



*François-Xavier Bagnoud Center*  
University of Medicine & Dentistry of New Jersey

# **Trainer Manual**

*for Community Advisory Boards*

**Module 2**  
Introduction to  
Clinical Trials

Version 1.0 – May 2007



## MODULE 2: INTRODUCTION TO CLINICAL TRIALS

### Proposed Agenda

**Opening Activity: “Alphabet Soup” Game** *(20 minutes)*

**Part I Slides and Discussion** *(45 minutes)*

**Activity: The Clinical Trials HIV 1-2-3 Game** *(60 minutes)*

**Part II Slides and Discussion** *(45 minutes)*

**Case Study and Discussion** *(30-45 minutes)*

**Participant Evaluation** *(15 minutes)*



# OPENING ACTIVITY

## Module 2

### Alphabet Soup Game

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Time frame *(20 minutes)*

#### Purpose

This exercise can help participants have fun while teaching each other common initials or abbreviations used in HIV care and research.

#### Materials needed

- 3 different noise-makers, one for each team. Example: whistle, hand clappers, can with seeds or small stones. Use your imagination to make the noise makers. Alternative: Have one team be whistlers, one team clap their hands and the last team hit pencils or sticks together.
- Acronym List
- Acronym Questions
- Each acronym from the list written on a card or piece of paper
- *Optional game prizes*

#### Instructions

- In preparation for the exercise, review the list and decide if you would like to add or remove any of the acronyms. (For example, abacavir [ABC] may not be available at your site and therefore should not be used.)
- Form the participants into teams of 2-6 people. (For very small groups, each individual may be their own “team”, or there may be only 2 groups—whatever seems best)
- Start the game by telling the teams you will call out a set of letters. Also tell them you will be holding up a card or piece of paper with the letters written on it. These are commonly used terms in HIV research and care that CAB members will hear used by researchers and healthcare workers.
- Each team has 10 seconds to talk about the answer. When they are ready, they need to make the team noise. The first team to make the noise gives the answer to the question.
- Repeat the steps with the other terms. **Note:** If no group knows the answer to a question, after waiting a moment or two, read the answer out loud and go on to the next set of letters.
- When all questions are answered, call the game to a close, thanking participants for playing.
- Optional: Give all participants a sweet.

### Acronyms for Alphabet Soup Game

HIV	Human Immunodeficiency Virus (infection)
AIDS	Acquired Immune Deficiency Syndrome
CAB	Community Advisory Board
PI	Principal Investigator (or protease inhibitor)
MTCT	Mother-to-child (HIV) transmission
VL	(HIV) viral load
PACTG	Pediatric AIDS Clinical Trials Group
IRB	Institutional Review Board
CTU	Clinical Trials Unit
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
VCT	Voluntary Counseling and Testing
ABC	Abstinence, Be faithful, (use) Condoms
OI	Opportunistic infection
TB	Tuberculosis
VL	Viral load
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
NIAID	National Institute of Allergy and Infectious Diseases
DAIDS	Division of AIDS
HCV	Hepatitis C virus
GCP	Good Clinical Practice
DMC	Data management center
CTS	Clinical trials site <i>or</i> clinical trials specialist
ARV	Anti-retroviral
ART	Anti-retroviral therapy



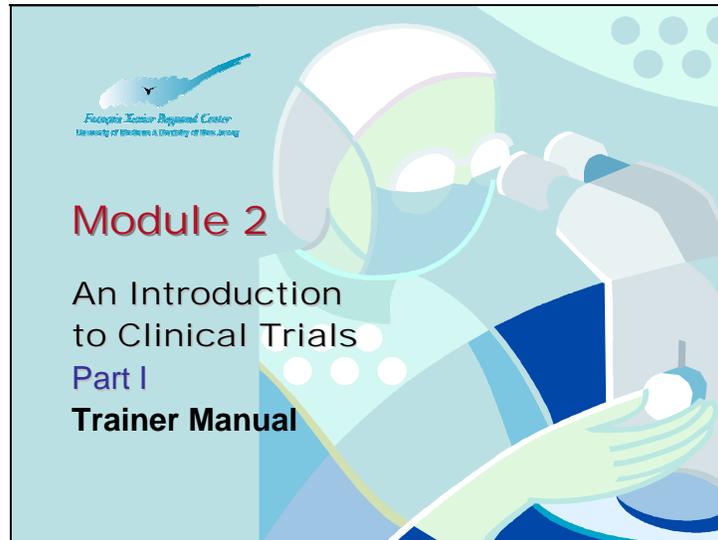
## **Module 2**

### **Part I Slides - Insert Here**





Slide 1



## Slide 2

This teaching tool was developed by the François-Xavier Bagnoud Center at the University of Medicine and Dentistry of New Jersey, with the support of the International Maternal Pediatric and Adolescent Clinical Trials (IMPAACT) network.

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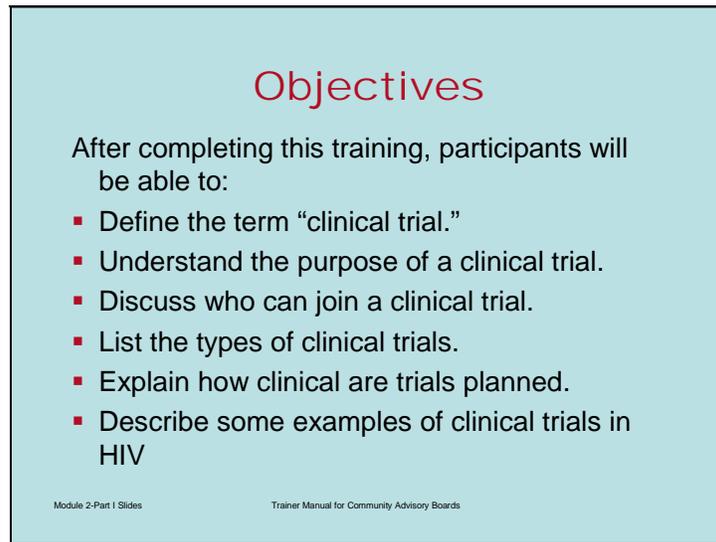


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Module 2-Part I Slides                      Trainer Manual for Community Advisory Boards

## Slide 3



The slide is a light blue rectangle with a black border. At the top center, the word "Objectives" is written in a red, serif font. Below it, the text "After completing this training, participants will be able to:" is in a black, sans-serif font. This is followed by a bulleted list of six objectives, each starting with a red square bullet. At the bottom left, there is small text: "Module 2-Part I Slides". At the bottom center, there is small text: "Trainer Manual for Community Advisory Boards".

## Objectives

After completing this training, participants will be able to:

- Define the term “clinical trial.”
- Understand the purpose of a clinical trial.
- Discuss who can join a clinical trial.
- List the types of clinical trials.
- Explain how clinical are trials planned.
- Describe some examples of clinical trials in HIV

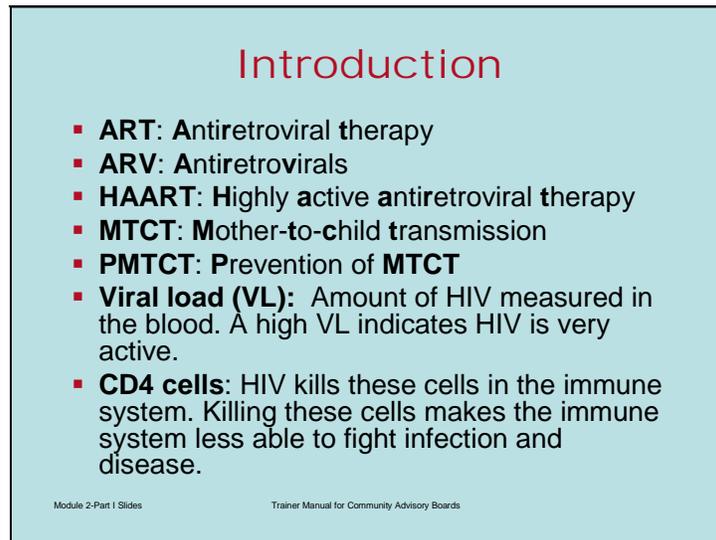
Module 2-Part I Slides

Trainer Manual for Community Advisory Boards

This slide shows the goals for this training program. The slides we will show and the activities planned for this training all are meant to answer these questions:

- What is a clinical trial?
- What is the purpose of a clinical trial?
- Who can participate in a clinical trial?
- What types of clinical trials are there?
- How are clinical trials planned?
- What are some examples of clinical trials with HIV medicines?

## Slide 4



**Introduction**

- **ART: Antiretroviral therapy**
- **ARV: Antiretrovirals**
- **HAART: Highly active antiretroviral therapy**
- **MTCT: Mother-to-child transmission**
- **PMTCT: Prevention of MTCT**
- **Viral load (VL):** Amount of HIV measured in the blood. A high VL indicates HIV is very active.
- **CD4 cells:** HIV kills these cells in the immune system. Killing these cells makes the immune system less able to fight infection and disease.

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- This training is about clinical trials of medicine to treat HIV infection in women, children, and adolescents. The training includes words used to discuss HIV infection that we hope are familiar to you. We will review some of them here. (Review slide).
- We will be explaining other words that may not be familiar to you. But if you want to review the explanation, or look up another word that you do not understand, you can look up the word in the Pocket Glossary you received. We hope that this “portable” glossary will be helpful to you as you learn and as you teach others about these issues.

## Slide 5

## What is a clinical trial?

- Planned **study** involving people



- The goal of a clinical trial is to find better ways to prevent or treat a disease in people.

