A PRIMER

FOR MEMBERS OF COMMUNITY ADVISORY COMMITTEES IN HIV CLINICAL TRIALS & OBSERVATIONAL STUDIES

March 1, 2010

IN TRANSLATION

the CTN
CIHR Canadian
HIV Trials Network

le Réseau
Réseau canadien
pour les essais VIH des IRSC

CIHR Canadian HIV Trials Network (CTN)
A project of the CTN's Communications & Information Programme

Dedication

PHOTO: STAN BEHAL

Maggie Atkinson

This *Primer* would not have been possible without the knowledge and experience of the people sitting on the CIHR Canadian HIV Trials Network's Community Advisory Committee (CAC). In particular, the leadership and commitment of Maggie Atkinson, Committee Chair from 1993-1997, made the development of the first edition possible.

James Kreppner

This second edition of the *Primer* is dedicated to James Kreppner (1962-2009). James was a hemophiliac who was treated during the 1980s blood scandal from which he acquired HIV and hepatitis C – a tragedy that ignited his courageous battle for his own life and rights, and those of millions of Canadians. Amongst his national lobbying initiatives for human rights and people's right to health, he co-founded and served on the CTN's Community Advisory Committee from 1993-2007.

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INTRODUCTION & HISTORY

WHO IS THIS MANUAL FOR?

This manual is for anyone who wants to serve on an HIV and AIDS clinical trials community advisory committee and needs to know more about the process and ethical considerations involved in clinical trials and observational studies. In 2007, the CTN expanded its mandate beyond clinical trials to support selected observational studies that are multi-centred, peer-reviewed, grant-funded by a national peer-review agency, and aimed at answering questions related to HIV treatments and vaccines. This manual also benefits community-based treatment information providers who wish to help clients understand specific informed consent forms.

WHAT WILL I LEARN?

This manual concentrates on the core information about clinical trials that you need to know to be an effective member of an advisory committee. This manual will walk you through:

- The basic principles of clinical research ethics
- Clinical trial terminology
- The informed consent process

Reviewing a clinical trial requires more knowledge than can be summarized in this manual. In addition to understanding ethical issues, basic terminology, and the informed consent process, committee members must also be willing to learn more about the science of HIV and the mechanisms of action for treatments under review. As well, they must eventually be able to understand a scientific protocol (the plan for a research study) and learn to evaluate the results of previous trials upon which the research plan is based.

You should be able to find answers to many of your basic questions about the science of HIV on the Internet. The Research Services section of the CTN website (www.hivnet.ubc.ca) provides a good jumping-off point for online research.

You will likely find it helpful to have a copy of the CTN's Model Informed Consent form on hand when you read through chapters 3 and 4 of this manual. The form is available for download, in PDF format, from the CTN website (www.hivnet.ubc.ca). A hard copy can be obtained by calling the Network at 1-800-661-4664.

The manual is divided into this introduction and four chapters, followed by appendices:

Chapter 1: Human Experimentation and Ethics briefly describes the concept of ethics, the history of research involving human participants, and some basic ethical principles to consider when reviewing informed consent forms, and especially HIV informed consent forms.

Chapter 2: Clinical Trials—An Overview provides an overview of HIV clinical trials. This chapter describes the clinical trial protocol, the different trial types, the four phases of clinical trials, the types of treatments and treatment strategies being tested in HIV-related trials, and other information specific to HIV clinical trials.

Chapter 3: Volunteer Rights and Informed Consent focuses on the informed consent process. This chapter defines informed consent, and includes a comprehensive list of the elements of an informed consent form, as well as questions you should ask when reviewing such a form. The chapter also discusses participant rights and the general risks and benefits of participating in clinical trials.

Chapter 4: Sample Informed Consent Form Exercise is a hands-on practice section where you can review what you have learned in this manual. It includes a sample informed consent form from an actual clinical trial, as well as its review by the CTN's Community Advisory Committee.

The appendices include a list of HIV and AIDS organizations, a list of literature relating to HIV information, clinical trials and ethics, and a glossary of terms used in this manual.

CONTEXT OF HIV AND AIDS COMMUNITY ADVISORY COMMITTEES

Before the community of people affected by HIV and AIDS organized themselves, there was little active participation by study volunteers in the review of clinical trials either in Canada or the U.S.

Beginning in the late 1980s, people living with HIV and AIDS demanded more access to the decision-making process in research. Scientists and drug companies responded by adding people living with HIV and AIDS to existing committees, and in the case of the CIHR Canadian HIV Trials Network (CTN), by adding another level of review by community-based reviewers. The CTN's Community Advisory Committee (CAC) was formed in 1993 to provide support and input for the community members sitting on the other CTN committees. By offering a broader, national perspective from a nine-member committee, the community felt their input was more representative of the community at large.

HIV scientists and clinical trial investigators now rely on CAC's advice to determine if trials may or may not be of interest to participants and to recommend specific changes that can be made to make their studies more attractive to participants. They also realize that their studies can benefit from this input, without any loss of ability to answer the research questions that the studies address.

Now, many years after the CTN's Community Advisory Committee was formed, many pharmaceutical companies regularly ask the community for their input into HIV clinical trials and informed consent forms, as do other research bodies.

In general, community advisory committees do the following:

- they ensure that the proposed research is of relevance and interest to the HIV and AIDS community, and that it actually moves the agenda forward in important areas;
- they ensure that the proposed research is ethical and does not put potential trial volunteers at undue risk (Note: evaluating the risks of a

proposed clinical trial is primarily the responsibility of scientific review committees and hospital review boards, but community advisory committees do have a role to play in ensuring the safety of trial volunteers);

- they ensure that the informed consent form clearly and accurately explains the protocol to potential volunteers;
- they provide a community forum for the discussion of clinical trials;
- they improve communications among community representatives and researchers; and
- they improve the flow of clinical trial information to community groups.

REPRESENTATION AND COMMUNITY ADVISORY COMMITTEE MEMBERS

The membership of an organization's community advisory committee should represent the interests of people who might participate in clinical trials. For example, HIV research is of interest to a wide range of HIV-positive people, including people from different parts of the country, people representing different risk groups (i.e., Aboriginal people, gay men, hemophiliacs, IV drug users, women, etc.), people representing different language groups, and people from a variety of backgrounds in terms of their education and experience. In general, a scientific background is not required to join a community advisory committee. A keen interest in treatment, a passion for human rights and an eye for detail are the only prerequisites. Study of this manual, along with practical, on-the-job experience, should make any community member eligible to serve on such a committee. Although not all committees require such affiliations, a connection to and familiarity with a community group will help you bring a broader perspective to the table.

1 HUMAN EXPERIMENTATION & ETHICS

THIS CHAPTER WILL FOCUS ON:

- the concept of ethics;
- the history of research involving human participants;
- the major biomedical ethics guidance documents;
- the ethical principles to consider when reviewing informed consent forms as a member of a community advisory committee; and
- ethics in action.

DEFINING ETHICS

Before jumping into the nuts and bolts of clinical trials, it is important to understand the background and context of human experimentation and the role of ethics in safeguarding human participation.

RESEARCH VS. TREATMENT

Within the realm of treatment, the well-being of the person being treated is the main priority. For example, when you visit the doctor, his/her focus is on treating your ailments and improving your health. However, when it comes to research, the focus shifts to include the interests of science and society in general. Therefore, a research participant should not be viewed as a patient exclusively receiving care. There is a fine line between research and treatment, with ethics helping to keep the well-being of a clinical trial participant equal to the advancement of science and medicine.

WHAT IS THE FIELD OF ETHICS?

Ethics is the study of real life issues that require the application of moral principles to specific cases. Ethicists examine problems and try to find solutions that most reasonable human beings would commonly agree upon in a specific cultural setting and in a specific time period. Biomedical ethics, or bioethics, deals with moral issues that arise in the practice of medicine.

THE BEGINNINGS OF BIOMEDICAL ETHICS

Ethical protection for participants in human research exists today as a result of past abuses. In 1947, the Nuremberg Code established ethical guidelines for biomedical research in response to the terrible experiments carried out by Nazi doctors on concentration camp prisoners during World War II. The Nuremberg Code emphasized that research is risky, and that research participants must be protected from coercion and harm.

The most important guideline to come out of the Nuremberg Code is that all scientific research involving humans requires the consent of the research participants. Consent is a legal and ethical requirement based on the ethical principle of autonomy—i.e., the participant's right to make decisions about his or her own medical care, without being forced or pressured to participate.

HISTORY OF BIOMEDICAL ETHICS

The history of biomedical ethics has been shaped by individuals determined to place the rights and well-being of study participants ahead of scientific advancement. The development of modern research ethics was fuelled in part by the work of one such individual, Dr. Vikenty Veresaev, who published *The Memoirs of a Physician* in 1916. In his book, the Russian doctor describes experiments conducted in the late 1800s in Europe and the United States, in which researchers injected microorganisms carrying gonorrhea and syphilis into sick and dying people (including babies), without their knowledge or consent. The results of these experiments were published in eminent medical journals of the period. Dr. Veresaev concluded, "Society must take its own measures of self protection against the zealots of science who have ceased to distinguish between their brothers and guinea pigs."

Further reading: Veresaev, Vikenty. The Memoirs of a Physician, translated by S. Linden. New York: A.A. Knopf, 1916.

CONCEPTS: THE NUREMBERG CODE

To qualify as ethical, consent must be:

1. **Voluntary** — The participant must make the decision to participate freely, without force, pressure or manipulation.

2. **Informed** — The participant must be provided with all available information regarding risks and benefits, including available alternative options.

3. **Comprehensible** — The participant must clearly understand the information provided, and be capable of making a knowledgeable decision.

To read the Nuremberg Code on the Web, visit ohsr.od.nih.gov.

PROCESS: DECLARATION OF HELSINKI

After Nuremberg, many other safeguards were put in place to protect human study participants. In its 1964 Declaration of Helsinki, the World Medical Association stated that experimental procedures involving humans should be clearly explained in a research protocol, a plan that describes in detail what the researcher is studying and how he or she intends to conduct the study. They also recommended that this protocol be given to an independent committee or research ethics board to review from an ethical perspective. It is now common practice for these boards to be based at the local level (i.e., each hospital participating in trials), as local conditions will influence what is considered ethical.

To read the Declaration of Helsinki on the Web, visit www.wma.net.

GUIDELINES: JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

In 2000, the *Journal of the American Medical Association* published seven suggested guidelines that should be considered in determining whether a research trial is ethical:

1. **Value** — Is the trial providing any social or scientific value? Resources should be utilized effectively and participants should not be exploited. Clinical research involving humans can be justified only if society can benefit from the trial in terms of knowledge gain, sharing of results, or improvements in health and well-being.

2. **Scientific Validity** — The trial should use valid methods of research, have a clear scientific hypothesis that could improve upon standard treatments, adhere to accepted principles and practices of trial design, and have the necessary resources to carry out the study.

Despite the development of major international safeguards such as the Nuremburg Code and the Declaration of Helsinki, unethical research continued close to home. In 1961, the University of Saskatchewan conducted a study on a new anesthetic in which student Walter Halushka took part for a $50 honorarium. Unbeknownst to him, the anesthetic had never been used before. As well, a catheter was inserted into his arm and then advanced towards the heart without his prior knowledge or consent. The anesthetic was administered, and within the hour, Halushka suffered a cardiac arrest. To resuscitate him, his chest had to be sliced open, ribs pulled apart, and his heart massaged by hand. He was unconscious for four days, remained in the hospital for ten, and then given his $50 and discharged.

Halushka sued, and in the court's final decision, it was determined that Halushka had not been advised fully about what would happen or what the risks of the experiment were. Despite signing a consent form, an uninformed consent was considered the equivalent of no consent at all.

3. **Fair Participant Selection** — Participants should be selected based on the objectives of the study, not vulnerability, bias, privilege, or convenience. Likewise, criteria for exclusion should not be without good scientific reasoning or susceptible risk to the well-being of the group being excluded.

4. **Favourable Risk-Benefit Ratio** — Potential risks to the participant should be minimized while the potential benefits should be enhanced. Overall, the potential benefits (to the individual as well as society as a whole) should outweigh or at least be proportionate to the risks.

5. **Independent Review** — The design of the trial, as well as the risk-benefit ratio and target population, should be reviewed by a group of individuals (unaffiliated with the trial and with a diverse range of expertise) who will have the authority to approve, change, or stop a study.

6. **Informed Consent** — A trial participant should be accurately informed of and be able to understand the study's purpose, research methods, potential risks/benefits, and alternatives that can be pursued. With this knowledge, the participant can then make a voluntary, uncoerced decision to participate or not.

7. **Respect for Participants** — Participants should be treated with respect, whether they are in a trial, approached for a trial, or have refused enrolment to a trial. Respect includes allowing withdrawal from the study at any time, confidentiality, informing a participant when new risks or benefits develop, sharing the results of the study, and maintaining the welfare of participants.

To read the full article, visit www.jama.com for the May 24/31, 2000 issue – Vol 283, No. 20.

CANADIAN CODE OF CONDUCT: TRI-COUNCIL POLICY STATEMENT

In 1998, the Medical Research Council of Canada (MRC – now known as the Canadian Institutes for Health Research), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC) released their own code of conduct called the Tri-Council Policy Statement (TCPS). Researchers who carry out studies on human beings

must comply with the TCPS in order to be eligible for funding. The TCPS lists the following as the guiding principles of ethical research:

- Respect for human dignity (i.e., the obligation to protect "the multiple and interdependent interests of the person—from bodily to psychological to cultural integrity")
- Respect for free and informed consent
- Respect for vulnerable persons
- Respect for privacy and confidentiality
- Respect for justice and inclusiveness
- Balancing harms and benefits
- Minimizing harm (the TCPS emphasizes "non-maleficence," which it defines as "the duty to avoid, prevent, or minimize harm to others")
- Maximizing benefit

To read the Tri-Council Policy Statement on the Web, visit www.pre.ethics.gc.ca.

The concepts, processes and principles outlined in the Nuremberg Code, the Declaration of Helsinki, the *Journal of the American Medical Association,* and the Tri-Council Policy Statement provide the basic codes and tools available to you when evaluating a research protocol. We will examine these and other issues in greater detail in Chapter 3.

