs.

Some of the key non-profit institutions engaged in prevention research are product development partnerships (PDPs). PDPs are non-profit enterprises created to accelerate the development of new tools to fight diseases in resource-poor settings. They work with pharmaceutical companies that do not have the economic incentive to pursue these products on their own. Typically, PDPs manage resources and partnerships from across public, private and philanthropic sectors to drive the development of new products. Examples of PDPs working on new HIV prevention technologies are the International Partnership for Microbicides (IPM) and the International AIDS Vaccine Initiative (IAVI).

Pharmaceutical Companies

Large pharmaceutical companies have not invested significantly in this field, primarily because most new prevention technologies are classic “public health goods” which would yield tremendous benefits to society but for which the profit incentive to private investment is low. One of the exceptions to this is HIV vaccines, which have seen some investment from large pharmaceutical companies already experienced in vaccine development. Still, most HIV vaccine research is conducted by non-profit and academic institutions and small biotech companies. Some large pharmaceuticals have allowed non-profit groups to test products that they own. The pharmaceutical companies do not pay for the trials for these products, they simply lend the product to these non-profit organizations.

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Donors

For the most part, prevention research is funded by charitable foundations and government grants. In addition to clinical trials, these public and philanthropic funds also support basic science, social and behavioural research, and clinical trial infrastructure that contribute to HIV prevention research.

Investments in microbicide research and development illustrate the significance of public funding for prevention research. In 2008, the public-sector provided 85% (US\$207 million) of the funds allocated to microbicide research and development, the philanthropic sector provided 14% (US\$35 million), and the commercial sector accounted for 1% (US\$2.5 million)ⁱⁱⁱ.

Community Members and Organizations

Community engagement in prevention research can occur at many different levels. At a local level where trials are taking place, the community may include the individuals living in the area of the trial, their leaders, local media, and community-based organizations that serve or represent them.

In addition, prevention trials usually involve the establishment of community advisory structures such as Community Advisory Boards (CABs), Community Advisory Groups (CAGs) or Community Advisory Councils (CACs). These community advisory structures are in place to represent community concerns, provide input in trial design and negotiate ethical challenges with trial staff. Community structures can also help develop community acceptance and preparedness for NPTs and facilitate clinical trial recruitment.

Beyond the communities where clinical trials are taking place, national stakeholders and international civil society play important roles in prevention research. In collaboration with local communities, national and international organizations can raise awareness about the role community based organizations can play before, during and after trials; incorporate NPTs into prevention education and training programs; develop strategies for promoting and distributing NPTs once available; participate in efforts to highlight and address important ethical considerations; and advocate for investment in NPT research and development. Some of the key international civil society organizations advocating for HIV prevention research include the Global Campaign for Microbicides and AVAC.

Conclusion

Research into new HIV prevention technologies is, like all research, a long and complex process. Understanding this process and the players involved is important for stakeholders wanting to improve the process and to understand better the results that emerge from the process.

ⁱ AVAC. *From Results to Delivery*.

<http://www.avac.org/ht/d/sp/i/299/pid/299>

ⁱⁱ UNAIDS and WHO 2007. *Ethical Considerations in biomedical prevention trials*.

http://data.unaids.org/pub/Report/2007/jc1399_ethical_considerations_en.pdf

ⁱⁱⁱ HIV Vaccines and Microbicides Resource Tracking Working Group 2009. *Adapting to Realities: Trends in HIV prevention research funding 2000 to 2008*.

<http://www.avac.org/ht/a/GetDocumentAction/i/2711>

Sources of Additional Information

AVAC. *HIV Prevention research: Timeline of expected efficacy of trial results*

http://www.avac.org/ht/d/Contents/contenttype_id/18/order/date/direction/asc/pid/1891/displaytype/iframe/afterdays/1290/beforedays/-1215/TPL/Timeline/cfs/1/

Global Campaign for Microbicides (GCM) 2010. *Microbicide Clinical Trials: How do they work? What ethical guidelines must be followed?* <http://www.global-campaign.org/clientfiles/FS-TrialEthics%5BE%5D.pdf>

GCM 2010. *Microbicides Research and Development*. <http://www.global-campaign.org/clientfiles/FS-R&D%5BE%5D.pdf>

Interagency Coalition on AIDS and Development (ICAD). *Tools, Trends and New Technologies in HIV Prevention (2010); Pre-exposure Prophylaxis as a Potential HIV Prevention Method (2010); The Impact of AIDS Vaccine Research on Health Systems Strengthening (2008)*. <http://www.icad-cisd.com/content/en/publications/prevention>

Program for Appropriate Technology in Health (PATH) 2009. *Standards of Prevention in HIV Prevention Trials: Consultation report and recommendations*. <http://www.global-campaign.org/clientfiles/SOP-report-FINAL-.pdf>

ICAD's mission is to lessen the spread and impact of HIV and AIDS in resource-poor communities and countries by providing leadership and actively contributing to the Canadian and international response. Funding for this publication was provided by the International Partnership for Microbicides (IPM) and the International AIDS Vaccine Initiative (IAVI). The opinions expressed in this publication are those of the authors/researchers and do not necessarily reflect the official views IPM and IAVI. ICAD would like to thank Marc-André LeBlanc for his assistance in developing this fact sheet.