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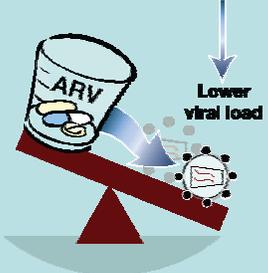
## What is a clinical trial?

- A clinical trial involves people. It is a planned study of a new treatment or a new medicine for a disease. Clinical trials are conducted after the medicine has been tested in the laboratory and in animals and found to be safe.
- The goal of a clinical trial is to find better ways to prevent or treat a disease (e.g. HIV), or symptoms of disease (e.g. pain).

## Slide 6

**Asking the  
research question**

- Does this new medicine work against HIV?



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- Every clinical trial begins with a research question. Usually, the question is “Does this new medicine work against this disease?” or “Does this combination of medicines work against this disease?”
- This picture shows an example of a more specific question, as it is asked in HIV research: “Does this combination of antiretroviral (ARV) medicines work against HIV by lowering HIV viral load?” ARV regimens that can successfully lower viral load in clinical trials are usually able to improve the health of the HIV- infected person.

**Discussion question:** What other research questions about ARVs could we ask? **Trainer:** give participants a chance to think of examples before using the examples listed below):

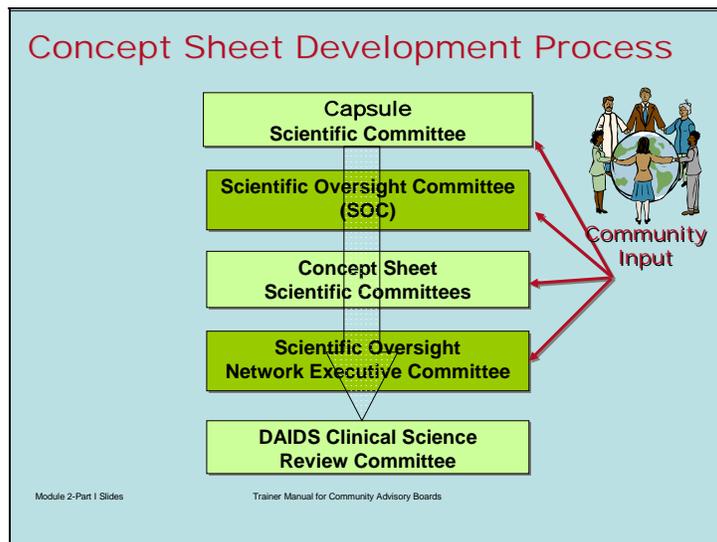
- Can we find simpler, easier to take ARV regimens that are as effective as the more complex combinations we have now?
- What can we do to help people improve their adherence to ARV regimens?
- Is there a better ARV treatment for prevention of mother to child transmission of HIV that is affordable and able to be implemented in resource-poor settings?

## Slide 7



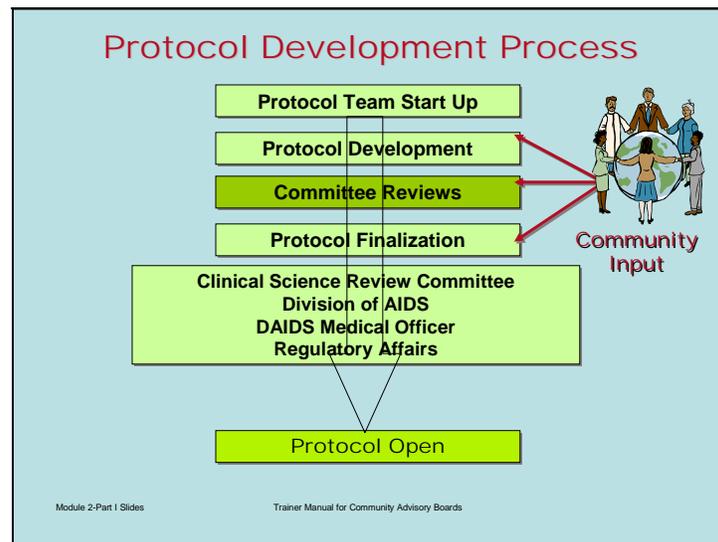
- Once an IMPAACT researcher decides on the research question, the next step is to get input from others and get approval from the appropriate IMPAACT committees to go forward with the development of a detailed plan for a clinical trial. This detailed plan for a clinical trial is called a **protocol**. The goal of the protocol is to design a clinical trial to accurately answer the research questions while keeping study participants safe.
- The protocol must provide a detailed method for getting answers to all of the questions on this slide (and more!):
  - What is the purpose of the study?
  - Who will the participants be?
  - Who is in charge?
  - Where will the trial be done?
  - When will participants need to be available to be in the study?
- The people who work together to develop the protocol are part of the **protocol team** (investigators, nurses, laboratory personnel, etc.). Protocol teams also include a person from the community — a CAB member. Part of the purpose of this CAB training curriculum is to help CAB members better understand protocols and how to review them.

## Slide 8



- This slide shows that the protocol development begins with what is called a **capsule**, which is a very short description of the study question. If the capsule is approved, the next step is to develop a longer, more detailed **concept sheet**.
- Before writing the detailed protocol, the researcher must get advice and approval from other experts. This slide shows the first steps in the protocol development process for the IMPAACT network. We won't go into detail now, but you can see on this slide and the next that there are many steps involved. These reviews by experts are necessary to make the clinical trial as safe, as scientific, and as respectful of the needs of the community and the research participants as possible.
- You can also see on this slide and the next that there are many opportunities for community representatives to take part in the discussion and to influence the protocol as it is being developed. This is why we want to help you to learn about protocols — so you can be an informed participant in the process.
- Often, protocol review is a long, slow process. But there is an important reason for this: the more reviews a protocol undergoes, the safer the protocol will be for the participants.

## Slide 9



- This slide shows the continuation of the process of protocol development. These are the next steps, after those in the previous slide.
- Once a concept sheet is approved, a full team of people who are experts in different areas related to the study are gathered to become part of the **protocol team**. A community representative is part of the protocol team (if a representative is available), and the expertise that they bring to the group is knowledge of their community.

## Slide 10

## Answering the research question

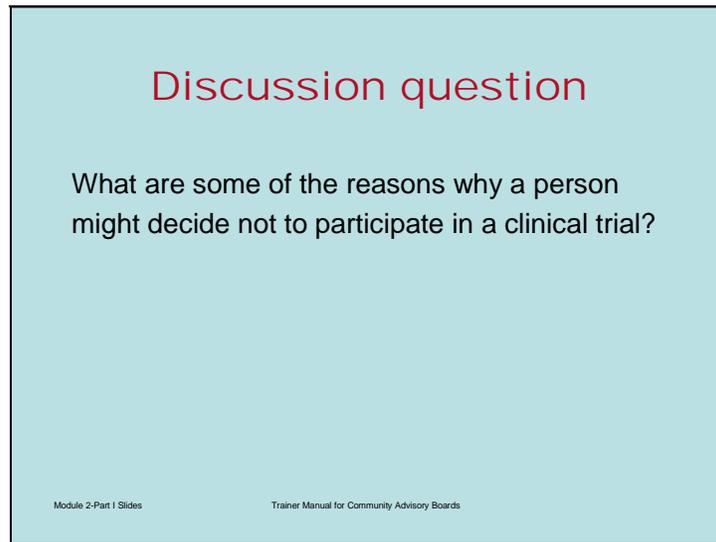


- Once **protocol** is approved, clinicians may offer participation in the study to patients.
- People who choose to join the trial are called participants.

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- After a protocol has been approved at all levels (including the local **Ethics Committee** or **Institutional Review Board** at the local research site), then the CTU may begin to offer patients the chance to participate in the clinical trial. People who choose to join a clinical trial are called **participants** or **subjects**.
- Joining a clinical trial should *always* be a choice. No one can be told he or she *must* participate in a trial. Even if no other treatment is available outside the trial, the person may still choose not to participate in the trial and not to receive treatment. Also, participants may choose to leave the study at any time, even if they previously gave their consent to participate.
- It is critical that patients who are thinking about being in a clinical trial understand *all* of their choices for treatment, and that they freely choose to join the trial. We will talk in much more detail about the **informed consent** process in another training module, because the process of teaching people about a clinical trial is very important.

## Slide 11



**Discussion question**

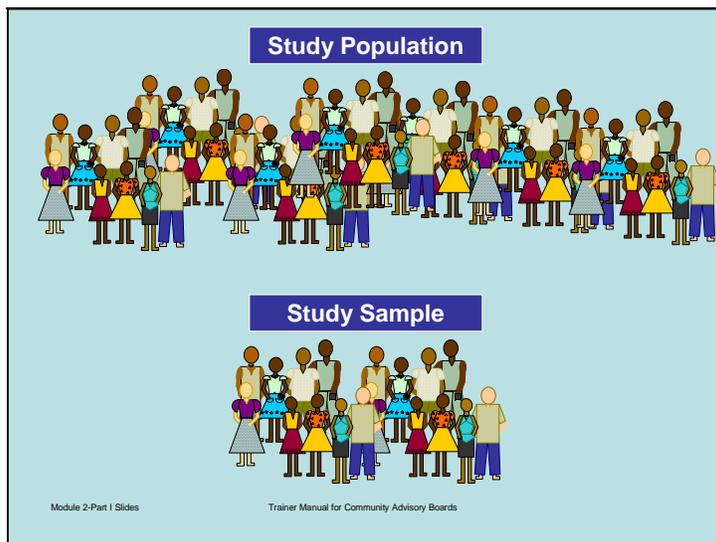
What are some of the reasons why a person might decide not to participate in a clinical trial?