In December 2008, CIHR, NSERC and SSHRC released the revised Draft 2nd Edition of the Tri-Council Policy Statement. Section 6, "Research involving Aboriginal Peoples", was developed in partnership with the Aboriginal Capacity and Developmental Research Environments (ACADRE) centres and other relevant stakeholders. The produced guidelines aim to reflect and respect the larger Tri-Council process, and Aboriginal values, knowledge, methodologies and decision-making processes. To read the *Draft 2nd Edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, visit www.pre.ethics.gc.ca/english/pdf/newsandevents/TCPS_Dec_4_en.pdf

ETHICS IN ACTION

While a basic knowledge and understanding of ethics will help enhance your role on a CAC, providing advice on ethics is not your sole responsibility. In fact, a number of formal mechanisms exist to ensure that researchers are meeting stringent ethical standards before proceeding with their studies.

RESEARCH ETHICS BOARDS

A research ethics board (REB) is an independent committee established to protect the rights and interests of clinical trial participants. REBs help to ensure that ethical principles are upheld during research involving human participants. A board can act as a consultative body and thus, contributes to the education portion of research ethics; it is also responsible for independent, multidisciplinary review of the ethics of research to see whether the research should be allowed to start or continue.

Canada's model of ethics review involves the application of national norms by a local REB for reviewing the ethical standards of research projects developed within their institutions. The institution is responsible for mandating the REB to approve, reject, propose modifications to, or terminate any proposed or ongoing research. The role and authority of the REB should be respected and defined clearly by the institution. A formal appeal process should be set in place in case an institution disagrees with a REB decision.

All research that involves living human participants requires review and approval by a REB in accordance with the Tri-Council Policy Statement, before the research is started.

NATIONAL COUNCIL ON ETHICS IN HUMAN RESEARCH

In 1989, at the request of MRC and with funding from MRC and Health Canada, the Royal College of Physicians and Surgeons of Canada established the National Council on Ethics in Human Research (NCEHR). Incorporated in 2003 as a non-governmental organization, NCEHR's mission is to advance the protection and well-being of human participants in research and to foster high ethical standards for the conduct of research involving humans.

For more information on the NCEHR, visit www.ncehr-cnerh.org.

2 CLINICAL TRIALS— *an Overview*

THIS CHAPTER WILL FOCUS ON:

- the basic goals and purposes of clinical trials;
- the clinical trial protocol;
- the different types of clinical trials;
- the four phases of clinical trials; and
- the types of treatments and treatment strategies being tested in HIV-related clinical trials; and the most common methods used by researchers to evaluate the results of clinical trials.

THE BASICS

WHAT IS A CLINICAL TRIAL?

A clinical trial is a carefully designed study that allows scientists to test their research questions on people. Many clinical trials evaluate new drugs, but they are also used to test a range of other ways of treating diseases or health problems. In HIV, these include vaccines (preventative and therapeutic), other prevention methods, treatment management and adherence strategies, optimized diets, and nutritional and herbal supplements. Clinical trials allow researchers to test how well a particular treatment works, to compare different treatments and to answer specific questions such as how much of a treatment should be administered and how often. Clinical trials also allow researchers to determine the side effects, toxicity and interactions of a new treatment, and to determine other potential risks that the treatment may pose to a person's health or quality of life.

WHAT IS A CLINICAL TRIAL PROTOCOL?

Every clinical trial begins with a protocol. A protocol is the written plan of a trial; a researcher's description of why and how the study will be conducted. A protocol outlines the following:

- what the experimental treatment (or other intervention) is, with background information;

- why the treatment is relevant, and how it addresses the health problem in question (i.e., the study hypothesis);
- how the trial is constructed (testing methodology, e.g., double-blind, randomized)
- how the treatment will be evaluated (study objectives);
- who is eligible to take part in the trial;
- the number of participants to be enrolled in the trial;
- how all study treatments (experimental and other) will be administered (including dosage amounts and frequency, if applicable);
- the schedule for tests and procedures;
- the number of required clinic visits, and length of study;
- how the safety of participants will be monitored; and
- how the study results will be analyzed (details of statistical analysis).

A protocol ensures that if the trial is being conducted in more than one place, the exact same procedures are followed in each location. By standardizing the procedures, researchers can pool the results from the different sites together with the knowledge that the experiment was conducted the same way.

HOW IS A PROTOCOL DEVELOPED?

A protocol can be initiated by a group of doctors, researchers or representatives of a drug company, or it may be initiated by the community. In Canada, clinical trials are often sponsored (designed and paid for) by a company that has developed a new treatment. However, "investigator-driven" trials—studies developed by independent researchers—are also common, especially for research questions that are not necessarily of interest to the pharmaceutical industry.

The sponsor or trial initiator appoints a principal investigator (or investigators) to act as the researcher who supervises the trial (usually a doctor with experience running clinical trials). If a trial takes place at several locations across the country, the sponsor or initiator must appoint a site investigator—

again, usually a doctor—for each trial site. Each site also needs its own Research Ethics Board to approve the protocol before the study can begin.

Due to issues of confidentiality, drug companies did not always give community advisory committees the entire protocol. Instead, they provided a summary of the protocol along with the informed consent. Now that companies and advocates in the community have learned to trust one another we usually receive the full protocol just as any scientific review committee would. (Note: The CTN would not accept to review a protocol if the community reviewers only received a summary.)

INCLUSION/EXCLUSION CRITERIA

Most clinical trials restrict trial entry to people who meet certain criteria. Criteria is set for two reasons:

1) to ensure that people who are most likely to be harmed by potential side effects are excluded from the study; and

2) to reduce the variables that might confuse the results; volunteers should be of similar health status and taking similar medications outside the study.

Most inclusion/exclusion criteria in HIV and AIDS trials include a particular CD4 and/or viral load range, the presence or absence of a certain illness or condition, the use or absence of certain other drugs, among others. HIV trials may also be designed specifically for the following population groups:

- Naïve patients (patients who have no previous antiretroviral experience)
- Experienced patients (patients with previous antiretroviral experience)
- Patients with acute or early HIV infection
- Patients with chronic HIV infection
- Children
- Patients with co-infections
- Women
- Injection Drug Users (IDUs)
- Prisoners
- Men who have sex with men (MSM)
- Aboriginal peoples
- People from endemic countries

** Note: the above list is not inclusive and will follow the trajectory of the epidemic.*
Each inclusion/exclusion criterium must have a sound rationale, and be specific to the trial.

TYPES OF STUDIES

Researchers use a number of terms to describe the testing methodology of a clinical trial. Studies rarely fall into just one of the categories listed below. For instance, you usually won't hear a trial described simply as a comparison trial, whereas it is quite common for a trial to be a controlled, randomized, blinded comparison trial. These terms are defined and discussed below:

OBSERVATIONAL STUDIES

A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given). An observational study observes characteristics of a subset of a population(s) or a cohort.

RANDOMIZED

A study is randomized when participants are assigned to one of the study groups (also called "arms") by chance rather than by choice to prevent bias and to distribute individual characteristics evenly among study groups. A study can have two or more groups. In most cases, the randomized assignment is 1:1 (read one to one) and it gives all participants an equal chance of receiving either the experimental treatment or the standard-of-care treatment. However randomized assignment can also be designed to be 2:1, where participants have two chances out of three to be assigned to the experimental treatment group, and one chance out of three to be assigned to the other group.

CONTROLLED, COMPARISON

All clinical trials require specific rules to be followed by both researchers and participants to ensure clear and accurate results. These rules include having an experimental group (with the experimental treatment) and a "control" group against which to compare the experimental treatment.

Types of comparison trials

1. New vs. standard treatment

One group of participants gets the new treatment, while the other group gets the standard treatment. Researchers then compare the two groups to see which treatment works best. This is the most common type of comparison trial. For instance, when a new antiretroviral treatment is being tested, it is added to a standard backbone anti-HIV treatment, forming a new 3-drug antiretroviral combination. This new antiretroviral drug regimen is being compared to either a chosen standard-of-care drug regimen or any of the approved standard-of-care drug regimens.

2. New treatment vs. placebo

One group of participants gets the experimental treatment, while the other gets a placebo. A placebo looks, smells and tastes like the experimental treatment, but has no drug or active agent in it. A placebo trial is a quick, accurate way to assess whether the experimental treatment is better than doing nothing. **However, in Canada we consider it unethical to give a placebo to trial participants if a standard treatment is available.** A placebo is only used when a new treatment is added to the standard treatment, or when there is no existing standard treatment.

3. New + standard treatment vs. standard treatment alone, or + placebo

Researchers investigate whether adding a new treatment (usually a new drug) to a standard treatment (in HIV, usually a standard-of-care drug regimen) is more effective than the standard treatment alone.

4. Different-dose comparison

Researchers compare different doses of a particular treatment to see which works most effectively and has the fewest side effects.

In the early years of HIV/AIDS research, before the approval of the first antiretroviral drugs, clinical trials often compared an experimental treatment to a placebo in order to determine whether the new treatment was safer and more effective than no treatment at all. Now that a number of antiretroviral drugs have been approved for use in combination therapy, the only drug trials that include a placebo are those examining a drug from a new class of antiretroviral drug. In such cases, all participants receive a standard drug regimen, with either the experimental drug or a placebo added to that regimen. In preventative vaccine and microbicide trials, on the other hand, testing against a placebo is still the norm. Since no treatments have been approved for HIV prevention, placebo trials are considered an ethical method of testing new prevention options. However, these trials must have special ethical considerations, should they harm or infect people.

BLINDED

Types of blinded trials

1. Single-blinded

Single-blind trials are those in which researchers know which treatment participants are getting but the participants do not.

2. Double-blinded

In double-blind trials, neither researchers nor participants know who is getting the experimental treatment and who is getting the standard treatment.

The purpose of blinding is to make sure that biases do not affect the results of the trial. For example, if a researcher knows which participants are receiving a particular treatment, it may influence the way the researcher views those participants. Without blinding, researcher expectations may affect the outcome of the trial. If a trial is not blinded, it is often because one of the treatments causes obvious side effects (such as having a strong taste or turning urine a bright colour).

THE FOUR PHASES OF CLINICAL TRIALS

To get government approval to test an experimental treatment on humans, the trial sponsor must submit to Health Canada all the information they have obtained on the experimental treatment in previous *in vitro* (test-tube) and animal studies, and demonstrate that the treatment is safe enough to be tested in people. The sponsor must also submit a protocol to Health Canada. If Health Canada approves the protocol, researchers can begin clinical trials. Clinical research on a new treatment usually goes through four phases, although in HIV and AIDS research, some of the phases are sometimes combined to speed up the process. (Note: While new drugs and vaccines must be tested through the four-phase framework, some methods of treatment—including certain treatment management and adherence strategies, and non-pharmaceutical methods of addressing drug side effects—do not. In such cases, however, researchers will often conduct a pilot study. This very small, exploratory trial sets the direction for future clinical research on the experimental treatment before developing a larger trial aimed to inform health and healthcare practices.

If a trial shows that the drug is neither safe nor effective during any phase of clinical trials, the trial is stopped.

The four phases of clinical trials are as follows:

Phase I — Safety and dosage range trials
Researchers give the new treatment to a small number of people (healthy volunteers and/or people without the disease in question) to study how it is processed by the body. Researchers generally begin in single doses that are gradually increased. Phase I trials are riskier than later phases because, in general, little is known of the treatment's effects on humans. Phase I trials are short, usually no more than two or three months, and generally involve 20-100 participants.

Phase II — Early safety and efficacy trials
If a new treatment is found to be safe enough in Phase I, a Phase II trial may proceed. Researchers test the treatment over a longer period of time in a larger number of people who are living with the disease to see if it is working, to determine the most effective dose, and to learn its side effects and toxicities. If researchers find that the treatment is not working against the disease at this point, the trial will be terminated. Phase II trials span a few months to a year, and involve 100-300 participants.

Phase III — Large scale comparative trials
If the treatment seems to work in Phase II, researchers test it in a much larger group of people (usually 400-800, though in some cases thousands), generally for at least 48 weeks, to see if it remains effective or has any side effects or toxicities that only show up after a longer period of time. Researchers also compare new treatments with treatments that are already in use. If the treatment is successful at this point, the manufacturer may apply for marketing approval from Health Canada.

Why stop a trial early?
Sometimes, the discovery of new risks associated with a particular treatment or combination of treatments leads to the early closure of a trial. For example, in 2003, the CTN's Safety and Efficacy Review Committee decided to close a Network study of combination therapy for people co-infected with HIV and hepatitis C after the U.S. Food and Drug Administration issued a new report that advised against the co-administration of two of the study treatments, ddI and ribavirin. In other cases, one treatment shows to be superior to the other, and thus it is unethical to give the inferior drug to one group of participants. Stopping a trial early may also be due to poor enrolment and lack of funding.

In HIV and AIDS, Phase I and II or Phase II and III are often combined in one protocol, with a stepped process.

At the end of each phase of testing, researchers must receive approval from Health Canada before they can move to the next phase. Once researchers have finished testing a treatment and it appears to be both safe and effective, the pharmaceutical company applies to Health Canada for review to obtain full approval or approval with conditions to promote or sell the treatment. The company must provide all the results from any clinical trials. Based on this scientific evidence regarding the safety, efficacy and quality of the new treatment, Health Canada decides whether to allow the new treatment to be marketed, under which circumstances, and whether with conditions. A Notice of Compliance (NOC) is an authorization to market a drug in Canada. In some cases, the NOC is conditional on the sponsor undertaking additional studies to verify the clinical benefit.

A word of warning: just because the federal government approves a new treatment does not necessarily mean it is effective or safe for all people at all times. Approval only means that the benefits of a treatment have outweighed the risks in a majority of people within a clinical trial setting. In Canada, for the monitoring of drug safety in the general population, we rely on information about the drug experience through post-approval surveillance.

Phase IV & Post-marketing trials

Once a treatment is approved, pharmaceutical companies should conduct "post-marketing" trials to monitor drug performance and frequency of side effects, as these may be different in a "real world" setting compared to a clinical trial setting. In other Phase IV trials, independent researchers test different strategies for treatment and/or prevention. They also test for risky interactions with drugs and other substances. From a community perspective, not enough Phase IV trials are being carried out.

Phase	Duration	# of Participants	Questions asked about drug
I	A couple of weeks to a couple of months	Small group	· What is the maximum safe dose? · Is it safe enough to test in more people?
II	Several weeks to several months	Larger group	· What is the most effective dose? · Does it work? · Are there any side effects?
III	Several months to several years	Much larger group	· How well does it work long-term? · Are there any long-term side effects? · Is it better than current treatments?
IV	Years	Drug approved, in widespread use	· Are there side effects that only show up years later?