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## Examples of potential answers:

- May not get to choose which treatment is assigned
- Experimental treatment may have unexpected side effects, or the treatment may not be effective
- May require too many clinic visits, or very long clinic visits and tests
- May require the use of contraception, or a specific type of contraception for the duration of the study
- May not really understand the study or how to make a choice
- May be fearful of the use of experimental treatment
- May not trust the researchers
- May feel he/she is being “used”.

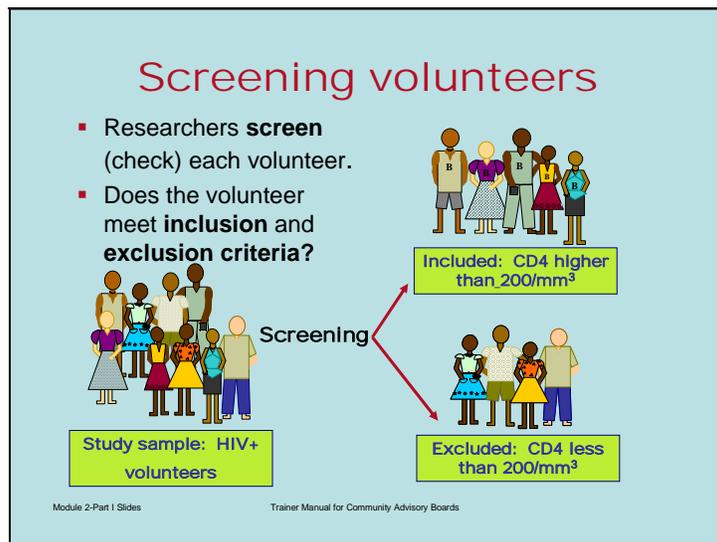
## Slide 12



Before we go further, we should explain these terms:

- When a research question is identified, it always includes a description of the basic characteristics of the people who will be studied, for example “HIV-exposed infants” or “HIV-infected pregnant women not receiving ART”. This broad description is a description of the **population**. The population includes all of the people who share the health characteristics of the people to whom the protocol applies.
- It’s important to remember that the results of the study, scientifically speaking, **ONLY** apply to the population studied. For example, if the clinical trial population is pregnant HIV-infected women with a CD4 count above 500, the information gained from the results of the study only applies to women from this population, and does not directly apply to pregnant HIV-positive women with a CD4 count below 500. (Often the knowledge gained from a study is clinically applied to other populations, but there is no guarantee the same result will occur).
- **Sample** refers to the people from the population who actually enroll in the trial. For example, no study is large enough to enroll all HIV-exposed infants in the world. Therefore, the clinical trial will enroll a sample of people from the population that is being studied. Participants in the sample who enroll in the study will subsequently be assigned to a research group.

## Slide 13



- Before allowing a volunteer to join the study, researchers **screen** (check) each volunteer. They check to make sure he or she meets the **inclusion** and **exclusion criteria**. These criteria are specific health characteristics, which will help researchers judge if:
  - It is safe for the **volunteer** to participate in the study
  - If the volunteer has the health characteristics that will allow the researchers to answer the study question.
  
- This slide shows one example of inclusion and exclusion criteria: on the left side of this slide is the group who have agreed to be screened. On the right, you can see that some of the people meet the inclusion criteria; they will be included in the study, because they each have a CD4 count of at least 200/mm<sup>3</sup>. The other small group on the right represents those volunteers who did not meet the inclusion criteria for the study. These volunteers are not able to join the study because their CD4 counts are lower than 200/mm<sup>3</sup>. They will be excluded from the study.
  
- Again, once the researchers accept a volunteer into the study, the volunteer is then referred to as a study subject or study participant.

## Slide 14

## Collecting baseline data

- As one of the first steps in the trial, clinicians perform a physical exam and other tests for each participant.
- The results of these exams and tests are called **baseline data**.
- **Data = information**

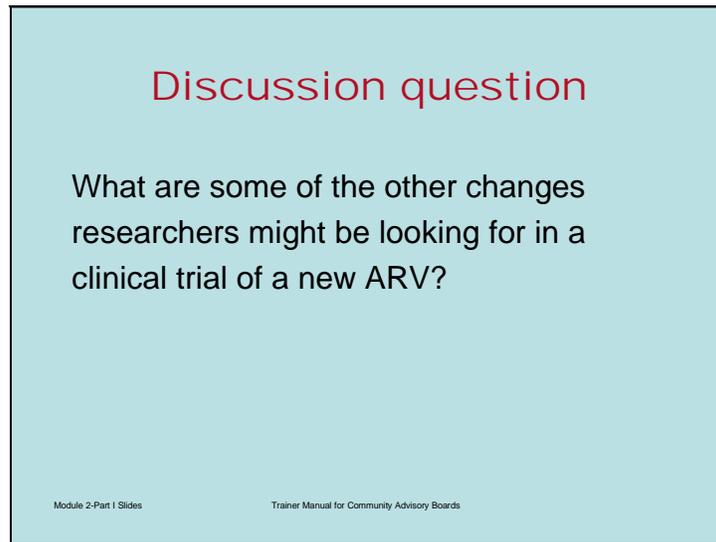


Module 2-Part 1 Slides  
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Before starting the study medicine or treatment, the researchers perform a medical examination and other health tests. The results of this pre-treatment examination and tests are called **baseline data** (information).

Once treatment starts, the information collected from examinations and tests is called **follow up data**. Baseline and follow up data are compared in order to measure the effect of the study treatment.

## Slide 15



**Discussion question**

What are some of the other changes researchers might be looking for in a clinical trial of a new ARV?

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**Trainer:** This is also discussed in the next slide.

Examples:

- Better health indicators (like no infections, weight gain, increased energy and better quality of life)
- Side effects, such as a rash, symptoms like headaches or diarrhea, anemia
- Trouble with adherence to the medicine schedule
- Lower viral load (less active virus)
- Higher CD4 count (strengthening immune system)

## Slide 16

## Schedule of Events

- After treatment starts, participants are examined and tested at regular times (followed up) based on the **Schedule of Events**.



Mon	Tue	s			Sat	Sun
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

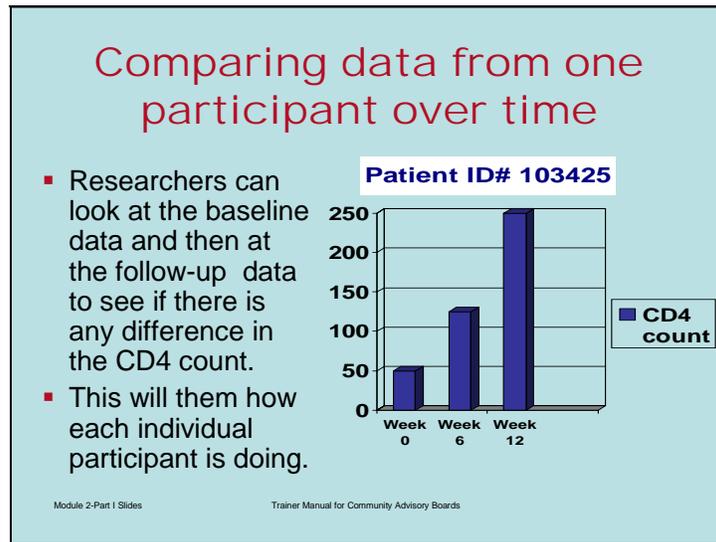


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- After treatment starts, participants are examined at regular time visits (weekly, monthly, every 3 months) based on the **Schedule of Evaluations**. These are called follow-up visits. At follow-up visits researchers look for changes that may have happened in the health of the individual participant since baseline.
- The changes the researchers find will tell them if the medicine being tested is working (is **effective**) and if it is safe for that participant. For example, the Schedule of Events may require that a participant have a viral load and a CD4 test each month. If an ARV regimen is effective for the participant, viral load will be lower at follow-up visits than at the baseline visit.

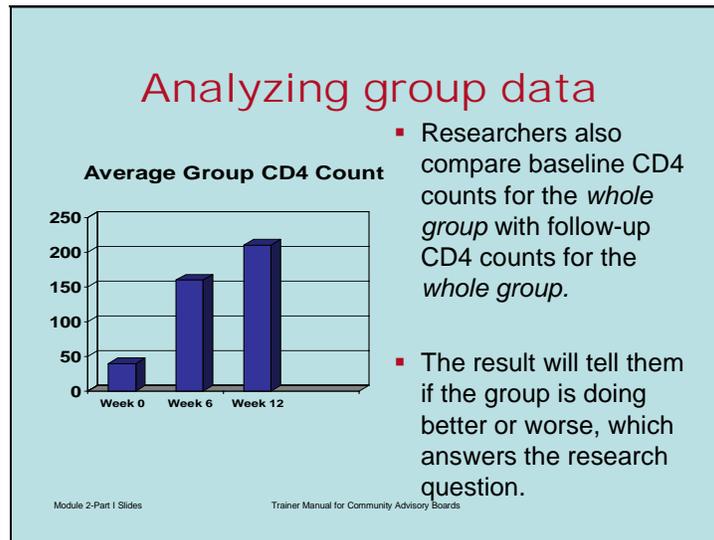


## Slide 18



- This slide shows baseline and follow-up data for one participant. The blue bars are the CD4 count. Each set of bars shows the CD4 count at a different week in the trial (Look at the line showing the number of weeks at the bottom of the graph.)
- As you can see, the CD4 count for this patient was low at week 0 (the first blue bar is at about 50). At each of the two follow-up visits — week 6 and week 12 — the CD4 count was higher (blue bar is at about 125 for week 6 and at 250 for week 12).

## Slide 19



- Then researchers analyze (study) the data they collect on all of the participants to learn about the safety and effectiveness of the study medicine. Although each participant is followed carefully, it is by looking closely at the data from the entire group of participants that can answer the research question: is the medicine safe and effective?
- In the example shown on the graph, you can see that the average CD4 count of participants taking the study medicine increased from week 0 to week 12.

## Slide 20

## Publishing results



- Researchers publish results in scientific journals.
- Clinicians and researchers learn from the results.
- Researchers present results to study participants and the CAB
- CAB members help teach community about results.

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- When a study is complete and all of the data have been analyzed, researchers seek to publish the results in a scientific journal. Scientific journals usually have the data reviewed by other scientists (not on the study) before publishing it. They check to make sure that the study was performed scientifically and ethically. This is called a **peer review**.
- Publishing the study results in a journal allows doctors, nurses, other healthcare workers, and other researchers who care for people with HIV to read the results and learn from them. The results of clinical trials can then guide the clinical care of people with HIV. For example, we use ARVs to lower the risk of transmission of HIV from an HIV+ pregnant woman to her infant because clinical trials have proven that ARVs are both safe and effective for this purpose.
- Researchers must also make sure that study participants hear and understand the results of the clinical trial in which they participated. One of the roles of the CAB is to help communicate study results to study participants and to others in the community.

## Slide 21



- To review: The hope for any clinical trial is that we will learn more about preventing or treating a disease. By learning more about medicines for HIV and its complications, we can improve patient care and the lives of people with HIV and their families.
- This slide reviews the process we just discussed: identifying a research question, developing a protocol, enrolling subjects, analyzing data, and publishing results to improve treatment HIV infection and related diseases.
- Community representatives (CAB members) can help to identify and prioritize research questions, participate in protocol development, help educate and recruit people who may want to participate in the trial, and communicate the results of the clinical trial to people who care about it.

# CLINICAL TRIALS HIV 1-2-3 GAME

## Trainer Instructions

### Module 2

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Time frame (**60 minutes**)

#### Purpose

- To reinforce learning from Modules 1 and 2
- To allow learners the opportunity to demonstrate what they know
- To allow the group experts to teach others in their group
- To cover basic and some advanced HIV/AIDS clinical trials and Community Advisory Board information in an easy and enjoyable way
- At the completion of the game, the facilitator should answer unanswered questions and clarify misconceptions.

#### Note to Trainers

You may add, subtract, or otherwise adapt the game to meet the needs of your group.

#### Object

The team that is first to answer *one question from each category of questions* is the winner. Answering a question correctly wins the team a color-coded category game piece. Once the team has answered five questions from five categories correctly (they will have a game piece of each of all five colors) the team has won the game.

#### Format/Materials

- Game questions (5 categories; one color per category) for each participant
- Game questions with answers (for the trainer)
- Color-coded game pieces (one set of game pieces = one piece for each of 5 colors. You need as many sets of game pieces as there are teams.
- Two to four teams. Try to construct teams so that each group has an equal number of experienced vs. inexperienced community members). Groups usually have at least 3, and no more than 10 players. Name the teams “Group 1”, “Group 2” etc.
- (Optional) prizes

## Steps

- Form teams
- Distribute game questions to all participants
- Give the teams about 25 minutes to work together to answer as many questions as possible—tell them not to linger too long on any one question if it is difficult to answer
- Give warning when close to time limit (“5 more minutes”).
- Go over rules of how the game is played (see below)
- *Please note:* It is an advantage to go first, so it’s important to have a random way of deciding the order in which teams will be asked questions

## Rules

- The first team begins by choosing a color category and a question to answer, then reads the question out loud and gives the answer. (They have 10 seconds to answer.)
- Judgment should be used by the trainer: Answers do not have to be absolutely perfect, but should in general be accurate. Where some questions have long answers provided for the trainer, the entire answer is not required, and a partial accurate answer can be accepted.
- If correct, the team gets credit for that category, and they do not answer questions in that category again. (To keep track of each team’s categories and credits for correct answer, the trainer usually takes the game piece representing the correctly answered category for that team, and tapes it to the wall or the flip chart under the team name. This way, everyone can see what categories have been answered correctly by each team.)
- Then the next team takes a turn. Make sure all participants hear the complete, correct answer to the question.
- If the question is incorrectly answered, the next team gets to answer that question or another question of their choosing.
- Once a question is answered correctly, no other team can use it.
- Each team only answers one question from each category. Once they have answered a question from a category correctly, they can no longer pick questions from that category to answer.
- The first team to achieve 5 different color game pieces first is the winner (They are first to answer one question correctly from each of the 5 categories of questions).



# Clinical Trials HIV 1-2-3 Game

## Questions and Answers for Trainer

### Module 2

#### Introduction to Clinical Trials

#### CATEGORY I (Pink):

#### HIV Infection

1. What is the "viral load" test?

**Answer:** The viral load is a blood test that measures the amount of HIV in the blood. This gives an idea of how active the virus is, and also can be used to measure whether antiretroviral medicine is working.

2. Why do we measure CD4 cells in a person with HIV infection?

**Answer:** The number of CD4 cells indicates how much damage has been done to the immune system. We measure CD4 cells in a person with HIV because the virus specifically attacks CD4 cells, thereby damaging the immune system.

3. What does "PMTCT" stand for?

**Answer:** Prevention of Mother-to-Child Transmission (of HIV)

4. What does "HAART" stand for?

**Answer:** Highly Active Antiretroviral Therapy

5. What is the purpose of the body's immune system?

**Answer:** To protect the body from infections (and other foreign invaders, such as cancer).

## CATEGORY II (Blue): Clinical Trials Part 1

### 1. What is a clinical trial?

**Answer:** A clinical trial involves people in a planned study of a new treatment or medicine to treat or prevent a health problem.

### 2. Give one (general) example of a research question.

**Answer (examples):**

- Will this new medicine reduce the risk of mother to child transmission?
- Will this vaccine prevent HIV infection?
- Will this medicine lower viral load? or Does this new medicine work against HIV?

### 3. What is a protocol?

**Answer:** A protocol is a detailed plan for a clinical trial.

### 4. What is the goal of a clinical trial?

**Answer:** The goal of a clinical trial is to find better ways to prevent or treat a disease or symptoms.

### 5. What is a clinical trial (research) network?

**Answer:** A clinical trials network is an organized group of clinics/hospitals in different locations who work together on the same clinical trials. Volunteers in different geographic locations can enroll in the same clinical trial. Researchers in many locations can work together on a common problem (like HIV).

## CATEGORY III (Green): Clinical Trials Part II

1. What do we mean by “baseline” or “baseline data” in a clinical trial?

**Answer:** “Baseline” refers to the information about a participant that is gathered before treatment on the study begins. Baseline data is later compared to information collected later, while the participant is being treated on the study.

2. In a clinical trials protocol, what is meant by the “Schedule of Events”?

**Answer:** The “Schedule of Events” is the schedule of clinic visits and testing that a trial participant is expected to follow over the course of the study. For example, a participant might be expected to have a physical examination and viral load and CD4 testing every four weeks while on study.

3. What are “inclusion and exclusion criteria”? (also called eligibility criteria)

**Answer:** These are the health characteristics used to determine if a volunteer may join a clinical trial. These criteria are meant to determine if it is safe for a volunteer to join the study, and if the volunteer has the health characteristics that will allow the researchers to answer the study question. (Example: Inclusion criteria=CD4 count over 200, Exclusion criteria CD4 count below 200).

4. What is the purpose of the protocol review process?

**Answer:** The protocol review process ensures that the trial is well-designed, respects the rights of the participants, and includes enough monitoring and other safety measures to protect participants.

5. What does it mean to analyze study data?

**Answer:** Analyzing data refers to checking all of the information collected from study participants in the trial, comparing baseline data to data collected while on treatment. Also comparing data from one treatment group to a group receiving a different treatment.

## CATEGORY IV (Gray): Community Participation in Research Part I

1. What does "IMPAACT" stand for?

**Answer:** IMPAACT stands for International Maternal, Pediatric, and Adolescent Clinical Trials.

2. Name two reasons for community participation in research

**Answer (examples):**

- Advocates for the community
- Encourage investigators to respond to the community's questions and concerns regarding research
- Monitor research to ensure that it is fair to the community and volunteers
- Assist researchers with planning the trial and with conducting the research
- Teach community members about research

3. Name at least two categories of people who might be effective CAB members for an IMPAACT clinical trial unit.

**Answer (examples):**

- Parents or caregivers of children exposed or infected by HIV;
- People who live in the geographic area and are infected or affected by HIV;
- People who have influence or are leaders within the geographic community
- Stakeholders (a person with a direct interest, involvement, or investment
- Health care workers involved in HIV treatment
- Pregnant women with HIV +/- or their partners

4. Explain the difference between a CAB and a Support Group?

**Answer:** A support group is a gathering of people with a similar problem (HIV) who meet to give and receive support for personal issues. Emotional support is provided in order to help members cope with the personal issues they face.

A CAB exists in order to advocate for the community. A CAB serves as a liaison to the researchers from the community: Communicating with researchers about community needs, and communicating with the community about research.

5. What are the 3 levels of community participation within IMPAACT?

**Answer:** IMPAACT is structured so that there are community representatives at the local level, at the regional level, and at the network (ICAB) level of the organization. In addition, IMPAACT is represented in the group "Community Partners", which includes representative community members from all of the DAIDS-funded research networks.