MONITORING CLINICAL TRIALS

The conduct of clinical trials is regulated by Health Canada, which has adopted the Good Clinical Practice (GCP) guidelines developed by the International Committee of Harmonization. The Health Canada publication *Good Clinical Practice: Consolidated Guidelines* gives a detailed list of the responsibilities of investigators, sponsors and Research Ethics Boards. In 2003, Health Canada started conducting routine inspections to ensure that clinical trials are conducted according to good clinical practice. Researchers are expected to put assurances in place to ensure the integrity of the data being collected. This is normally done by arms-length monitoring organizations.

STOPPING A TRIAL EARLY

In the protocol, researchers estimate how long the trial needs to last to demonstrate the trial's hypothesis. Trials can last anywhere from a few weeks to several years. In the case of many large clinical trials, a data and safety monitoring board (a group of independent researchers and lay people) checks regularly on the results of the trial while it is taking

place. If it finds that one group of participants is doing much better than another group, it can recommend that the trial be stopped earlier than planned so the best therapy can be offered to all participants. The board can also recommend that a trial be stopped if one group of participants develops serious side effects.

CLINICAL TRIALS IN HIV INFECTION

WHAT TREATMENTS DO HIV AND AIDS CLINICAL TRIALS TEST?

Researchers are conducting HIV and AIDS clinical trials that fall into the following categories:

1. Antiretrovirals — different classes of antiretroviral drugs fight HIV at different stages of its lifecycle in order to stop or delay damage to the immune system. Drug resistance and toxicity continue to stimulate the demand for new classes of drugs and new options in existing classes.

2. Methods of preventing HIV infection — vaccines designed to develop immunity to HIV, or topical applications such as microbicides that inhibit HIV transmission

3. Therapeutic vaccines — vaccines designed to boost the immune response to HIV in people already infected with the virus

4. Immunomodulators or immunostimulators — drugs that improve or strengthen the immune system

5. Therapies for co-infections — drugs and other treatments for diseases such as hepatitis C, hepatitis B and the human papilloma virus, in people who also have HIV

6. Treatment strategies — strategies for optimizing HIV care and minimizing costs, including treatment interruptions, drug-class sparing regimens, monotherapy (one drug only) for people with viral suppression, and psycho-educational sessions for better adherence to treatment

7. Therapies for side effects and toxicities — drugs and non-pharmaceutical methods of regulating and minimizing drug side effects such as insulin resistance, dyslipidemia, lactic acidosis, lipodystrophy, liver damage, renal damage, heart disease, and depression

8. Complementary and nutritional strategies for optimizing HIV therapy or for better health

9. Treatments for HIV-related opportunistic infections (such as tuberculosis) and cancers (non-Hodgkin's lymphoma or Kaposi's sarcoma, for example)

10. Gene therapies — researchers are trying to find a gene that may provide immunity to the HIV virus

HOW DO RESEARCHERS EVALUATE RESULTS?

Researchers use categories of data called clinical endpoints to determine outcomes. Sometimes, hard clinical evidence such as whether the volunteers in the experimental study group live longer than the volunteers in the control group serves as the main endpoint of a clinical trial. However, to speed up the process researchers often evaluate the effects of HIV therapies using what's known as a surrogate marker. A surrogate marker is a substitute measure used to predict the eventual effect of a therapy when no other direct measure is immediately available or feasible.

CD4 count and viral load are the two most common surrogate markers used in HIV research. The CD4 count, a blood test that measures a specific subset of white blood cells targeted by HIV, allows doctors to evaluate the health of the body's immune system. No change or a dropping CD4 count is a sign of progressing HIV disease. An undetectable viral load (less than 50 copies/ml) indicates that HIV is controlled within the blood. However, HIV is also in other parts of the body that the antiretrovirals do not penetrate, such as the brain, gut, and testes. These and other sites are known as reservoirs for HIV. A rising or high viral load (more than 1,000 copies) indicates that the therapy is not optimal, which can lead to resistance mutations.

In HIV-related trials involving treatment methods other than antiretroviral therapy, other clinical endpoints often come into play. For example, in a trial

of a preventative vaccine or microbicide, researchers evaluate effectiveness by comparing the rates of HIV infection in the different study groups. In a lipodystrophy trial, researchers measure lipid levels (the amount of fat and fat-like compounds in the blood) and body fat to determine a treatment's effectiveness.

Often, the data categories that serve as the trial's endpoints or surrogate markers of a trial are also used in the trial's entry criteria to ensure that volunteers are of similar health status when they begin the study.

Antiretroviral drugs have proven very effective at reducing the amount of HIV in the blood. However, the often harmful side effects and toxicities associated with antiretroviral therapy, along with the complicated dosing schedules of some drugs, make it difficult for people to adhere to their medications. Poor adherence in turn can lead to drug resistance. Clinical researchers are studying a variety of strategies to address and reduce these complications. To learn more visit the CIHR Canadian HIV Trials Network website at www.hivnet.ubc.ca.

NOTES

3 PARTICIPANT RIGHTS & INFORMED CONSENT

THIS CHAPTER WILL FOCUS ON:

- the informed consent process;
- the importance of informed consent;
- the rights of participants in clinical trials;
- general risks and benefits of participating in a clinical trial;
- the elements of a typical informed consent form; and
- the questions you should ask when reviewing an informed consent form as a member of a community advisory committee.

INFORMED CONSENT BASICS

WHAT IS INFORMED CONSENT?

Informed consent is a process whereby the purpose, methods, risks and requirements of a trial are clearly explained to a clinical trial volunteer or potential participant so that he or she can make an informed decision about whether to participate in the trial.

If a potential participant meets the study entry criteria and is strongly considering taking part in a trial, he or she will be asked to give informed consent. The informed consent form should fully explain in plain language (readable by most people, even people with a low level of literacy) the trial as well as the possible risks or dangers of participating. The form must be signed by the potential participant, a witness and the principal investigator or designated study staff.

IMPORTANCE OF INFORMED CONSENT

From a participant's perspective, the informed consent form is the most important part of a protocol because it helps to protect his or her rights. Participants in clinical trials should not confuse treatment with trial participation. In treatment, the doctor's main goal is to look after the

interests of the patient. In a clinical trial, the researcher's priority is to gain knowledge about a new therapy, although within a carefully controlled environment to minimize any risks to the individual. Therefore, the informed consent should clearly explain which aspect(s) of the trial is experimental and which is considered standard-of-care.

WHEN IS CONSENT INFORMED?

Consent is considered informed when a potential participant:

- has all the information needed to make a decision about enrolling in a trial;
- fully understands this information; and
- agrees to participate in the trial based on this knowledge.

Once the requirements of informed consent are met, and if the potential participant meets the broad inclusion criteria for the trial, he or she will be asked to sign the informed consent form before being enrolled in the trial.

As part of the informed consent process, potential participants are usually given an information package that outlines:

- the reasons for doing the trial;
- the experimental treatment and any other treatments administered as part of the trial;
- the potential risks, discomforts and side effects of the study treatments;
- the number of visits participants will be expected to make to the trial site;
- the amount of time, per visit, that participants will be expected to spend at the trial site;
- the types of tests that will be performed; and
- the alternative treatments available outside the particular trial.

Before they sign the consent, potential participants should be allowed to spend time reviewing the information in the form, to discuss the study with the trial nurse and/or doctor, and to consult with a community group and/or friends and family members. They may need literacy help, or even an interpreter, and someone to take them through the trial. They should be made aware that informed consent is an ongoing process that does not end after they have signed the form. Researchers have a responsibility to give participants any new information about the study treatment(s) or the trial as it arises. Even after they sign an informed consent form, participants can change their minds at any time and leave the trial whenever they want without compromising their future access and right to health care.

PARTICIPANT RIGHTS

Clinical trial participants have certain rights that you should keep in mind when reviewing protocols and informed consent forms. The following list provides an overview of the major rights of participants in clinical trials, as described in Canada's Tri-Council Policy Statement, the international Good Clinical Practice guidelines and the Declaration of Helsinki.

Clinical trial participants have the right to be:

- given an explanation of the nature and purpose of the research;
- given an explanation of the nature of participation, including procedures that are to be followed and any treatment that is to be administered;
- informed of the probability of being randomly assigned to each study arm;
- informed of the expected duration of participation;
- given a description of the reasonably foreseeable risks that may arise from participation in the study, as well as the potential consequences (physical or psychological harms) of a failure to comply with the requirements of participation;
- given a description of the reasonably foreseeable benefits that may arise from participation in the study;

- informed of alternative treatments or procedures that could serve as an option to participating in a clinical trial, and their important potential risks and benefits;
- given the opportunity to decide to consent or not to consent voluntarily, without manipulation, coercion or undue influence;
- given time to contemplate their participation in the study and the opportunity to ask questions about the research or any of the procedures involved throughout the study's duration;
- given access to a qualified designated representative who can explain scientific aspects of the study;
- assured that they are free to withdraw from the study at any time without penalty or loss of benefits, and that they will be given ongoing opportunities to decide whether they wish to continue to participate;
- informed of any new information about the study treatment(s) or other aspects of the research as it arises;
- provided with adequate medical care for adverse events during and following participation in the study;
- assured that should it be beneficial, experimental treatment will continue to be provided after the end of the study and until it is covered by the provincial reimbursement plan or private insurance;
- assured that their records will be kept confidential and that if the study is published, their identity will remain confidential unless otherwise required by law;
- informed of the identity of the researcher(s) and the funders of the study and of any potential conflict of interest between investigators, institutions and/or sponsors involved in the study; and
- provided with a copy of the signed and dated consent form.

During the review process, committee members should request further explanation of any issue that is not clear so as to best represent the interests of trial participants.

PROS AND CONS OF PARTICIPATING IN CLINICAL TRIALS

HIV and AIDS clinical trials involve both positive and negative aspects. While each trial may be different, there are general positive and negative aspects that must be understood by potential research volunteers:

Clinical trial participation is sometimes associated with the opportunity to access a new therapy, but it's important to remember that while a trial may yield such a benefit, there is no guarantee. The primary motivation for enrolling in a trial should always be altruism. In other words, individuals should choose to participate in order to help others living with HIV in the future by contributing to the advancement of clinical knowledge.

General positive aspects

- being one of the first to benefit if an experimental intervention proves to be effective;
- potentially receiving specialized care and closer follow-up that are a part of the clinical trial process (remember, providing health care is not the purpose of a clinical trial);
- participating in a process in which new therapies are developed and medical knowledge is advanced to help others living with the disease; and
- having the opportunity to be empowered by either choosing or not to participate in clinical trial(s).

General negative aspects

- having no guarantee of a personal benefit from the trial;
- experiencing potentially life-threatening side effects (some side effects are not immediately apparent in the early stages of a trial);
- having to stop taking other medications that are working well because they conflict with the requirements of the trial;
- potentially not being eligible for other trials of the same or similar treatments (for e.g., naïve trials);
- not knowing if you are receiving the experimental or standard treatment (in a randomized, blinded study);
- having to make changes in lifestyle, such as taking medication at very regular intervals, with a meal, or on an empty stomach; and
- possibly having to make frequent, lengthy visits to clinical sites for checkups and testing.

ELEMENTS OF A TYPICAL INFORMED CONSENT FORM

The consent form informs the participant of all the relevant points in the study plan (or protocol) one needs to know to make a decision about whether to join a clinical trial or not. As a community committee member, you should check to make sure that the form is easy for prospective participants to understand and does not sound legalistic or patronizing. You should ensure that the form gives the participants all the information they need to make an informed decision, and that it does not exert any undue influence to give consent.

An ethically acceptable informed consent form must include the following elements or sections. Forms can vary slightly, so the elements may not appear in the same order as listed below, and some elements may appear under different headings.

NAME OF STUDY AND PRINCIPAL INVESTIGATOR

This section must list the name and the telephone number of the physician who is the principal investigator of your site, the full title of the protocol, and a 24-hour emergency telephone number for trial participants.

A model Informed Consent form is available for download in the Research Services section of the CTN website (www.hivnet.ubc.ca). The document includes suggested phrasing and structure for many of the requirements described below.

INTRODUCTION

This section usually states what is being studied and what kind of trial it is, as well as who is conducting the research and who is sponsoring the research. All names of the treatments (e.g., pre-approval code name, generic name and/or trade name) used in the trial should be provided on first mention.

PURPOSE AND DESIGN

Researchers explain why they believe the clinical trial is important and what they hope it will accomplish if it is successful. For example, they may

hope to learn if a combination of drugs can improve the immune system, lessen side effects or optimize adherence.

This section should also explain how the researchers plan to test the experimental treatment; in other words, it should explain the study design. The explanation must include the total number of volunteers to be enrolled; the number of trial sites (within Canada or internationally); the number of study groups (also called "arms") involved; how participants will be assigned to the study groups (e.g., randomly); whether the study is single blinded, double blinded or open label (and what these terms mean); the probability of receiving one treatment versus another; and, if applicable, the procedures for initiating and breaking double-blinded allotment.

Many people have trouble understanding probability, so the informed consent should instead use frequency when explaining how participants will be assigned to the study groups. For example, rather than saying that each participant has a 50/50 chance of being assigned to the experimental group or the control group, the informed consent should state that five participants will receive the experimental treatment and five will be in the control group.

For a basic introduction to probability, try the probability lesson featured on the Math Goodies website <www.mathgoodies.com>.

This section may also include background information on the study, as well as an evaluation of the safety and effectiveness of the proposed research. Researchers should emphasize that the research is experimental and that there are no guarantees of benefits.

INCLUSION/EXCLUSION CRITERIA

This section outlines the conditions that potential participants must meet to take part in the study (inclusion criteria) and the conditions by which potential participants will be disqualified (exclusion criteria). For example, an HIV clinical trial may require participants to have a CD4 count or viral load within a specific range. Many trials do not allow women who are pregnant or breastfeeding to join.

METHODS/PROCEDURES

This section describes the procedures that must be followed by participants if they qualify for the study. Experimental procedures should be clearly identified, and the importance of following all trial procedures should be emphasized. The description should outline the following:

- frequency and duration of visits;
- amount of blood to be drawn (shown in millilitres and teaspoons or tablespoons) for testing;
- other tests to be done, including details of all invasive procedures;
- types and dosages of medication(s) to be taken;
- form of treatment (e.g., injection, pill, liquid); and
- special instructions on how to take the study medication(s), such as scheduling, food restrictions or requirements, and the storage of drugs.

LENGTH

Researchers should specify the duration of the study, as well as the time commitment expected of participants. A trial may last two days or several years. Participants may have to make only a few short visits to the trial site, or they may have to make frequent, lengthy visits.

POTENTIAL BENEFITS

Researchers should always include a sentence stating that no benefits are guaranteed because the research is experimental. The consent form should not include explicit or implicit claims of effectiveness that will bias participants, nor should it include overly optimistic representations, as these can be misleading. The following examples demonstrate this kind of overstated and coercive language:

- "Drug A may be helpful in treating HIV disease and may make you feel better."
- "You will receive Drug A free of charge as long as you are part of the programme."