## CATEGORY V (Purple): Community Participation in Research Part II

1. Name one responsibility to the CAB of the Principal Investigator at a local site:

**Answer (examples):**

- Provide overall vision for the site
- Attends CAB meetings as needed
- Gives the CAB updates on clinical trials in development, clinical trials that are open and enrolling patients at the site, and clinical trials that have been completed (results of clinical trials)
- Assign a CAB liaison from the research team
- Listen to community concerns and questions
- Support CAB training so that CAB members are prepared to do what they are asked to do

2. Name one responsibility of the CAB liaison at a local site:

**Answer (examples):**

- Initiate the CAB
- Provide support for communications, coordination of meetings and activities
- Act as a resource
- Coordinate CAB orientation and training
- Assist with CAB recruitment
- Assist PI with providing relevant materials, information, trial updates

3. What is a "mission statement"?

**Answer:** A mission statement is a broad statement about the CAB purpose. The statement gives a general overview that answers who the CAB serves, what the CAB does, and how the CAB plans to accomplish the goal.

4. Give one reason that someone might want to join a CAB

**Answer (examples):**

- To do something for my community
- Interested in the work
- To learn more about research and treatment of HIV
- Personally affected by HIV
- To advocate for people with HIV
- Enjoy it and like the people

5. Name one example of a possible policy (rule) that a CAB might want to have.

**Answer (examples):**

- Schedule of meetings
- Roles of various members
- Define membership criteria
- Define number of members and length of service
- Confidentiality rule
- Dropping members: why, when, how

# Clinical Trials HIV 1-2-3 Game

## Question Pages for Participants

### Module 2

#### Introduction to Clinical Trials

#### CATEGORY I (Pink):

#### HIV Infection

1. What is the "viral load" test?

2. Why do we measure CD4 cells in a person with HIV infection?

3. What does "PMTCT" stand for?

4. What does "HAART" stand for?

5. What is the purpose of the body's immune system?

## CATEGORY II (Blue): Clinical Trials Part 1

1. What is a clinical trial?

2. Give one (general) example of a research question.

3. What is a protocol?

4. What is the goal of a clinical trial?

5. What is a clinical trial (research) network?

## CATEGORY III (Green): Clinical Trials Part II

1. What do we mean by “baseline” or “baseline data” in a clinical trial?

2. In a clinical trials protocol, what is meant by the “Schedule of Events”?

3. What are “inclusion and exclusion criteria”? (also called eligibility criteria).

4. What is the purpose of the protocol review process?

5. What does it mean to analyze study data?

CATEGORY IV (Gray):  
Community Participation in Research Part I

1. What does "IMPAACT" stand for?

2. Name two reasons for community participation in research.

3. Name at least two categories of people who might be effective CAB members for an IMPAACT clinical trial unit.

4. Explain the difference between a CAB and a Support Group?

5. What are the 3 levels of community participation within IMPAACT?

**CATEGORY V (Purple):**  
**Community Participation in Research Part II**

1. Name one responsibility to the CAB of the Principal Investigator at a local site:

2. Name one responsibility of the CAB liaison at a local site:

3. What is a "mission statement"?

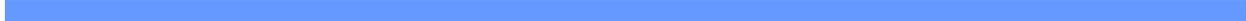
4. Give one reason that someone might want to join a CAB.

5. Name one example of a possible policy (rule) that a CAB might want to have.



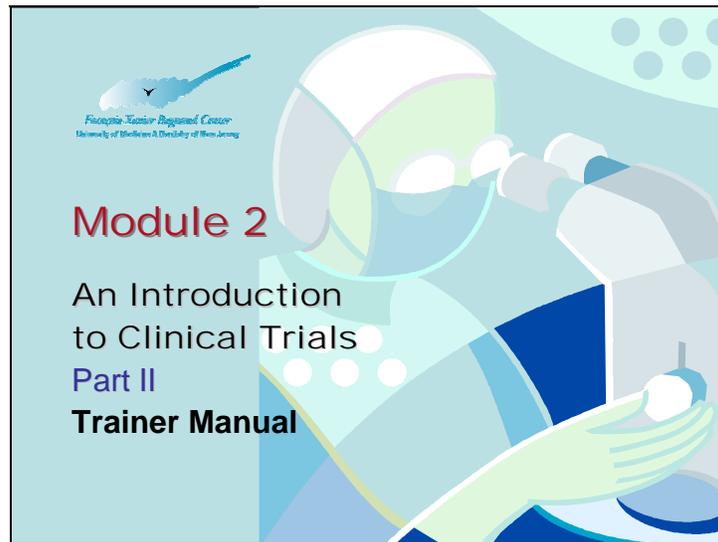
## **Module 2**

### **Part II Slides - Insert Here**





Slide 1



## Slide 2

This teaching tool was developed by the François-Xavier Bagnoud Center at the University of Medicine and Dentistry of New Jersey, with the support of the International Maternal Pediatric and Adolescent Clinical Trials (IMPAACT) network.

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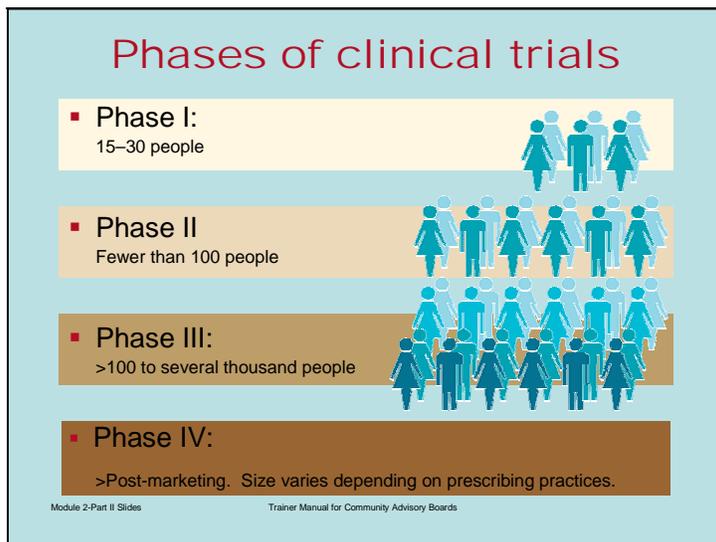


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**Version 1.0 – May 2007**

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## Slide 3



- Clinical trials testing new medications or treatments are done in phases. Trials start with Phase I trials, with very few participants, to test the safety of the treatment. If there are no serious problems, trials continue through Phases II and later Phase III. Sometimes there is also a Phase IV.
- The early Phases are only checking for safety. To determine the effectiveness of a treatment, researchers generally must study the treatment in larger numbers of people in Phase III trials.
- Pharmaceutical companies (and sometimes others) may continue to collect information about a medicine even after it has been approved. This helps to give information about the long term benefits or problems. This type of study is a “Phase IV”, or “post-marketing” study.
- We’ll talk about each of these phases in more detail in the next few slides.

## Slide 4

**Phase I: safety**

- **Goal:** to determine if medicine is safe in a small group of healthy volunteers



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- If a new medicine works well in the laboratory, and is safe when tested in animals, a **Phase I** study to see if it is safe for humans is the next step. Phase I trials focus on testing the medicine in about 10-30 healthy volunteers. They test the medicine in healthy people because they are less likely to have serious bad effects from medicines. For example, a new ARV medicine for HIV would first be tested in the laboratory, then tested in animals, and then tested in a small group of Phase I study participants who do not have HIV and are generally healthy.
- In Phase I studies, most often the study participants receive the medicine for only a few days. During this time, the researchers check the participants very closely. For this reason, they often do Phase I studies in the hospital.

## Slide 5

**Phase II study: safety and effectiveness**

- If there are no serious safety problems in the Phase I, the medicine is tested in a **Phase II** study with more people.



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- If the researchers do not find safety problems in the Phase I trial, they test the medicine in a **Phase II** trial with a larger group of people (31-100). Unlike the healthy participants in Phase I studies, the participants in Phase II studies *do* have the disease being studied. Unlike Phase I studies, a new ARV medicine for HIV in a Phase II study would be tested in people who are infected with HIV.
- If it is a trial to *prevent* a disease rather than to *treat* a disease, the participant may *not* have the disease. For example, in a study of a medicine to prevent mother-to-child transmission of HIV, the goal is to prevent the infant from getting the disease.
- The goals of a Phase II study are to determine if the medicine is safe and effective, and to find out how much medicine a person needs to take for the medicine to be effective.
- Studies focusing on how much medicine to take are called **dose-finding studies**. Phase II studies are sometimes dose-finding studies. Dose-finding studies usually involve many blood tests to determine the amount of medicine in the blood at different times. This is called **pharmacokinetic** testing, or **PK** testing. This type of testing, while difficult, is crucial to finding the right doses of medicine that is both safe and effective.

## Slide 6

## Phase III: safety and effectiveness

- If Phase II results show medicine has no major safety problems and seems to be effective, researchers do a **Phase III** study.



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- If the results of the Phase II study show the medicine is safe and effective, the researchers conduct a **Phase III** study. This study includes an even larger number of patients (hundreds or thousands). In the Phase III study, the researchers continue to check the safety of the medicine, but increase the focus on how well it works (how effective it is) to treat or prevent the disease.

## Slide 7

**Phase III: effectiveness and safety**

- Goals
  - Find out how well medicine works (effectiveness).
  - Continue to check safety.



Experimental treatment

vs.

Standard treatment

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- In Phase III studies, researchers also study how well the new medicine works compared to a medicine they already know is safe and effective. This type of medicine is called the **standard treatment** for the disease. This type of study is called a **comparison trial** or a **controlled trial**. (Later in this training, we will be discussing what the word “controlled” means when describing a study.) For example, a Phase III study might compare a new medicine to treat HIV infection with an HIV medicine that is already being used and is known to be effective for treating HIV.
- Comparing the data from the two groups is a *much* more accurate way to study a new medicine than to simply look at the effects of a new medicine in one group of people.

## Slide 8

Phase IV study

- Goal: to determine long-term safety and effectiveness in large numbers of people

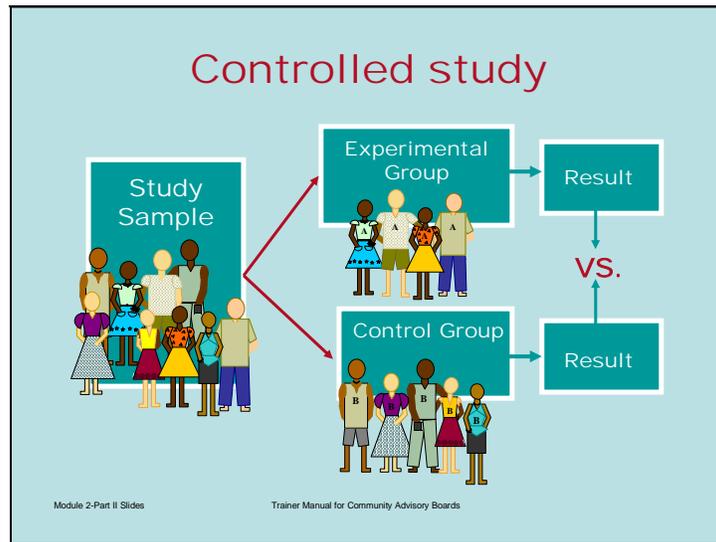
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- **Phase IV** studies are done *after* a new medicine is approved for sale and is being used. They are also often called "**post-marketing studies**" because the medication has already been approved and can be prescribed and sold.
- In these trials, data is just collected from people who have been prescribed the medication by their clinician. There is no control group or comparison group. The main reason to do post-marketing studies is to study the long term effects of the medicine.
- Sometimes problems or good effects from a medicine can be seen only after participants take the medicine for many years. These studies are usually done by the pharmaceutical company that developed the medicine rather than by a clinical trials network like IMPAACT.

**Discussion question:** If the researchers already know the medicine works and is safe, why are Phase IV studies very important? Can you think of an example where a long-term problem with a medicine was discovered *after* it was approved and sold?

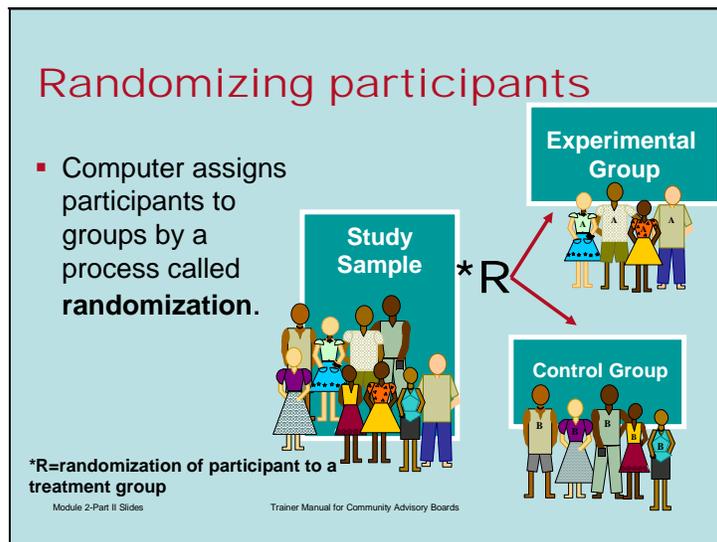
*Example:* Over time, it has become clear that a class of medicines used for arthritis increased the risk of heart attacks in people who took one of these medicines. This was not clear in the clinical trials in earlier Phases. It became clear once data was available from thousands of people over a long period of time.

## Slide 9



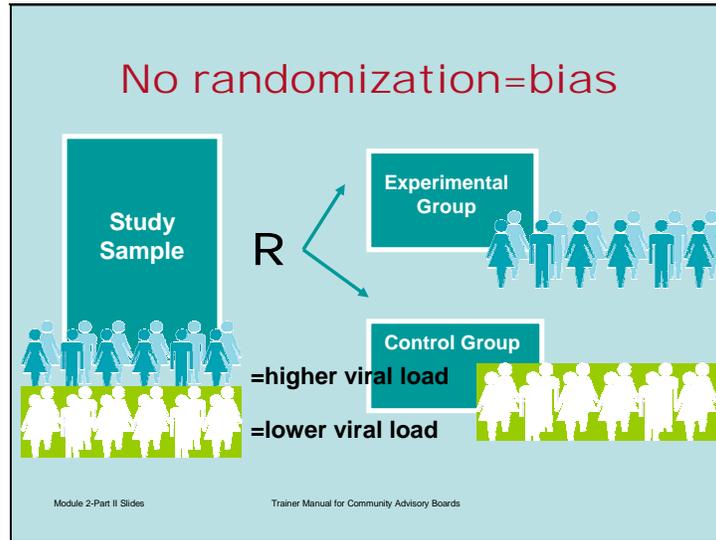
- Now we're going to talk more about what is called the "study plan" or "study design". Researchers must design a study in the best (most scientific) way to find the most accurate answer to the research question.
- This slide shows the plan for a **controlled clinical trial** comparing two medicines. On the left, you see the study sample, which includes all of the participants in the clinical trial. On the right, you can see that each of the volunteers in the study sample has been assigned to the experimental group (receiving new medicine) or the control group (receiving standard medicine).
- After the experimental group has taken the new medicine and the control group has taken the standard medicine for many weeks, the researchers compare the results for the two groups. And they will be able to find out if the new medicine is more or less, or equally as effective as the standard medicine. As important, they will also find out if the new medicine is safe.

## Slide 10



- In this picture, you can see that about one-half of the study sample will be in the experimental group (also called **treatment group**), and about one-half in the control group. The researcher does not choose the group each participant will be in. And the participant is not allowed to choose. A computer decides who will be in what group by a process called **randomization**.
- Here is an example of how randomization works. Imagine if there were a large jar containing a 50:50 mixture of blue and red beads. When a participant is enrolled in the study, he or she picks a bead from the jar *while blindfolded*. Neither the participant nor anyone else controls which bead she picks.....the choice of bead is *random*. If the red bead indicated the experimental group, and the blue bead indicated the control group, then about ½ of the sample of participants would be in each group. What's more, other characteristics of the groups would be likely to be equal too (such as the number of men and women, for instance).
- Randomization is very important because it prevents **bias** (unfair favoring of one group over another). In the research network, we don't use beads, but a computer randomizes participants in a way that is random and not under the control of the researcher or the participant.
- **Quick demonstration of randomization:** To demonstrate randomization, place a pile of two types of beads, beans, pasta or other common item on the table. The number of items on the table must be equal to the number of participants in this exercise. Have participants come to the table one by one. The participant must close eyes, the trainer mixes up the pile a bit, and the participant picks an item.

## Slide 11

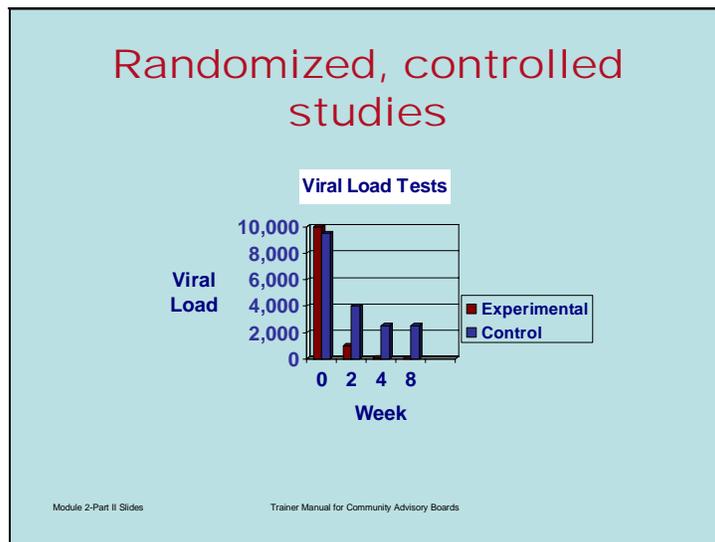


- This slide shows an example of how bias can occur if a study is not randomized. Imagine if participants with higher viral load were most interested in the experimental medicine because they believed it would help them more than the standard medicine that would be given to the control group. So participants with high viral loads (blue people) were much more likely to choose to be in the experimental group. In contrast, participants with low viral load were not as worried about their viral load, and were confident that the standard medicine would be adequate to take care of them. They did feel they needed experimental medicine that might expose them to unexpected side effects. So those participants with a low viral load (in green) tended to enroll in the control group.

**Discussion question:** Would this trial reach an accurate conclusion? Why or why not?

Answer: No, the groups are unequal, and therefore bias has been introduced and will influence the results. The groups are not equal, because the experimental group has many more people with high viral loads, which might effect the outcome of the study.

## Slide 12



- In a randomized, controlled clinical trial, the researchers look at the effects of the medicine in the experimental group and the effects of the medicine in the control group. The graph in this picture shows how the viral load data from the two groups are nearly the same at the beginning of the trial. In this chart, the red bars represent the experimental group, and the blue bars represent the control group. At the bottom of the graph, the numbers indicate what week the viral load data was collected, beginning at Week 0 (baseline) and continuing through week 8. This graph represents the mathematical average viral load result at each of the 4 weeks from each group.
- Every participant in both groups had a viral load test about every 2 weeks. At the **baseline** (before treatment) Week 0 the viral load in the 2 groups is about the same — both the red bars (and the blue bars are about the same height, showing that the viral load for both of the groups is about 10,000). This is an important point supporting randomization of participants, because at baseline the 2 groups *should* be about the same if the trial is to be accurate. Can you see how important it is for the two groups to be about equal, and to avoid bias in treatment assignment?
- The groups start to receive treatment, and have their viral load measured at weeks 2, 4, and 8. As you can see by looking at the bars, as time goes on, the results from the groups start to look a little different. The viral load tests in the experimental group are starting to be lower than the results in the control group. At week 8, the blue bar for the control group indicates an undetectable viral load (below 50) and the red bar for the experimental group indicates a viral load over 2000.