POTENTIAL RISKS, SIDE EFFECTS AND HARMS

This section should describe any reasonably foreseeable risks or discomforts

to the participants. It should note whether previous research studies (on animals, as well as humans) revealed side effects and whether or not they were reversible. If the risk posed by the experimental treatment is unknown, this should be stated. If available, information on other, similar treatments should be provided. It should be stated that long-term side effects may not be known or other unknown side effects could also occur.

This section should also state that taking part in the study could prevent participation in future studies due to exposure to the study treatment because exposure to the study treatment will make you no longer naive to that class of drugs. For antiretroviral drug trials, this section should state that exposure to the study drugs may make participants resistant to other drugs of the same class if you are getting a suboptimal dose or do not take the drugs as prescribed. This section should also mention that failure on the participant's part to follow the study's dosing schedule might lead to drug resistance. For instance, resistance could develop if a participant misses pills or takes them at the incorrect time.

Finally, any foreseeable harms—physical, emotional, psychological, social, legal, financial and so on—should be noted. The section should state that participants are entitled to and should receive updates about risks, side effects and potential harms as information becomes available.

POTENTIAL DRUG INTERACTIONS

This section may appear in the informed consent form's description of risks. It should list the drugs that participants are not permitted to take due to negative interactions, including street drugs and alcohol, if applicable. The list of street drugs should use street names and generic names. Over-the-counter medications, including complementary therapies, herbal and vitamin supplements, as well as any foods that may interact with the study drugs should also be listed.

The section should list the known side effects that could result from potentially dangerous drug interactions. If any previous studies revealed side effects, researchers must disclose the percentages of participants who had any drug reactions.
As well, this section should note whether there are any known or potential interactions with oral contraceptives which might make them ineffective

as a means of birth control. Make sure that the level of detail provided in the protocol on this subject is appropriately transcribed in the informed consent form.

This section should also instruct readers that throughout the study, participants are asked to inform the study coordinator or investigator of any changes in their medications, including over-the-counter medications, vitamins and herbal medicines or remedies, and other complementary therapies and supplements.

As a reviewer, if you are not familiar with a particular drug, you should

Many people with HIV and AIDS choose to take herbal supplements to improve their immune system or to address side effects of HIV treatment. However, some combinations of herbs and drugs can prove extremely dangerous. For example, St. John's wort, which is often used to treat mild to moderate depression, should not be taken with any protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI), because these combinations can decrease the amount of antiretrovirals in the blood up to 90%, which can quickly lead to resistant mutations in HIV. Grapefruit juice can do the opposite, it increases the amount of drug which can increase side effects of this class of drugs. For similar reasons, a large quantity of raw or processed garlic should not be taken with any protease inhibitor. Some people do not think to tell their physicians about the herbal supplements they are taking, since they do not realize that mixing herbs and drugs can sometimes be harmful. So, it is particularly important that a study's informed consent form warns candidates about risky herb-drug combinations.

Further reading: A Practical Guide to Herbal Therapies for People Living with HIV. Toronto: Canadian AIDS Treatment Information Exchange (CATIE), 2004.

ask what the risk is of allergic reactions, side effects and drug interactions. If the drug is unknown and one of the aims of the protocol is to determine its safety, participants should be warned about this in the informed consent form. As well, you should check to see if the protocol includes adequate strategies to monitor adverse side effects.

CONCEPTION, PREGNANCY AND CHILDBEARING POTENTIAL

This section should state the risks associated with the study treatment(s) and pregnancy, including all available information about the potential risk of fetal toxicity. If no relevant information is available, a statement should explicitly note the potential for fetal risk. Risks of breastfeeding should also be stated, as well as risks to the sperm of male participants,

if known. If these risks are unknown, this should be stated. It should be recommended that all participants who choose to continue taking the experimental treatment after the study should keep using acceptable methods of birth control.

DISCLOSURE OF OTHER SOURCES OF TREATMENT

Researchers must disclose approved treatment options and other experimental research that might be of use to participants and that no treament is also an option. For example, there are several effective combinations of antiretroviral drugs approved by Health Canada to treat HIV. If there are no other treatments available, this should be stated. There should also be a sentence advising participants that they will be told about any new therapies that become available during the course of the study.

PARTICIPATION IN CONCURRENT STUDIES

An optional section, this states that participants should not take part in any other research study without advising the researchers. It is included to protect participants from possible injury due to extra blood drawing, extra x-rays or interaction of research drugs. Participants choosing to participate in another study may be asked to leave the trial. Participating in other research studies may confuse research results, making the data collected on participants difficult or impossible to evaluate. However, participating in other studies is often an exclusion criteria confirmed at the outset of a trial.

REIMBURSEMENT AND COMPENSATION

This section should include information on financial costs to the individual participating, and should explain whether and how he or she will be reimbursed for costs associated with treatment, travel and childcare. (Note: All trials under the CTN cover treatment, travel and childcare costs.) As well, for research involving more than minimal risk, there should be a statement of whether any compensation or medical treatment is available if injury occurs during the course of the trial and, if so, where to get further information about this. There may also be a section that clarifies whether the participant's family will be compensated if this individual dies or becomes disabled as a result of participating in the trial. If no reimbursement and/or compensation is offered, this should be stated.

PARTICIPANT WITHDRAWAL

This section should state that participation in the study is voluntary, and that participants are free to leave the study at any time without penalty or loss of benefits to which they are otherwise entitled.

LEAVING THE STUDY EARLY

This section should outline the health consequences of a participant's decision to leave a trial, as well as the procedures involved in leaving a study early (for example, the investigator may ask for a final visit to the clinic to close the file). The section should state clearly that a participant is under no obligation to follow any procedure to leave the trial. However, there may be instances where sudden withdrawal may have harmful effects on the participant's health. In these cases, the informed consent form should clearly explain the details and necessity of any special withdrawal procedures that are required for the participant's safety.

CIRCUMSTANCES UNDER WHICH PARTICIPANTS MAY BE ASKED TO LEAVE A TRIAL

This section should state the circumstances under which participants may be asked to leave a trial. Participants should be told that if they fail to follow the instructions given to them by the researcher, they might be asked to leave. For example, participants may be asked to withdraw from the trial if they miss three consecutive visits to the trial site without reasonable explanations given to and acceptable by the researchers, do not adhere to the medication schedule, or become pregnant.

CONTINUED ACCESS

This section should indicate which of the study treatments will continue to be made available to participants once the trial is over and for how long, as well as whether they will be available free of charge. If the trial in question is a Phase II trial and participants received a benefit, they should be allowed to "roll over" immediately into subsequent further studies. If it is a Phase III trial, participants must have continued access until the drug is approved by Health Canada and appears on the provincial reimbursement plan or is covered by private insurance. This section should also indicate whether or not participants will continue to have access to the treatment if they withdraw from or are asked to leave the study.

DISCLOSURE OF RESULTS

This section should explain to participants that researchers will inform them about any new findings on the effects of the drug promptly. This section may also specify whether and how participants can find out the results of the trial after it is completed.

CONFIDENTIALITY

This section should describe the extent of the confidentiality (privacy) of records that identify participants. A sentence should state that any data published in scientific journals will not reveal the identity of participants, or that all information collected during the course of the study will be confidential unless otherwise required by law. A description of how confidentiality will be protected should be provided. For example, the research staff may choose to use codes rather than names on documents and labels.

Agencies or organizations in Canada or abroad that may have access to the data—such as Health Canada, the United States Food and Drug Administration, the U.S. Patriot Act and its access to personal medical records, a drug company or a data safety monitoring board—should be named. It should be stated if, and when, any agency would have access to study data by participant's name (rather than by ID number or birthdate).

FUTURE RESEARCH

This section should explain that explicit consent from participants is required before investigators may use the information or samples collected in the trial for research extending beyond the scope of the study.

INCENTIVES AND CONFLICTS OF INTEREST

Any incentives that the investigator, the participant's physicians or the research institution might receive for recruitment of participants and any other possible conflicts of interest should be described.

CONTACT PERSON

A standard section on most forms, this provides participants with the name and number of a study coordinator whom they can contact if they have any questions about the trial. Failure to provide a contact person

for the trial restricts opportunities for participants to ask questions. The inclusion of this section is usually a good indication that researchers are trying to keep participants informed. The name and number of a 24-hour emergency contact must also be included.

This section may also include the name and number of a person that participants can contact to ask questions about their rights. To avoid conflicts of interest, this contact should not be connected to the research study in any other way.

SIGNATURE AND COPY OF INFORMED CONSENT

This is the "bottom line" of the informed consent form. Signing the form means that the participant has read and understood the information, and has decided to participate based on the information provided. It should be clear within this section that the consent form is not a contract and the participant does not give up any legal rights by signing it. A sentence should restate that the participant can leave the study at any time. Another sentence should note that researchers will give a copy of the signed informed consent form to participants.

The signature page should have a checklist of important things participants should be aware of, including key protocol-specific issues (for example, "I understand that tuberculosis is a life-threatening disease"). The document should have the full trial title at the top and be formatted so that the checklist fits on the page with the signatures of participants.

Note: See the sample signature pages provided in the Model Informed Consent form on the CTN website at www.hivnet.ubc.ca.

QUESTIONS TO ASK ABOUT INFORMED CONSENT FORMS

This section discusses some general issues that you should consider when

reviewing an informed consent form to ensure that it is written in a way that sufficiently respects the rights of the participants.

INVITATIONAL PHRASING

Informed consent forms should avoid invitational phrasing (e.g., "You are *invited* to participate…") which gives the impression of an exclusive opportunity from which participants will benefit. Instead, it should say something like, "You are being asked to take part in an experimental study."

PLAIN LANGUAGE

Is the form easily understandable to the average person? Researchers are sometimes under the mistaken impression that because they can understand a consent form and the accompanying trial information, potential participants will also understand it. This is not always the case. Studies have shown that information about clinical trials is often written well above participants' education level. Informed consent forms should be written in plain, clear language. Eighth-grade English (the Canadian average, and the level of many daily newspapers) is appropriate. Participants should be addressed in the second person (i.e., "you") in order to acknowledge and make clear their role in the trial. Technical and scientific words must be adequately explained and common terms substituted for complex scientific terms whenever possible. For example, instead of using the term "hepatic," researchers can use the phrase "relating to the liver," or both.

TRANSLATIONS OF INFORMED CONSENTS

Informed consent forms must also be written in a language that is understandable to the participant or his or her representative. It is unethical to enroll a participant who may not understand the information provided due to a language barrier. When a study population includes people who do not speak English, researchers must provide translated copies of the informed consent form. If the interview is conducted in English, consent should also be in English. If it is conducted in another language, consent must also be in that language. Those who speak and understand English, but do not read and write it, can enroll in a study by "making their mark" on the consent document. An impartial person should witness the explanation of the study to the participant. (Note: Of course, the same principles apply for trials in which the primary language

used is French.)

DISCRIMINATORY INCLUSION/EXCLUSION CRITERIA

Are any of the inclusion or exclusion criteria discriminatory? Individuals cannot be excluded from a trial because of race, religion, ethnicity, national origin, sex, age, sexual orientation, disability, another medical condition (such as hemophilia) or history of drug or alcohol use, unless there is a scientifically valid reason.

CONFLICT OF INTEREST

Are conflicts of interest evident in the form? As a clinician, the physician has only the best interests of the patient in mind. However, as a researcher, the physician is primarily interested in studying the effectiveness of an experimental treatment, and may lose sight of the participant's needs. Is someone other than the investigator available to discuss the trial with the participant? Are participants told that the Medical Doctor is an investigator?

Some forms of discrimination in clinical trial entry criteria are obvious, such as trials that explicitly exclude women. However, subtler forms also exist. For example, not providing reimbursement for transport and childcare may prevent women to participate in a study due to domestic or child-rearing responsibilities. Or, the exclusion of drug users is often based on a perception of unreliability. The reasons for excluding drug users must be a safety or efficacy concern.

EXAGGERATION OF BENEFITS

Does the form contain any unjustifiable assurances or claims of effectiveness, implicit or explicit, that may make participants overly optimistic? Researchers should not overstate potential benefits associated with a clinical trial like "results are fairly positive."

You should advise participants to be skeptical about a clinical trial that claims to have no possible risks, as this is rarely true of any treatment, much less an experimental one.

As a reviewer, you can ask that participants be provided with take-home documents outlining all the known information about the experimental treatment that they can read at their leisure.

PATRONIZING LANGUAGE

Does the form use condescending language? It is inappropriate to use words or phrases that imply that the researcher knows better than the participant what is in the participant's best interests. Researchers should not treat participants as if they are children who do not understand the nature of their illness or their treatment options.

INAPPROPRIATE LANGUAGE

Does the form use alarmist or judgmental language? For example, using the term "devastating" when discussing the results of an experiment could be viewed as alarmist and insulting. An example of judgmental language is using the term "intravenous drug abuser" rather than the more neutral "intravenous drug user."

The form should also use the term "volunteer" or "participant" rather than "subject" or "patient." Subject or patient implies a passive kind of involvement whereas participant or volunteer implies an active engagement in the research process.

OTHER SOURCES OF TREATMENT

Does the form mention other treatment options? Participants considering enrolling in a clinical trial as a way of obtaining a new treatment should make sure they are not missing out on other options in order to take part in a trial whose benefits are unclear. Participants need to be informed that joining a clinical trial is not the only way to gain access to experimental treatments.

Ethical standards require that researchers mention other ways of getting these treatments. Two common options are expanded access programmes and—more rarely in the case of HIV therapies—Health Canada's Special Access Programme (SAP).

EXPANDED ACCESS PROGRAMME

Is the experimental therapy available through an expanded access programme (sometimes referred to as a "compassionate access

programme" or an "open-label programme")? A company sponsoring a clinical trial may also release a limited amount of an experimental treatment through such a programme, which allows participants to use experimental treatments without taking part in a clinical trial. In expanded access programmes, the experimental treatment is not tested against a standard treatment, however, safety data is being collected.

Expanded access programmes are usually limited to people who do not meet a clinical trial's entry requirements or who do not wish to participate in a trial. However, participants may still have to meet certain requirements, such as having a CD4 count below a certain level or a viral load above a certain level.

SPECIAL ACCESS PROGRAMME (SAP)

Through the SAP, Health Canada decides whether to allow access to some treatments that are not yet approved in Canada. Access is granted on an individual emergency basis for people with serious or life-threatening conditions, when conventional therapies have failed, are unsuitable or unavailable. Anyone who wishes to receive a treatment through the SAP must have his/her doctor contact Health Canada.