## Slide 13

## Double-blind studies

- **Double- Blinding:** Neither the participant nor the researcher know the treatment assignment during the entire trial



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- Not letting the participant or the researcher know which group a participant is in is called **double-blinding**. Like randomization, blinding reduces the risk of bias. For example, imagine a study where one group of participants receives an experimental medicine to treat pain, and the other group of participants receives a standard type of medicine to treat pain. In a double-blind study, neither the researcher nor the participant knows whether the participant is assigned to the experimental or the control group. This way, neither the researcher nor the participant can be influenced by what they “expect” to happen.
- When all of the information has been collected in a blinded study, the study is “unblinded” and the researchers analyze the data. Then they will know which medicine is more effective and safer. The researchers will also tell the participants about the results and about which medicine they are taking.

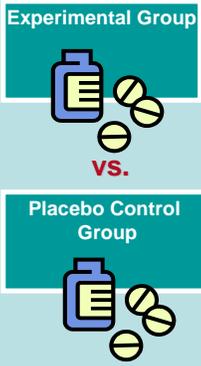
**Trainer:** To demonstrate the concept of “blinding”, assign all the participants in the training to a group, but don’t tell them which group they are in. Tell participants that they have been assigned to a group, and that each group is going to receive lunch. Explain that participants in Group 1 will be receiving a lunch that is made from a recipe the cook has never tried to use before, and that participants in Group 2 will be receiving lunch that is made from a recipe the cook has successfully used many times in the past. Lunch will be served, but each participant will be taking it home to eat rather than eating it in a group. They will take an evaluation form with them to rate their enjoyment of the lunch. Data from the evaluation forms will be collected and studied, and then participants will be told to which group they were assigned.

**Discussion:** Do participants think their evaluation of the lunch could be biased if they knew in advance to which group they had been assigned?

## Slide 14

## Placebo-controlled studies

- What if there is no medicine known to be an effective treatment?
- Researchers compare new medicine with a **placebo**.
- The placebo and experimental treatment are made so that they look exactly the same.

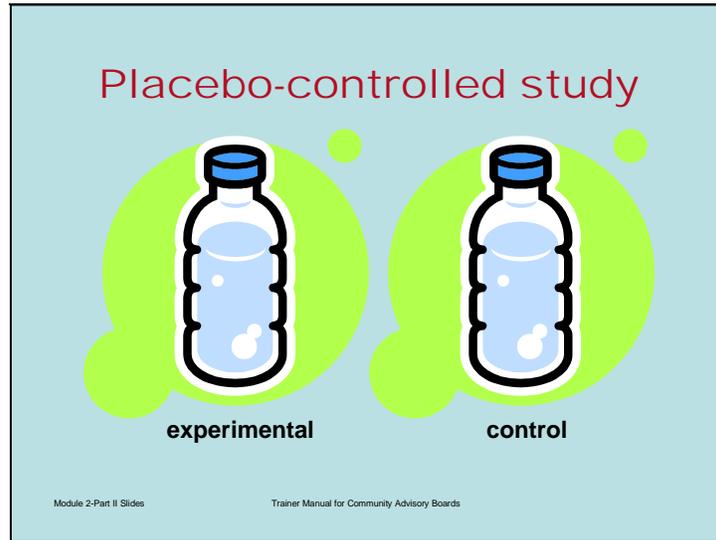


The diagram illustrates a placebo-controlled study. It features two teal boxes. The top box is labeled 'Experimental Group' and contains an icon of a blue pill bottle and three yellow pills. Below this box is the text 'vs.' in red. The bottom box is labeled 'Placebo Control Group' and contains an identical icon of a blue pill bottle and three yellow pills. The entire diagram is set against a light blue background.

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- We said earlier that to judge the effectiveness of a new medicine, we must compare it with a medicine known to be effective. But what if there is no medicine known to be effective? For example, when doctors first discovered AIDS in the early 1980s, no treatment existed. It was several years before researchers tested the first antiretroviral (ARV) medicine. Because they were testing the *first* ARV, there was no medicine to use for the control group. The standard of care was, unfortunately, no treatment for HIV at all.
- When researchers are studying a new drug, and there is no other treatment available, they usually compare the new medicine with a **placebo**, a pill that looks exactly like the new medicine but *contains no medicine* (inactive). The placebo and the pills are made to look exactly the same. That way, the researchers and participants do not know who is taking the pill with medicine and who is taking the placebo. And the risk of bias is reduced.
- When the control group is receiving **placebo**, the study is called a **placebo-controlled** study.

## Slide 15



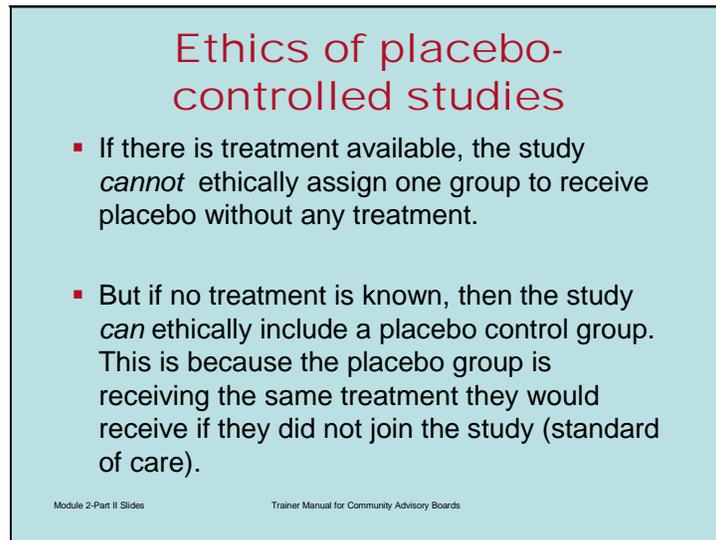
**Trainer:** If you'd like to demonstrate the concept of placebo, show 2 bottles of water that look exactly the same. Tell the group you have added a very small amount of salt to one bottle, and that this salted water represents the experimental medicine, while the placebo control group is represented by the water with no added salt. Ask them to imagine that they are given one of the bottles (without knowing which type of bottle it is), and an hour after they drink the water, they are asked to report on how thirsty they are.

Do participants think that their evaluation of their thirst would be influenced had they known which type of water they received?

Now, ask participants to imagine that ½ the glass was given a bottle of water (the experimental group) and the other half was given nothing.

Ask "Would the knowledge of receiving water or not receiving water influence your perception of how thirsty you think you feel?"

## Slide 16



### Ethics of placebo-controlled studies

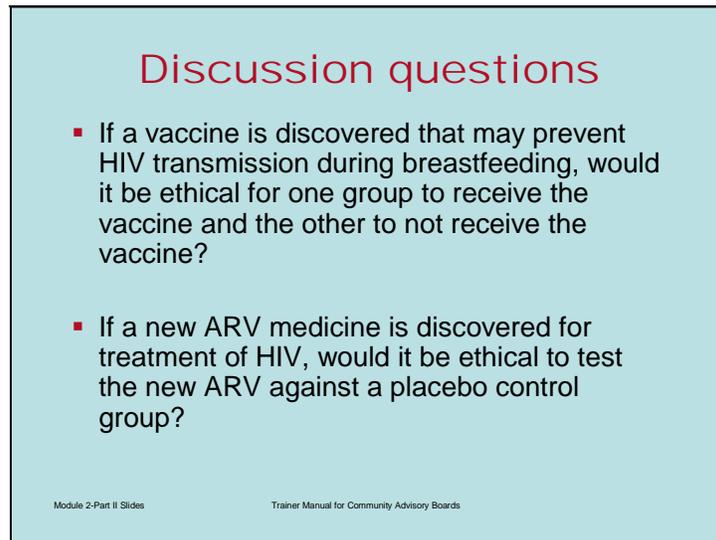
- If there is treatment available, the study *cannot* ethically assign one group to receive placebo without any treatment.
- But if no treatment is known, then the study *can* ethically include a placebo control group. This is because the placebo group is receiving the same treatment they would receive if they did not join the study (standard of care).

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There are strict international rules about clinical research to make sure that research is **ethical** (fair, right, or just). We will have an extensive discussion of the ethics of placebo use in clinical trials in another training (Module 6).

In short, if there is treatment available, it is unethical to have a group that does not receive any treatment—only placebo. If there is no treatment available, then the standard of care is no treatment, and it is ethical to use a placebo group to compare with an experimental treatment.

## Slide 17



The slide is a light blue rectangle with a black border. At the top center, the title "Discussion questions" is written in a red, sans-serif font. Below the title, there are two bullet points, each starting with a red square. The first bullet point asks if it would be ethical to give a vaccine to one group and not to another. The second bullet point asks if it would be ethical to test a new ARV medicine against a placebo control group. At the bottom left, there is small text that says "Module 2-Part II Slides". At the bottom center, there is small text that says "Trainer Manual for Community Advisory Boards".

### Discussion questions

- If a vaccine is discovered that may prevent HIV transmission during breastfeeding, would it be ethical for one group to receive the vaccine and the other to not receive the vaccine?
- If a new ARV medicine is discovered for treatment of HIV, would it be ethical to test the new ARV against a placebo control group?