Just because a treatment is available through the SAP does not mean it is safe. The SAP is an emergency programme. Companies are not required to provide experimental treatments through the SAP, and may charge a fee for the treatment or even its full future retail cost.

OTHER ACCESS OPTIONS

Anyone interested in a particular experimental treatment or treatment strategy should ask a physician to look into the various options for access outside a clinical trial. One can also approach pharmaceutical companies directly to provide a drug as a short term bridge to its broader availability on the market.

UNNECESSARY BURDEN/COST TO PARTICIPANTS

It is standard practice that the cost of all treatments and lab procedures is covered by the trial itself, the company or organization that developed

the experimental treatment, or provincial health insurance. It is unethical to offer payment incentives for clinical trials in Canada. However, sometimes an honorarium is offered, the amount of which usually reflects the inconvenience of procedures that are more time consuming in comparison to a "regular" study visit (e.g., daily drug infusions). Typically, the honorarium is small. But in very rare cases, when a trial has extraordinary requirements (extremely time-consuming or inconvenient procedures), a larger honorarium may be offered in recognition.

Trials sponsored by the CTN must also state that reasonable childcare and travel expenses will be covered.

During the 1990s, thousands of Canadians accessed potentially life-saving, though unlicensed, antiretroviral drugs such as 3TC and saquinavir through expanded access programmes. These and many other effective drugs are now licensed for use in combination therapy. However, while there is less demand for unlicensed drugs, expanded access programmes are still an important treatment access option. Without such programmes, people who do not have many treatment options for their HIV may feel they have no choice but to participate in a clinical trial, a situation that compromises the ethical standards of clinical research.

NOTES

4 SAMPLE INFORMED CONSENT FORM *Exercise*

THIS CHAPTER PROVIDES AN OPPORTUNITY FOR YOU TO APPLY WHAT YOU HAVE LEARNED IN THE PRIMER. YOU CAN:

- read through an actual informed consent form that was reviewed by the CTN's Community Advisory Committee;
- perform your own review of the informed consent form using the checklist provided; and
- check your work against the CTN's Community Advisory Committee review.

This hands-on chapter will take you through an informed consent form for a clinical trial of the drug citalopram for the prevention of depression in HIV/hepatitis C co-infected individuals starting treatment for hepatitis C. You will find a checklist after the informed consent form that you can use for your own review. The actual community review, performed by the CTN's Community Advisory Committee, is at the end of the chapter.

- Sample Informed Consent Form
- Checklist
- Sample Review

NOTES

Centre universitaire de santé McGill
McGill University Health Centre

SERVICE D'IMMUNODÉFICIENCE
HÔPITAL ROYAL VICTORIA HOSPITAL
IMMUNODEFICIENCY SERVICE

Participant Informed Consent

Title: A Randomized, placebo-controlled trial of citalopram for the prevention of depression and its consequences in HIV-Hepatitis C co-infected individuals initiating pegylated interferon/ribavirin therapy

Sponsors: Canadian HIV Trials Network
Canadian Institutes of Health Research

Principal Investigator: Marina B. Klein, M.D.

Study Site: Montreal Chest Institute
3650 St-Urbain
Montreal, Que

INTRODUCTION

You are being asked to take part in a medical research study. Before deciding whether or not to participate, you should take the time to read this document very carefully and to ask as many questions as you need. The goal of this process is informed consent. Informed consent assures that you will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate.

You are being asked to participate in this study, involving a combination of medications, because you are infected with both the human immunodeficiency virus (HIV) and the Hepatitis C virus (HCV) and your doctor feels that you should receive treatment for HCV. This consent form will provide you with detailed information about the research study, about the study medications, what will be expected of you, how often you must visit the clinic, the risks you might face and the possible benefit to you if you participate. Please feel free to ask the study investigator or nurse about any words that you do not understand.

Your decision to participate in this study is entirely voluntary. Refusal to take part will not affect the availability or quality of your medical care at this institution in any way, either now or in the future. Please understand that if you sign this consent form, you will have agreed to take part in this study. You are free however to withdraw at any time without giving a reason and this will not affect your care. You will be given a copy of the signed form to keep for your own records.

L'INSTITUT THORACIQUE DE MONTRÉAL DE L'HÔPITAL ROYAL VICTORIA
MONTREAL CHEST INSTITUTE OF THE ROYAL VICTORIA HOSPITAL
3650 St. Urbain, Montréal (Québec) H2X 2P4
Tél./Tel.: (514) 843-2090, Téléc./Fax: (514) 843-2092

PURPOSE OF THE STUDY

You are infected with both the human immunodeficiency virus (HIV), the virus which causes AIDS and the Hepatitis C virus (HCV). Although drug treatments exist for both these infections, their effectiveness is sometimes limited because of side effects. You may already be receiving treatment for your HIV infection (although not for the HCV) through triple combination therapy or HAART. HAART (Highly Active Anti-Retroviral Therapy) is a combination of different classes of anti-HIV drugs.
An approved treatment for HCV infection is a combination of two drugs – Pegylated Interferon and Ribavirin (Rebetron™). Interferon is a substance which is produced naturally in the body, where it has antiviral (including anti-HIV) and anti-tumour effects. In previous studies in participants who were not infected with HIV, this combination has been shown to be effective in eradicating HCV in 60% of patients overall who receive this therapy for 24-48 weeks.

However, a major side effect of this treatment is the development in approximately one third of patients (1 in 3) of symptoms of anxiety and depression. In addition, most patients experience tiredness, lack of appetite and irritability. All of these symptoms may limit the effectiveness of the treatment. People who become depressed frequently cannot take their medications properly and may even have to stop the treatment prematurely which ultimately could affect how well the HCV treatment works. Depression that develops because of Interferon therapy can be successfully treated using a class of antidepressant medications called serotonin-re-uptake inhibitors (SSRIs). Since not everyone develops depression with HCV treatment, the current practice is to use antidepressants only once symptoms of depression appear. It isn't known if taking an antidepressant even before these symptoms develop can have additional benefits.

This study is being done to see if the administration of an SSRI antidepressant (Citalopram; Celexa™) during combination of therapy with pegylated interferon and ribavirin can improve the tolerability of HCV treatment. The goal is to determine if preventive antidepressants will reduce symptoms of depression and anxiety and therefore allow better adherence to the drug treatment and ultimately better responses to HCV therapy.

A total of 60 patients will be enrolled in this study, at different centres across Canada. Treatment will last for 48 weeks then you will continue to be followed for an additional 24 weeks to determine long-term response to therapy. This is a "placebo-controlled" study which means that some participants will be given the antidepressant and some a placebo, which will look and taste just like the antidepressant but will have no biological activity.

ELIGIBILITY

To be eligible for this study you must:

1. be at least eighteen years of age
2. be HIV positive
3. be HCV positive
4. not have been previously treated for Hepatitis C
5. not be pregnant or breast-feeding

Both men and women must agree to use effective contraception while taking the study medications and for 6 months afterwards.

You may not participate if you have any of the following :

- Recently been diagnosed with depression or have taken antidepressants within the past 6 months.
- Ever tried to commit suicide by violent means
- Schizophrenia or mania
- Decompensated liver cirrhosis, liver cancer or certain other chronic liver diseases
- Opportunistic infections such as pneumonia or viral infections requiring therapy
- Certain blood abnormalities such as low red or white blood cell count
- Abnormal kidney function, seizures, thyroid disease, uncontrolled diabetes or immune arthritis
- If you drink more than 7 alcoholic drinks per week
- previously have not tolerated any of the study medications

STUDY PROCEDURES

If you are interested in participating in this study, you will have to read this informed consent and discuss any questions you might have with your doctor. If you decide to participate, this informed consent must be signed before any study-related tests will be done to determine if you meet the requirements to be in the study. These are called "screening tests".

The procedures that will be done at the screening visit are:

1. medical history
2. complete physical examination
3. a questionnaire for depression symptoms
4. blood tests to measure the amount of HIV and HCV in your blood
5. blood sample for safety tests
6. urine test for drugs (such as heroin and cocaine)
7. pregnancy test for women

The amount of blood drawn for these tests at the screening visit will be approximately 45 ml (3 tablespoons).

If you are found to be not eligible for the study, you may decide on an alternate treatment after discussion with your physician.

Liver Biopsy

Liver biopsies are strongly recommended for all Hepatitis C-infected patients before starting therapy. Liver biopsies are important because they help evaluate the severity of the damage (inflammation and

scarring) that Hepatitis C has caused to your liver. Liver biopsy can also help diagnose other conditions that could be affecting your liver along with hepatitis C. Some of these conditions may need to be treated before you have therapy for Hepatitis C. We therefore recommend that all study participants have a biopsy before starting treatment. However the decision to have a liver biopsy will be made by you and your doctor after discussing the risks and benefits of this test. Whether or not you decide to have a biopsy will not affect your participation this study. If you do have a biopsy, the results will be noted in your study documents.

Following the screening tests, if you are found eligible, within two weeks you will be enrolled in the study and undergo "baseline tests" on the same day that you first receive your medication, which is Day 1 of the study. The baseline tests that will be done are:

1. blood tests to measure the amount of HIV and HCV in your blood
2. blood sample for safety tests
3. blood test to measure the immune system (CD4 and CD8 cells)
4. blood sample for HIV and HCV genetic typing
5. urine test for drugs pregnancy test for women
6. questionnaires on quality of life (1) and symptoms of depression (2)

Approximately 45ml (3 tablespoons) of blood will be drawn for these tests.

You will be asked if you wish to participate in one or more sub-studies for which you will be given separate information and informed consent.

DURING THE STUDY

All participants will receive Pegylated Interferon and Ribavirin (PEGATRON™), for 48 weeks of the study. In addition, participants will be randomized (like the toss of a coin) to receive either the antidepressant Citalopram or a placebo which resembles Citalopram. Neither you or your doctor will know which you are receiving.

Participants will begin taking the Citalopram or placebo 2 weeks before starting their PEGATRON and will be seen at the clinic at weeks 2 and 4 and once a month thereafter. At each visit, blood (approximately 30 ml (2 tablespoons) will be drawn for safety and immune system tests (CD4 and CD8 cells). Every 3 months HIV and HCV viral load measures (the amount of virus in your blood), safety measures, pregnancy test and drug screen will be performed. You will also be asked about adherence (whether you are taking your medication as prescribed, every day) and will be required to bring any unused medications as well as the containers to the clinic. You will fill out a short questionnaire designed to evaluate any symptoms of depression, called the Beck Depression Inventory (BDI) at each visit. The BDI will be the main way of evaluating whether or not you are experiencing depression symptoms and whether you need to have these symptoms treated. At the week 12, 24 and 48 visits and at the 6 months follow-up visit three additional questionnaires will be required – a self-administered quality of life assessment (MOS-HIV) , a depression symptom assessment (MADRS) and an anxiety symptom assessment (HAM-A) administered by the study nurse. The total amount of time for completion of these two questionnaires is approximately 20 minutes. At week 48, the study

medications will be stopped. A follow-up visit will take place six months after discontinuation of the HCV therapy, at which time your HCV will be monitored.

MEDICATION

Citalopram or identical appearing placebo: This will be administered at 10mg once a day (morning or evening), starting 2 weeks before the interferon and ribavirin. It will be increased to 20 mg once a day after 1 week. This dose could be increased to a maximum of 40 mg if your doctor feels it is necessary because of mild depressive symptoms.

Pegylated Interferon: Once a week, participants will receive Pegylated Interferon (PEG-Intron) by subcutaneous injection (placing a small needle under the skin), at a dose of 1.5 mcg/kg/ week. The initial dose will be administered at the clinic under medical supervision and any side effects closely monitored. Subsequently, you will be taught by the study staff to inject yourself at home. If you prefer not to inject yourself, arrangements can be made for you to come to the clinic to have the injection done by study personnel.

Ribavirin: Ribavirin (Rebetrol) will be administered according to weight (13 mg/kg) up to a maximum dose of 1200 mg/ day. The total dose will be divided in 2, and taken twice a day (morning and evening).

RISKS AND SIDE EFFECTS

Study Procedures:
When blood samples are taken you may have some slight discomfort at the site of the needle entry and a small bruise may develop and sometimes you may feel faint.

Study Medications:
Citalopram:
The most frequently reported side effects of Citalopram are nausea, sleepiness, sweating and dry mouth (10-20%), diarrhea, tremor, tiredness and sexual dysfunction (5-10%); lack of appetite and anxiety (less than 5%).

Placebo:
Although the placebo is identical in appearance to citalopram, it has no biologic activity ("sugar pill") and therefore has no side effects. It is possible that you may experience a greater frequency of depressive symptoms is you are assigned to placebo treatment. As part of the study you will be monitored closely for these symptoms and referred to a trained professional for care if necessary (see details below).

Pegylated –Interferon (PEG-Intron™):
The most commonly reported side effects of PEG-Intron are flu-like symptoms (fever, chills, nausea, headache, muscle and joint pain and tiredness) which can range from mild to severe. Some or all of these symptoms occur in up to 60% of patients treated with PEG-Intron. The most severe symptoms tend to appear with the initial doses, when you will be monitored by the study staff, who will advise you on medications (i.e. acetominophen (Tylenol ™) or naprosyn (Naproxen™)) which can be taken

to alleviate these symptoms. These symptoms tend to get better over time. You should report any symptoms you experience to the study nurse. Pain or swelling at the injection site is also common (up to 40%).

The first dose of PEG-Intron will be administered in the clinic so that you can be monitored for side effects. You will be observed for 30 minutes following the injection. As well, if you wish, you or a care-giver will be taught how to give injections so that you can administer subsequent doses of PEG-Intron at home. If you prefer, arrangements can be made to come to the clinic each week to receive your injection by trained personnel.

As therapy continues, you may experience some other side effects such as reversible hair loss (in up to 20%) and impotence (about 5% of subjects). PEG-Intron may make diabetes, thyroid disease and certain types of arthritis and skin conditions worse so you should tell your doctor before starting this medication if you have ever had this type of health problem. Approximately 20-30% of patients treated with PEG-Intron report feelings of depression, irritability and insomnia.

The most frequent laboratory abnormalities associated with PEG-Intron therapy are a reduction in the number of leucocytes (white blood cells) and/or platelets (cells involved in clotting) in the blood. Most subjects will experience these effects, which tend to occur in the first 4 weeks of treatment and then remain stable. It is rare (<1%) that blood counts fall to such low levels that it is necessary to stop therapy. However, blood counts will return to normal after PEG-Intron is stopped.. You will be monitored for these effects through blood testing.

If at any time you experience any of these side effects, or others not listed here, in particular feelings of anxiety or mood changes they should be reported to the study staff.

If you develop depression symptoms during the study:

PEG-Intron can give rise to mood disorders such as depression and in rare instances to ideas of suicide. When no antidepressants are given, depressive symptoms may occur in up to 30% of patients receiving PEG-Intron. These symptoms can be successfully treated using a combination of PEG-Intron dose reduction and administration of antidepressants.

If you do develop symptoms of depression you will immediately be referred to the appropriate health-care professional for follow-up (i.e. psychiatrist or psychologist). Several possible treatments may be proposed to help control symptoms of depression depending on how severe they are. For example, you may discontinue treatment for HCV, reduce the dose of HCV medications or continue in the study at the full treatment dose. If you have moderate symptoms of depression based on your depression score, the first step will be to add active citalopram in increments of 10 mg/week to your original antidepressant up to a maximum combined dose of 60 mg/day. For example if you were taking 40 mg of citalopram you could have up to 20 mg of additional citalopram added for a total of 60 mg/day. If you were originally on placebo at 40mg you would have 20 mg of active citalopram added. Most people's depressive symptoms will improve with 20-60 mg/day of citalopram. However, if your symptoms don't improve or if you develop severe depression, you will be switched to another approved antidepressant in consultation with a psychiatrist. Citalopram or placebo will then be stopped.

Ribavirin:
The most important side effect of ribavirin is hemolytic anemia (destruction of the red cells). This occurs usually in the first 2 weeks of treatment, in up to 10% of people taking the drug. Anemia may be associated with symptoms of tiredness, weakness and difficulty breathing. It is reversible when the dose is reduced or stopped. Severe anemia requiring blood transfusion may rarely occur. Ribavirin can also damage a fetus during pregnancy and **must not be taken by pregnant women**.

Other Medications:
You may receive antiretroviral therapy (HAART) while participating in the study. However, you must have been on the same regimen for at least 3 months prior to entering the study. This is to allow for early side effects to resolve and to allow your doctor to determine how well the HIV has responded to your therapy. You may take any licensed antiretroviral treatment with the exception of full dose ritonavir (400 or 600 mg twice a day) which will not be allowed to prevent significant drug interactions and possible liver damage. Changes in your antiretroviral therapy after study starts will be permitted if your doctor feels it is necessary. There is a small possibility that citalopram may affect the levels of your antiretroviral drugs in your system. This question will be examined in a sub-study.

The interaction of the study medications with street drugs i.e. cocaine, heroin, is not known.

You must inform the study staff of any other drugs that you take (prescription, over-the counter or street) while participating in the study. Because of possible dangerous interactions with the study medications, study participants are not permitted to take certain other drugs such as: Rifampin, Rifabutin (Mycobutin™), Isoniazid, Pyrazinamide (Tebrazid™), corticosteroids, hydroxyurea (Hydrea™), In addition, mood stabilizers such as valproic acid will not be allowed. Medications such as acetaminophen, non-steroidal anti-inflammatories and antihistamines will be permitted for relieving symptoms. Benzodiazepines will be permitted.

Pregnancy
Female participants who take ribavirin during pregnancy could experience damage to their unborn fetus, which can lead to birth defects and miscarriage. It is therefore very important for women of child-bearing potential to use barrier methods of birth control such as a diaphragm or condom during the course of the study. Hormonal methods of birth-control (oral contraceptives) are not considered adequate because of their interaction with the study medications. Pregnancy tests will be performed before enrollment and at each visit. If you become pregnant while on the study and choose to continue your pregnancy, you will be removed from the study and medication stopped.

Male participants must also use barrier methods of contraception (condom) during the study.

BENEFITS

If you receive citalopram, it may reduce the chance that you will develop symptoms of depression during treatment with PEG-Intron and ribavirin. This may allow you to tolerate and take your HCV treatment at the full dose for a longer period which may in turn allow a better chance to cure the HCV infection. However, it is not guaranteed that you, personally, will derive a benefit from this treatment. Your participation may also add to medical knowledge about the treatment of HIV and HCV coinfection.

ADDITIONAL INFORMATION

Besides the risks and side effects that have already been described, there may be some that are not yet known. If, during the course of this study, additional information becomes available that might affect your willingness to continue your participation, it will be provided to you in writing. You will have the opportunity to discuss it with your doctor.

ALTERNATIVE TREATMENTS

There are drugs to treat your HCV infection, approved by the Health Protection Branch (HPB) in Canada, available to you by prescription from your doctor. You do not need to be in this study to receive treatment for HCV infection. Before you decide whether or not to participate in this study, your doctor will discuss with you the benefits and risks of treatment.

VOLUNTARY NATURE OF PARTICIPATION AND WITHDRAWAL

Participation in this study is completely voluntary. Refusal to participate will not affect your medical care at this institution. Even if you decide to participate, you can always change your mind and withdraw at any time. If you do decide to withdraw, you must inform your study doctor or nurse. You will be asked to return for a post-study visit which will include blood tests similar to those required for a study visit.

Your participation in this study may be terminated at any time by your doctor or the Sponsor for reasons of, but not limited to:

- A severe adverse reaction experienced by you or other study participants
- Failure to comply with the instructions given to you by your study personnel.
- Your doctor feels it is in the best interest of your health and welfare to discontinue.
- Insufficient number of patients in the study

COSTS OF PARTICIPATION

All the tests and procedures required as part of the study will be provided at no cost. The study medications PEG-Intron and ribavirin are available by prescription. Citalopram will be provided at no cost.

Reimbursement for out-of-pocket expenses such as transportation costs to permit you to attend study visits, up to a limit of $10 per visit, will be available.

RESEARCH-RELATED INJURIES

In the event of an illness or injury that is reasonably determined to be related to the administration of the study medication, you will be provided with necessary medical and hospital care. By signing this informed consent, you do not give up any of your legal rights.In the case of research-related injury, you should contact **Dr. Marina Klein at the Immunodeficiency clinic at 843-2090 during work**

hours and after hours, the physician-on-call for the immunodeficiency service at (514) 934-1934, local 36111.

CONFIDENTIALITY

Your participation in this research study will remain confidential. However, it will be necessary for certain groups to inspect the study records and your medical records. The study sponsors, monitoring groups representative of the sponsor, the Canadian Health Protection Branch (HPB) or the Institutional Review Board/Ethics Committee(IRB/EC) may review the trial data. The IRB is a group that oversees the conduct of human research and assures the protection of patient rights and welfare at the institution where you will participate in the study. You will not be identified by name in any publication of information from this study. You will be identified by a code and initials only so your participation will remain confidential. By signing this document, you consent to inspection of your medical records.

PERSONS TO CONTACT

1. If you have any **questions** concerning the study, you may contact **Dr. Marina Klein at 843-2090**

2. If you have any questions about your **rights as a research subject** and wish to discuss them with someone not connected to the study, you may contact **the Ombudsman of the McGill University Health Centre at (514) 934-1934, local 35655.**

3. If you believe you have been injured as a result of being in this study, you may contact the **Director of Professional Service at (514) 934-1934, ext. 34329**

SIGNATURE PAGE

Title: A Randomized, placebo-controlled trial of citalopram for the prevention of depression and its consequences in HIV-Hepatitis C co-infected individuals initiating pegylated interferon/ribavirin therapy

By my signature below, I confirm:

- I have read this informed consent.
- I understand this is a research study and my participation is voluntary
- I understand that I may change my mind regarding my participation in this study at any time if I wish
- I have had the opportunity to ask questions and discuss my concerns with my doctor and my questions have been answered satisfactorily
- I have been given adequate explanation and understand the purpose, procedures, risks and benefits of this research study
- I authorize the release of my medical records to the sponsors or their representatives, the regulatory authorities and the IRB/EC for purposes of this study only, for a period of 15 years
- I understand I have not given up any of my legal rights by signing this form
- I understand I will be given a copy of this consent form once signed

I consent (agree) to participate in this study

_____ _____
Participant's Signature Date

_____
Participant's Name

_____ _____
Investigator's Signature Date

_____
Investigator's Name

CHECKLIST FOR REVIEWING INFORMED CONSENT FORMS

GENERAL QUESTIONS

- ❑ 1. Does the form use plain language (Grade 8 equivalent) throughout in the original or in any translated version?
- ❑ 2. Is the type of language respectful and appropriate (e.g., referring to participants or volunteers, not subjects or patients)?
- ❑ 3. Are all acronyms explained when first used, and used consistently?
- ❑ 4. As the form may have been adapted from a study from the U.S. or another country, does it refer to Canadian issues and institutions?
- ❑ 5. Are all drugs and/or other therapies involved in the trial referred to by both generic and brand names when first mentioned?

SPECIFIC ITEMS TO LOOK FOR

Overview of study

- ❑ 6. Is it clearly stated that the study involves experimental research?
- ❑ 7. Does it state the study's purpose, rationale and design in plain language?
- ❑ 8. Are the study's inclusion/exclusion requirements clearly explained?
- ❑ 9. Are the study's inclusion/exclusion requirements free of arbitrary or discriminatory criteria (e.g., specifying a certain age without justification)?
- ❑ 10. Are the various arms of the study fully discussed, including the use of placebo (if applicable)?
- ❑ 11. Does it give the probability of assignment to each study group? Does it mention the total number of volunteers to be enrolled in the study?
- ❑ 12. If the study is double-blinded, are the procedures for double-blinding explained, including procedures for breaking the double-blind?

- ❑ 13. Does it state in plain language the route of administration of the treatment in question (e.g., by mouth, by shot or pills, etc.)?

- ❑ 14. Is it explained that the trial will be monitored by a data and safety monitoring board that could stop the study if deemed necessary?

Procedures to be followed by volunteers

- ❑ 15. Does it state the expected duration of participation in the study?

- ❑ 16. Does it clearly state the frequency and duration of visits to be made by volunteers to the study clinic and who they are to see?

- ❑ 17. Does it clearly state when and how the study medication must be taken?

- ❑ 18. Does it state if and how adherence to the protocol will be assessed and does it provide a justification for this assessment (e.g., pill counts, interviews, etc.)?

- ❑ 19. Does it give a brief description of the procedures to be performed to monitor the volunteer during the study (e.g., x-rays, blood tests, etc.) and the frequency of these procedures? If blood is to be drawn, does it indicate how much (in milliliters and tablespoons)?

Overview of study treatments

- ❑ 20. Does it clearly state which treatments, delivery techniques or treatment strategies are experimental?

- ❑ 21. Does it clearly and fully explain the risks and side effects and toxicities (including percentage frequency) of all therapies and tests in the study? Does it state that some side effects may not yet be known?

- ❑ 22. Does it state that volunteers will be advised of new information about the study treatments promptly, especially information that would have an impact on their decision to participate?

- ❑ 23. If applicable, does it clearly explain how and why future treatment options may be compromised by participation in the study (e.g., resistance to other drugs in the same class)?

- ❑ 24. Are drug interactions (including alcohol, over-the-counter medications, and street drugs) fully explained?

- ❑ 25. Are issues related to diet and the study treatments clearly explained (e.g., taking medication on an empty stomach or with a high/low fat meal)?

The volunteer's options

- ❑ 26. Is it clearly stated that the decision to participate in the study is voluntary and that the volunteer can withdraw at any time without consequences to his/her healthcare?

- ❑ 27. Does it list the treatment options available to potential participants outside the trial?

- ❑ 28. Is it stated that participation in this trial might have an adverse impact on a person's eligibility for future trials? (And, if known, why?)

The volunteer's rights

- ❑ 29. In the section called "Benefits" or "Risks and Benefits," does it avoid claims about the experimental therapy that cannot be supported (e.g., may shrink tumours or may reduce viral load below detectable levels)?

- ❑ 30. Is it clearly stated whether information collected during this study will remain confidential? Does it indicate which agencies may access this information (e.g., the pharmaceutical company, Health Canada, the U.S. Food and Drug Administration, other government agencies in Canada or abroad, etc.)? Does it indicate whether a name or just a number will be linked to the information?

- ❑ 31. Does it state if compensation for study-related injury will be provided by the institution, company or insurer?

- ❑ 32. Are the names and phone numbers of (1) a physician and (2) a contact for the ethical review board provided?

- ❑ 33. Does it state the specific circumstances under which the volunteer

may be withdrawn from the study without his or her consent (e.g., missed appointments, non-adherence to protocol, changing health status, etc.)?

- ❑ 35. Does it state that significant new findings relating to treatment options will be discussed with the volunteer?
- ❑ 36. Does it state that the volunteer should feel free to ask for clarification or new information at any time during the study?
- ❑ 37. Will the results of tests, including measurements of viral load and other surrogate markers be given to the volunteer in "real time"—without delay—so that the volunteer can act quickly on the information?
- ❑ 38. Does it state when the trial results are expected and how they will be communicated to the volunteer?
- ❑ 39. Is it indicated that the volunteer will receive his/her own signed copy of the form to take away?
- ❑ 40 Does it state that signing the form does not waive the volunteer's legal rights or release the investigators, sponsors or involved institutions from their legal and professional responsibilities?

Birth control issues

- ❑ 41. Are women of child-bearing potential fairly warned of the risk of pregnancy without being unnecessarily forced to use certain forms of birth control?
- ❑ 42. Are women of child-bearing potential provided with options in deciding whether to participate in the study?
- ❑ 43. If specific forms of birth control or pregnancy tests are required, does it provide a clear rationale as to why?
- ❑ 44. Are volunteers warned if the experimental treatment's effect on sperm is unknown?

Issues for follow-up with study sponsor

- ❑ 45. Is the experimental treatment available through expanded or compassionate release to all Canadians living with HIV and AIDS who need it?

- ❑ 46. Can volunteers continue to receive the treatment if they are withdrawn from the study or when the study is over? For how long? (The treatment should be made available to participants until they can access it through their provincial reimbursement plan or private insurance.)

- ❑ 47. Will participants be reimbursed for reasonable expenses related to travel and childcare (a requirement for all CTN trials)?

SAMPLE COMMUNITY REVIEW

Keep in mind when you look at the points listed below that your review does not have to match the original community review point for point. This is not a math test; there are no absolutes. Political and medical issues change

as time passes, and a point that reviewers felt was particularly important or unacceptable then may not be as relevant now. However, you may find this sample review a useful introduction to the actual review process.

You might choose to follow CAC's model of separating comments into either *required* or *recommended* changes. Required changes are generally those issues that need to be resolved in order for the trial to go ahead. Recommended changes are generally those issues that you feel might enhance the informed consent, but are not a prerequisite for your final approval.

REQUIREMENTS AND RECOMMENDATIONS OF COMMUNITY ADVISORY COMMITTEE

CTN S194: A randomized, placebo-controlled trial of citalopram for the prevention of depression and its consequences in HIV/hepatitis C co-infected individuals initiating pegylated interferon/ribavirin therapy.

This protocol was approved by the Community Advisory Committee with the following required and recommended changes:

Required changes to the Informed Consent

1. Describe the form of citalopram (Celexa) to be used (tablet or capsule), its method of administration and any associated dietary requirements.

2. On page 3, Study Procedures, number 5, describe what type of safety tests will be done and why.

3. State that the study will cover reasonable expenses related to childcare, as well as to travel. (This is now standard for all CTN trials.)

4. On page 3, state that participants are to have no more than an average of one drink per day; explain what is meant by a drink (e.g., one beer, cooler or small glass of wine).

Recommendations for the Informed Consent

1. Clarify and give one consistent name for the combination of pegylated interferon and ribavirin (e.g., Pegatron).

2. Substitute "participant" or "volunteer" for "subject" wherever used (e.g., see page 9).

3. Give the trade name of citalopram, Celexa, in the title and on the signature page.

4. State the length of time needed for clinical visits.

5. On page 2, end of the third paragraph, revise this sentence as follows: "… even before these symptoms develop can have additional benefits, including the prevention of depression."

6. On page 3, Study Procedures, revise the first sentence: "… any questions you might have with your doctor or anyone that you choose."

7. On pages 3-4, Liver Biopsy, state that participants considering this procedure should discuss the risks with a doctor. (The CAC notes that this biopsy is not always easy, especially for hemophiliacs.)

8. On page 4, During the Study, first paragraph, revise this sentence: "Neither you nor your doctor…"

9. On page 4, under During the Study, give justification for measuring adherence.

10. State any dietary requirements associated with taking citalopram. If none, state this.

11. Confirm that study drugs are available to participants through their reimbursement plan in each province of the study sites.

12. On page 4, state that results of blood tests for surrogate markers (viral load and CD4/CD8 cell counts) will be discussed with the participant at each visit following the tests.

13. State how and when results of the study will be communicated to participants.

14. State that the effects of the study drugs on sperm are not known.

15. On page 4, number 5, clarify as follows: "urine test for drugs (heroin and cocaine) and pregnancy test for women." Also state how the study will use the results of these drug tests.

16. On page 4, bottom of final paragraph, put in plainer language: "a self-administered quality of life assessment…."

17. On page 4, last full sentence of final paragraph: "The total amount of time for completion of these three questionnaires is approximately [STATE HOW LONG]."

18. On page 6, third full paragraph, revise this sentence: "It is rare (less than 1% of cases)…."

19. On page 6, final sentence, revise as follows: "Citalopram or placebo will then be gradually stopped."

20. On pages 8 and 9, use Therapeutic Products Directorate (TPD) instead of HPB.

APPENDIX I: HIV AND AIDS TREATMENT INFORMATION

The CIHR Canadian HIV Trials Network (CTN) is a federally funded organization mandated to develop treatments, vaccines and a cure for HIV and AIDS through the conduct of scientifically sound, ethical clinical trials. The CTN publishes a regular newsletter as well as a continuously updated list of HIV and AIDS clinical trials in Canada. It operates a toll-free information line at 1-800-661-4664 and a website on clinical trials (www.hivnet.ubc.ca). The Canadian AIDS Treatment Information Exchange (CATIE) provides information on HIV and AIDS treatments, clinical trials and related issues. You can contact CATIE toll-free at 1-800-263-1638 or visit the CATIE website at www.catie.ca.

Many local community groups have superb treatment projects that are available as a resource to HIV-positive people. Please enquire at your local group to find out what information and/or counselling is available.

The following organizations and programmes provide information on treatment options and/or clinical trials:

ASIAN COMMUNITY AIDS SERVIVES (ACAS)

33 Isabella Street, Suite 107
Toronto, ON M4Y 2P7
Tel: 416-963-4300
Fax: 416-963-4371
info@acas.org
<www.acas.org>

BRITISH COLUMBIA PERSONS WITH AIDS SOCIETY (BCPWA)

2nd floor, 1107 Seymour Street
Vancouver, BC V6B 5S8
Tel: 1-800-994-2437 (toll-free) or 604-893-2243
Fax: 604-893-2251
treatment@bcpwa.org
<www.bcpwa.org>

CANADIAN ABORIGINAL AIDS NETWORK

6520 Salish Drive
Vancouver BC V6N 2C7
Tel: 604-266-7616
Fax: 604-266-7612
Email: info@caan.ca
<www.caan.ca>

CANADIAN AIDS SOCIETY (CAS)

309 Cooper Street, 4th Floor
Ottawa, ON K2P 0G5
Tel: 1-800-499-1986 (toll-free) or 613-230-3580
casinfo@cdnaids.ca
<www.cdnaids.ca>

CANADIAN AIDS TREATMENT INFORMATION EXCHANGE (CATIE)

505-555 Richmond Street West, Box 1104
Toronto, ON M5V 3B1
Tel: 1-800-263-1638 (toll-free) or 416-203-7122
questions@catie.ca
<www.catie.ca>

CANADIAN TREATMENT ACTION COUNCIL (CTAC)

Box 116, Station F
Toronto, ON M4Y 2L5
Tel: 416-410-6538
ctac@ctac.ca
<www.ctac.ca>

CIHR CANADIAN HIV TRIALS NETWORK

620B-1081 Burrard Street
Vancouver, BC V6Z 1Y6
Tel: 1-800-661-4664 (toll-free) or 604-806-8327
Fax: 604-806-8210
ctninfo@hivnet.ubc.ca
<www.hivnet.ubc.ca>

APPENDIX II: RELATED LITERATURE

This appendix is a resource that you can use to look for further information about clinical trials research ethics, and related subjects. This is by no means a complete list, and as publications are changing with time, website addresses are included whenever possible to allow access to newer publications.

When reviewing a clinical trial, it's useful to have basic medical reference materials on hand. The following is a selection of the reference books recommended by the Canadian AIDS Treatment Information Exchange and the Treatment Information Network as part of their "Library in a Box":

Dictionaries (only one of the following is necessary):
Stedman's Medical Dictionary
Taber's Medical Dictionary
Dictionnaire de médecine flammarion (French)

Treatment handbooks:
HIV/AIDS Treatments Directory (NAM)
Petit guide des antirétroviraux (French)

Textbooks/guides:
Harrison's Internal Medicine
Medical Management of HIV Infection (Johns Hopkins)
Positive Living Manual (BCPWA)
A Woman's Guide to Living with HIV Infection (Johns Hopkins)

HIV and AIDS General Information

AIDS Vancouver. *Contact: An AIDS Resource Guide for BC.* <www.aidsvancouver.org>

Canadian AIDS Treatment Information Exchange (CATIE). *Managing Your Health: The Must-Read Handbook on Living with HIV*. 1999. <www.catie.ca>

Canadian AIDS Treatment Information Exchange (CATIE). *A Practical Guide to Nutrition for People Living with HIV and AIDS*. 2007. <www.catie.ca>

Cohen, PT, ed. *AIDS Knowledge Base: A Textbook on HIV Disease from the University of California, San Francisco and San Francisco General Hospital*. Third Edition. Philadelphia: Lippincott, Williams & Wilkins, 1999. Note: Online edition is continously updated. <hivinsite.ucsf.edu>

Pinsky, L and Harding Douglas P. *The Columbia University Handbook on HIV and AIDS*. 2009. <www.health.columbia.edu>

HIV and AIDS Treatment Information

U.S. Department of Health and Human Services (DHHS) Clinical Guidelines. <aidsinfo.nih.gov/guidelines/>

Canadian AIDS Treatment Information Exchange (CATIE). *A Practical Guide to Complementary Therapies for People Living with HIV and AIDS*. Revised 2004.

Canadian AIDS Treatment Information Exchange (CATIE). *A Practical Guide to HAART (Highly Active Antiretroviral Therapy)*. Revised 2006.

Canadian AIDS Treatment Information Exchange (CATIE). *A Practical Guide to Herbal Therapies for People Living with HIV*. Revised 2004.

Canadian AIDS Treatment Information Exchange (CATIE). *A Practical Guide to HIV Drug Side Effects*. Revised 2006. <www.catie.ca>

Clinical Trials

AIDS Treatment Data Network. *Should I Join an AIDS Drug Trial? <www.atdn.org>*

CIHR Canadian HIV Trials Network and the Canadian AIDS Society. *Clinical Trials: What You Need to Know*. Third Edition. 2004. <www.hivnet.ubc.ca>

ClinicalTrials.gov. U.S. international registry of clinical trials, and "Understanding Clinical Trials." May 2005 <www.clinicaltrials.gov>

Ng, R. *Drugs: From Discovery to Approval*. Hoboken, NJ: Wiley-Liss, 2004.

An Analytical overview of the microbicide preclinical and clinical pipeline. Microbicides 2006 Conference, 23-26 April 2006, Cape Town, South Africa. < ww.microbicide.org>

IAVI Report. Publication on international AIDS vaccine research published bi-monthly by the International AIDS Vaccine Initiative (IAVI). <www.iavireport.org>

San Francisco AIDS Foundation. "A Guide to Clinical Trials Part I: Understanding Clinical Studies." And "A Guide to Clinical Trials Part II: Interpreting Medical Research." *Bulletin of Experimental Treatments for AIDS (BETA)* (Summer 2005 and Winter 2006). < www.sfaf.org>

Research Ethics

Collected Articles on Research Protections and Related Topics: Citizens for Responsible Care and Research. <www.circare.org/CAindex.htm>

Emanuel EJ, Wendler D, and Grady C. What makes clinical research ethical? *JAMA* 2000;283(20):2701-11.

Freedman B. Equipose and the ethics of clinical research. *N Engl J Med*, 1987;317:141-5.

James JS. Editorial: Time to End the Death Trials. *AIDS Treatment News* (2 August 1996).

Miller FG and Silverman HJ. The ethical relevance of the standard of care in the design of clinical trials. *Critical Care Perspective*, 2004;169:562-4.

Weijer C and Miller P. When are research risks reasonable in relation to anticipated benefits? *Nature Medicine* 2004;10(6):570-73.

Treatment Advocacy

Angell, M. *The Truth About Drug Companies: How They Deceive Us and What To Do About It*. New York: Random House, 2004.

Canadian Treatment Action Council (Quarterly newsletter). <www.ctac.ca>

Global Campaign for Microbicides. < www.global-campaign.org>

National AIDS Treatment Advocacy Project (NATAP). <www.natap.org>

TAGLine. Treatment Action Group: A Quartely paper of research and policy. < www.aidsinfonyc.org>

Looking for copies of the key research ethics documents? They are all available on the Web:

- Nuremberg Code <ohsr.od.nih.gov>
- Declaration of Helsinki <www.wma.net>
- Belmont Report <www.fda.gov>
- Tri-Council Policy Statement <www.pre.ethics.gc.ca>
- Good Clinical Practice: Consolidated Guideline <www.hc-sc.gc.ca>

APPENDIX III: GLOSSARY

This glossary provides definitions of many of the terms related to clinical research and HIV that are used in this manual. More complete glossaries of terms associated with HIV treatment and research can be found on the web:

- AEGIS (AIDS Information Global Information System) *Glossary* <www.aegis.org>
- AIDSinfo (a service of the U.S. Department of Health and Human Services) *HIV Glossary* <www.aidsinfo.nih.gov>
- Gay Men's Health Crisis *AIDS Medical Glossary* <www.gmhc.org>
- GeneEd *Biotechnology Glossary* <www.geneed.com>
- MedBioWorld's links to online medical and bioscience dictionaries, glossaries and terminologies <www.sciencekomm.at>
- NIAID (U.S. National Institute of Allergy and Infectious Diseases) *HIV Vaccine Glossary* <www.niaid.nih.gov>
- San Francisco AIDS Foundation *Glossary of HIV/AIDS-Related Terms* <www.sfaf.org>

In French:

- Links to a range of specialized French dictionaries, including an HIV and AIDS glossary, are compiled by the Université de Sherbrooke <www.usherbrooke.ca>

NOTES

ADHERENCE

Taking medication or following a treatment programme as prescribed. Adherence includes: Following instructions concerning food (i.e., taking medication with a meal, or not eating certain foods) and dosing schedules. A low level of adherence can lead to the development of drug resistance.

ADVERSE EVENT (AEs)

In a clinical trial, the undesirable change in health or "adverse side-effect" a participate may experience while they are receiving treatment (i.e., study medication, application of the study device, etc.) or within a pre-specified period of time after trial completion. All clinical trials have the potential to produce AEs and the term is applied whether or not the adverse event can be attributed to the study treatment.

ANTIRETROVIRAL (ARV)

A substance that stops or suppresses the activity of a retrovirus such as HIV (e.g., abacavir, efavirenz, atazanavir).

ANTIRETROVIRAL (ARV) DRUG RESISTANCE

When an individual's HIV continues to multiply despite the presence of antiretroviral drugs. This usually indicates that the drug regimen needs to be changed. ARV drug resistance is one of the main limitations of HAART.

ANTIRETROVIRAL THERAPY (ART)

Treatment that suppresses or stops the activity of a retrovirus such as HIV.

ARM

A group of participants in a clinical trial receiving the same treatment(s).

ASYMPTOMATIC

Without symptoms. In HIV and AIDS literature, a person is considered asymptomatic if they test positive for HIV antibodies, but show no clinical symptoms of the disease.

ATTACHMENT INHIBITOR

See *entry inhibitor*.

BASELINE

1) Information gathered at the beginning of a study from which variations found in the study are measured. 2) A known value or quantity against which an unknown is compared when measured or assessed.

BIOLOGICS

A preparation, such as a drug, a vaccine, or an antitoxin, that is made from living organisms or their products and used as a diagnostic, preventive, or therapeutic agent.

BLINDED STUDY

A clinical trial in which participants do not know if they are in the experimental group (receiving the study treatment) or the control group (receiving the standard treatment) of the study. See also *double-blind study* and *single-blind study*.

CD4+ CELLS

Usually referred to as CD4 T cells or CD4 cells, these are the preferred target of HIV. CD4 are white blood cells that direct the immune response by signaling other cells to perform their special functions. The destruction of CD4 is the major cause of the immunodeficiency observed in AIDS. Also called a "T-helper cell".

CD4+ CELL COUNT

A measure of the number of immune system cells that have CD4 receptors.

CD8 CELLS

CD8 or CD8 T cells are found on the surface of killer T cells (as opposed to CD4, ordinarily found on the surface of helper T cells). CD8s recognize antigens on the surface of virus-infected cells and bind to the infected cell to kill it.

CLINICAL TRIAL

An investigational study of the effects of a treatment or treatment strategy (see intervention) in humans. Researchers attempt to determine the intervention's efficacy (its effectiveness) and, in the case of a drug, its pharmacological effects—toxicity, side effects, incompatibility (possible conflicts with other drugs) and interactions (ability to work better when combined with other drugs).

CLINICAL TRIAL APPLICATION (CTA)

A clinical trial application must be filed with Health Canada before an experimental drug can be studied in a Phase I, II or III clinical trial (Phase IV trials do not need to be filed).

COHORT STUDIES

Research studies that focus on a group of individuals sharing a statistical factor (e.g., age or risk).

CO-INFECTION

A term used to describe infection with two or more viruses at the same time. Persons with HIV may also be co-infected with another virus, such as hepatitis B or C.

COMMUNITY ADVISORY COMMITTEE (CAC)

An independent committee that reviews and makes recommendations regarding the informed consent section of a clinical trial protocol. CACs exist primarily to lend a community perspective to clinical trial processes, and to improve communication between researchers and community representatives.

COMPARISON TRIAL

A study in which an experimental treatment is tested against the standard treatment or a placebo, or in which different doses of the same treatment are tested. See also dose comparison trial.

COMPASSIONATE ACCESS / USE

A process for obtaining/providing experimental drugs on an individual basis for/to very sick patients who have no treatment options.

CONCOMITANT MEDICATIONS

Drugs that are taken together. Certain concomitant medications can have adverse (harmful) reactions, while others can have beneficial effects (e.g., ritonavir is commonly used to boost other protease inhibitors).

CONTROL GROUP

The group of participants in a clinical trial who receive the standard treatment or a placebo. See also *controlled trial*.

CONTROLLED TRIAL

A clinical trial in which an experimental treatment is compared against the standard treatment or a placebo. Participants are usually blinded (i.e., they do not know which treatment they are receiving).

CROSSOVER TRIAL

A clinical trial in which all participants receive both treatments, but at different times. Halfway through the study, one group is switched from the experimental treatment to the control treatment (standard treatment), and the other group is switched from the control to the experimental treatment.

DEPRESSION

A common mental illness that involves the body, mood, and thoughts. Depression adversely affects the way a person eats and sleeps, feels about oneself, and thinks about things.

DOSE

The measured amount of a particular treatment to be taken at one time.

DOSE COMPARISON TRIAL

A trial that compares different amounts of the same drug.

DOUBLE-BLIND TRIAL

A clinical trial in which neither the researchers nor the participants know which participants are receiving the experimental treatment and which are receiving the standard treatment. Blinding prevents biases that may affect study results.

DRUG-CLASS SPARING REGIMEN

A treatment strategy in which a class of antiretroviral drugs is excluded from the treatment regimen in order to reduce drug toxicity and address or avoid side effects.

DYSLIPIDEMIA

A condition involving an increase in the level of fats (e.g., cholesterol and triglycerides) in the body. Dyslipidemia is a common side effect of highly active antiretroviral therapy (HAART).

EFFICACY

How well a treatment works (i.e., how effective it is).

ENDPOINT

An event used by clinical trial researchers to evaluate whether an experimental treatment is working. For example, developing AIDS or a low CD4 count may be the endpoint of a trial for people who had no previous symptoms.

ENTRY INHIBITOR

A class of antiretroviral drugs that interfere with HIV's ability to enter immune cells, which include CCR5 antagonists and fusion inhibitors.

EXPANDED ACCESS PROGRAMME

A trial that allows people who do not participate in the research study (because they do not meet the inclusion criteria or for other reasons) to have access to the drug or treatment being tested. Programme may have restrictions.

EXPERIMENTAL AGENT

A substance (drug or other treatment) not yet approved for marketing by Health Canada, which is being studied in a clinical trial.

FOOD AND DRUG ADMINISTRATION (FDA)

The U.S. Public Health Service agency responsible for ensuring the safety and efficacy of drugs and medical devices used in the diagnosis, treatment and prevention of HIV, AIDS and AIDS-related opportunistic infections.

FUSION INHIBITOR (FIs)

A type of antiretroviral medication that helps prevent HIV from entering and infecting human cells. See also *entry inhibitor*.

GENE THERAPY

An approach to preventing and/or treating diseases by replacing, removing or altering key genes, or manipulating genetic material.

GENOTYPIC RESISTANCE TESTING (GRT)

A test of HIV resistance that determines what changes (mutations) have taken place in a person's HIV structure. GRT is recommended to optimize antiretroviral therapy, in particular in patients with virological failure.

GOOD CLINICAL PRACTICE (GCP)

An international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials.

HEALTH CANADA

A department of the government of Canada with responsibility for national public health.

HEPATITIS

Inflammation of the liver, caused by a viral infection or drugs. Two forms of viral hepatitis, B and C, are fairly common in people with HIV infection. See also *co-infection*.

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

Combination antiretroviral therapy that typically includes three drugs from at least two different classes.

HUMAN PAPILLOMAVIRUS (HPV)

A family of over 100 viruses including those that cause warts and is transmitted by skin-to-skin contact. Some types of HPV are associated with tumors of the genital tract, notably, cancer of the cervix.

HUMAN LEUKOCYTE ANTIGENS (HLA)

Genetically inherited proteins present on the surface of human cells. HLAs are involved in activating the CD8s. Studies have noted a link between HLA type and HIV progression. Certain classes of HLA are associated with better disease prognosis, while others are associated with worse outcome.

IMMUNOMODULATOR

A therapy that strengthens the immune system and helps the body to fight off infections or diseases that attack people living with HIV and AIDS.

INCLUSION/EXCLUSION CRITERIA

The scientifically defined reasons why a person may or may not be allowed to enter a trial. For example, some trials only include people with a lowered CD4 count, while others exclude people who have already developed a specific infection. Most trials do not allow pregnant women to join.

INFORMED CONSENT

A process in which the risks, benefits and requirements of a trial are fully explained to study candidates so they can decide if they want to enroll in the study. Before enrolling in a trial, a participant should sign an informed consent form that contains, in writing, the risks, potential benefits and basic structure of the trial. An informed consent can be withdrawn at any time.

INNATE IMMUNE SYSTEM

Comprised of cells and mechanisms that defend the body from infection in a non-specific manner. The innate immune system serves as an early warning system for invading diseases.

INSTITUTIONAL REVIEW BOARD (IRB)

See *Research Ethics Board*.

INSULIN RESISTANCE

A condition in which the body is unable to use available insulin effectively. Insulin resistance is a common side effect of highly active antiretroviral therapy (HAART).

INTERVENTION

A treatment or treatment strategy tested in a clinical trial.

INTEGRASE INHIBITORS

A class of antiretroviral drugs designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell.

LACTIC ACIDOSIS

A condition involving dangerously high levels of lactic acid in the blood. Lactic acidosis is rare and is associated with the use of certain NRTI drugs (see below) that are seldom prescribed today.

LIPOATROPHY

Refers to the loss of fat from the face, a.k.a. "facial wasting", arms, butt and legs. This is a common adverse side-effect of some antiretroviral drugs.

LIPODYSTROPHY

A condition involving the defective metabolism of fat by the body. Lipodystrophy includes fat loss (e.g., wasting in the arms, legs and face) and fat displacement (e.g., "buffalo hump", the accumulation of fat in the upper back). Lipodystrophy is a common side effect of highly active antiretroviral therapy (HAART).

MICROBICIDE

Products (creams, gels, films, or pills, etc.) that are still being tested to reduce the transmission of HIV and other sexually transmitted infections. Microbicides are applied inside the vagina or rectum.

MONOTHERAPY

A treatment strategy in which only one drug is administered, instead of multiple drugs in combination. This strategy is often used to reduce drug toxicity and to address or avoid side effects.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI)

A class of antiretroviral drugs that inhibits the action of reverse transcriptase, one of the enzymes HIV needs to make copies of itself.

Unlike another class of drugs called NRTIs, NNRTIs are not effective against the type of HIV known as HIV-2.

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI/NtRTI)

A class of antiretroviral drugs that blocks the action of reverse transcriptase, one of the enzymes HIV needs to make copies of itself.

OBSERVATIONAL STUDIES

A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given). An observational study observes characteristics of a subset of a population(s) or a cohort.

OPTIMIZED BACKGROUND THERAPY (OBT)

A combination of antiretroviral drugs (ARVs) most likely to increase CD4 counts and decrease viral load based on a patient's ARV history and resistance testing. Also referred to as "optimized background regimen (OBR)".

OPEN LABEL

A clinical trial in which researchers and participants know who is receiving the experimental drug.

OPPORTUNISTIC INFECTION

An infection that occurs because of a weakened immune system and that can be potentially life threatening. When the immune system is damaged, the organisms take advantage of the "opportunity" to cause illness. Opportunistic infections are rare today since the introduction of HAART. A rare form of pneumonia known as PCP is usually the first and most common opportunistic infection seen in people with CD4 counts below 200, and is commonly associated with a diagnosis of AIDS.

PHARMACOKINETICS

A branch of pharmacology (the study of the body's reaction to drugs) that examines how the body processes drugs.

PHARMACODYNAMICS

The exploration of what a drug does to the body. Often studied with pharmacokinetics, pharmacodynamics examines the process and the effect of a drug's route through the body.

PHENOTYPIC TESTING

A laboratory test of a person's HIV resistance. A sample of HIV is grown in the laboratory then a dose of one antiviral drug is added. The growth rate of the HIV is compared to the growth rate of wild type virus (a typical strain of HIV; not mutated). If the sample grows more than normal, it is resistant to the medication.

PLACEBO

An inactive substance against which an experimental treatment is compared. A placebo looks, smells and tastes like the treatment being studied but has no active agent in it. Commonly referred to as a "sugar pill".

PREVENTATIVE VACCINE

A vaccine designed to prevent a disease by producing or artificially increasing immunity.

PROTOCOL

The detailed, written plan for a clinical trial, includes: The trial's rationale, purpose, participant criteria, treatment administration and duration, drug dosages, criteria for determining the trial's success or failure, and the methods of data analysis and interpretation. Research ethics boards and Health Canada must approve the protocol before a clinical trial can begin.

PROTEASE INHIBITOR

A class of antiretroviral drugs that interferes with the replication of HIV by inhibiting the HIV enzyme called "protease".

PROVINCIAL FORMULARY

A list of the treatments that are covered by a provincial government's funding plan.

QUALITY OF LIFE (QOL)

The quality of life scale was originally developed in the 1970s and adopted for use in chronic illness groups. Measurement of QOL provides a meaningful way to determine the impact of health care when cure is not possible.

RANDOMIZED TRIAL

A study in which a computer randomly assigns participants to receive either the experimental treatment or the standard treatment (or placebo when no standard treatment is available). This ensures that factors that might affect how people respond to treatment are equally distributed in the control and experimental groups.

RESEARCH ETHICS BOARD (REB)

An independent committee established to protect the rights and interests of clinical trial participants. Every institution or hospital that conducts human research must have its own REB. Also referred to as Institutional Review Boards (IRBs), Ethics Review Boards or just Ethics Boards.

ROLL-OVER TRIAL

A trial that only includes volunteers who participated in previous trials for the experimental agent in question.

SALVAGE THERAPY

The title of a treatment regimen for people who are non-responsive to or who cannot tolerate other available anti-HIV therapies. The best way to avoid salvage therapy is to make each regimen of ART last as long as possible.

SCREENING

The process whereby potential volunteers are assessed as to whether or not they meet the entry criteria of the trial. Screening generally precedes enrolment into the trial.

SIDE EFFECTS

Resulting actions or effects of a treatment that are other than those desired. Usually refers to undesirable or negative effects. Experimental treatments must be evaluated for both immediate and long-term side effects. Long-term side effects are often referred to as toxicities.

SPECIAL ACCESS PROGRAMME (SAP)

Health Canada can authorize a manufacturer to release any drug that has not yet been approved for sale in Canada on an emergency basis—including drugs in clinical trials. To apply for an un-licensed drug through the SAP, you must ask your doctor to contact the programme. Pharmaceutical companies do not have to provide the drug, and there may be a cost decided on by the company.

STANDARD-OF-CARE

A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance. Also called standard therapy or good clinical practice.

STRUCTURED TREATMENT INTERRUPTION (STI)

A temporary suspension of treatment; planned in consultation with a physician.

STUDY GROUP

See *arm*.

SURROGATE MARKERS

A surrogate is a substitute. If something under study is not readily measurable because it takes a long time to show up, researchers may use a surrogate marker to predict the eventual measurement. Surrogate markers in HIV research are important because the effectiveness of drugs in slowing down HIV disease progression or increasing survival may not be obvious for many years. Common HIV surrogate markers include CD4 count and viral load.

THERAPEUTIC VACCINE

A vaccine designed to boost the immune response to HIV in people already infected with the virus.

THERAPY

Any drug or other treatment intended to control symptoms of a condition, side effects or toxicities, or to relieve or cure a disease or illness.

THIRD-LINE THERAPY

Treatment that is given when both initial treatment (first-line therapy) and subsequent therapy (second-line therapy) fail.

TOXICITY

The extent or ways in which a treatment is poisonous to the body. Many HIV drugs are cleared from the body by the liver and have the potential to cause liver toxicity; HCV co-infection increases the risk by two to three times.

TREATMENT

A form of therapy, often a drug, used to control symptoms of a condition, side effects or toxicities, or to relieve or cure a disease or illness.

TREATMENT ARM

See *arm*.

TREATMENT INTERRUPTION

See *structured treatment interruption*.

TROPISM

HIV attaches itself to an immune cell using the CD4 receptor and one of two co-receptors either CCR5 or CXCR4. Tropism refers to HIV's preference for one or the other of these co-receptors.

VACCINE

A substance that teaches the body's immune system to recognize and/or protect against a disease caused by an infectious agent (virus or bacteria).

VIRAL LOAD

Also called viral burden. The amount of HIV virus in the blood. Chances are that the higher the viral load, the faster disease progression will be.

WASHOUT PERIOD

A period during which participants do not take certain drugs so that all traces of those drugs can be washed out of the body. A washout period may be necessary as a requirement before entering a trial, switching drugs, or other reasons.

the CTN
CIHR Canadian
HIV Trials Network

le Réseau
Réseau canadien
pour les essais VIH des IRSC