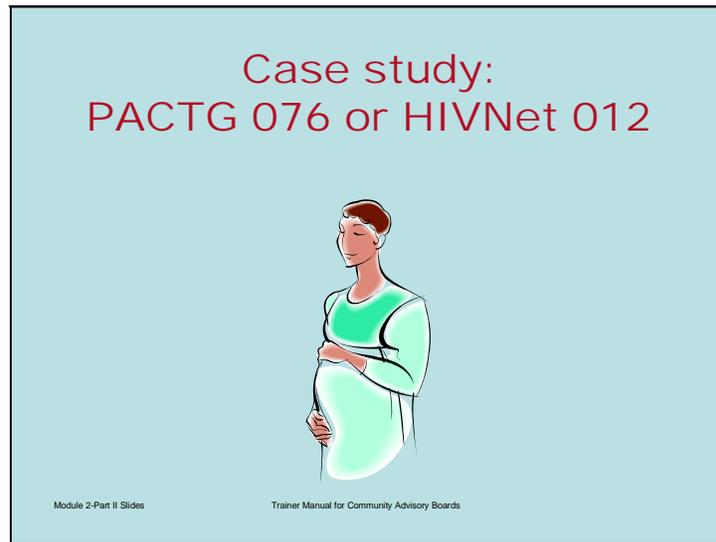
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**Trainer:** Please facilitate a discussion about ethics and placebos with the group. In answer to the questions above, the current standard of ethical research is below:

- In situation one, the answer is yes. It would be ethical for there to be a control group that did not receive the vaccine. However, both groups must receive whatever ARV treatment is being used to try to prevent MTCT during breastfeeding. (This is only applicable to areas of the world where breastfeeding is preferable to bottle feeding, even in HIV-infected women).
- This is not an ethical study design, because treatment for HIV is effective and available. It cannot be withheld. However, if both groups receive the standard ARV treatment regimen, then it would be ethical to add an experimental medication to one group, and a placebo medication to the other group. The group given a placebo are given the same treatment they would receive if they were not in the study, so ARV treatment is not being withheld from them.

## Slide 18



- **Note to trainer:** The notes for the case studies are written with the expectation that you will only be presenting one of the two cases: either PACTG 076 or HIVNet 012.
- The purpose for telling the story of PACTG 076 is to illustrate the concepts we've been discussing. We hope that discussing a real study will help you to remember what some of the words that have been introduced so far. This study was done only in the United States. In later modules, we will talk about studies done internationally to look at the same questions regarding prevention of mother to child transmission of HIV.

## Slide 19

**PACTG 076**

- In 1994, PACTG 076 was first clinical trial to ask:



“If you treat a pregnant woman and also treat her baby at birth with an ARV medicine, will the medicine lower the risk of the baby getting infected with HIV?”

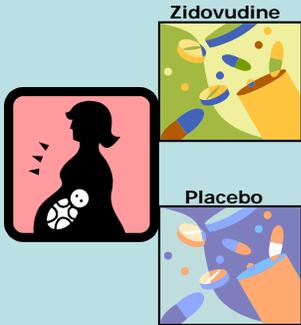
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- In 1994, researchers asked the question: “If you treat a pregnant woman and also treat her baby at birth with an ARV medicine, will the medicine lower the risk of the baby getting infected with HIV (also called mother-to-child transmission)? Will the medicine be safe for mom and baby? Will it work?”
- At the time of the study no ARV medicine had been tested in pregnant women to see if the risk of passing HIV from mother to infant could be lowered. Many people were worried about this study and whether ARVs were safe for pregnant women and infants. They said, “How can you give an ARV medicine to a pregnant woman?” (ZDV and other ARVs were approved and licensed medications, but were untested in terms of pregnancy)
- In fact, women who agreed to participate in the study were brave. For many of them, the decision was very difficult and frightening. Many women decided not to enter the study because they feared the medicine would harm their baby.

## Slide 20

**PACTG 076: study design**

- **Randomized:**  
ZDV vs. Placebo
- **Double-blind**
- **Placebo-controlled**



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**Discussion questions:**

Let's talk about the words you see on this slide.

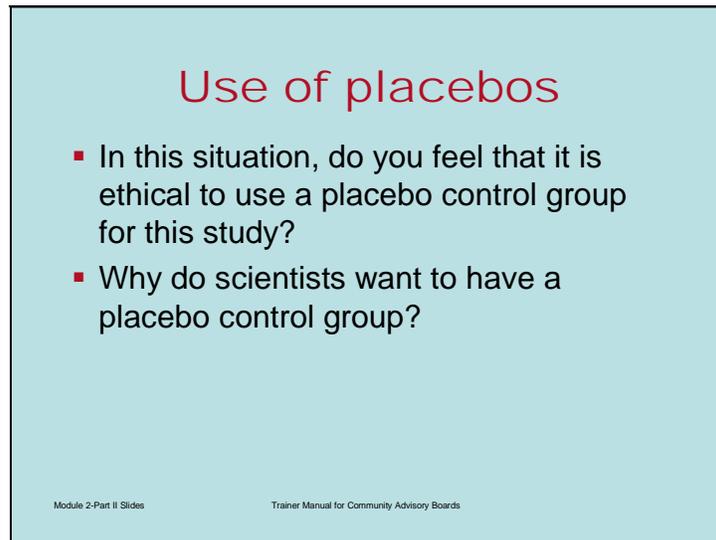
- What is randomization? Do you understand why it is desirable, from a scientific standpoint, to use a control group/placebo group? What is the definition of "double-blind"?
- What is the purpose of "blinding" clinical trials?
- What is a placebo? Why was a placebo used in this study?

**Review answers:**

- **Randomization:** Women were randomly assigned to one of the two groups. Neither the woman nor the researcher could pick which group to be in. A computer makes the assignment in order to reduce the risk of bias. Use of a control group and randomization ensures that the differences in the results between the two groups are not due to chance alone, rather than the treatment given. For example, if all women in the study were given ZDV, and there was a slightly lower rate of HIV transmission to their infants, do you know that the ZDV caused the difference? Could it be chance?
- **Placebo-controlled:** Because there was no medicine known to lower the risk of mother-to-child transmission, this clinical trial was designed to test the effectiveness of zidovudine (ZDV) against a placebo (pill that looks like the medicine but contains no medicine). The control in this study was a placebo; this type of study is called a "placebo-controlled" study. Pregnant women with HIV infection who agreed to participate in this study received either the medicine (ZDV) or a placebo.

**Double-blind:** Neither the women nor the researchers knew which women were getting ZDV and which were getting placebo. This is called a "double-blind" study. The moms took the pills during the last trimester of pregnancy and during labor and delivery, and they gave their infants the medicine every day for 6 weeks after birth.

## Slide 21



**Use of placebos**

- In this situation, do you feel that it is ethical to use a placebo control group for this study?
- Why do scientists want to have a placebo control group?

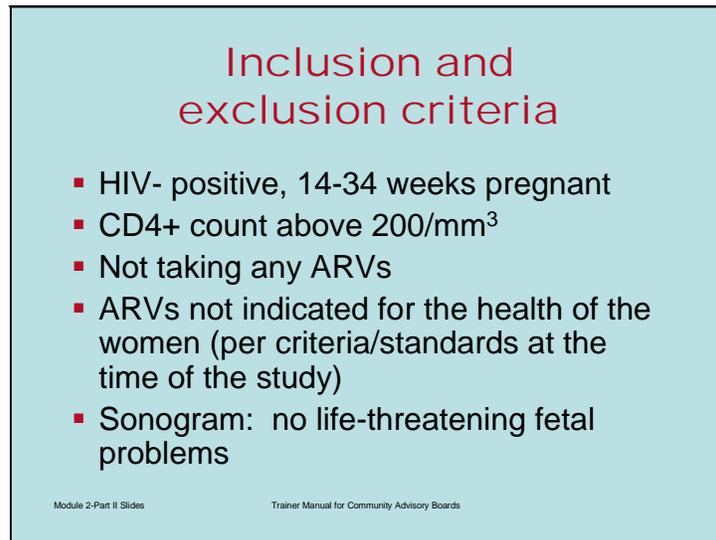
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- At the time this study was designed, there was no known treatment for PMTCT. No one knew whether giving ARV medicine would reduce the risk of HIV in the infant. No one could know for certain if ARV medicine could harm the fetus or cause a problem such as premature delivery. The standard of care for pregnant women with HIV infection prior to this study's completion was no HIV treatment (or PMTCT treatment)

**Discussion questions:**

- Do you think it was ethical (fair) to use a placebo control group in this study? Why or why not? (Note to trainer: There is an entire module devoted to ethics in clinical trials, and the use of placebos is covered extensively within that module. If there is a lot of reaction to this question, let participants know that we understand that the issue is very complex, and that there will be other opportunities to discuss placebo use and ethics.)

## Slide 22



**Inclusion and  
exclusion criteria**

- HIV- positive, 14-34 weeks pregnant
- CD4+ count above 200/mm<sup>3</sup>
- Not taking any ARVs
- ARVs not indicated for the health of the women (per criteria/standards at the time of the study)
- Sonogram: no life-threatening fetal problems

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**Discussion:** Have participants read the slide. Then ask: “Can you tell me what the inclusion criteria for the study are? Exclusion criteria?”

Inclusion: HIV-infected, 14-34 weeks pregnant CD4 count above 200, normal sonogram

Exclusion: Taking ARV medicine, not HIV-infected, CD4 count below 200, Life threatening problems for the fetus (based on sonogram), ARV treatment for the woman indicated based on her own health

**Discussion:** Can you think why some of these criteria are important?

- For example, if sonograms were not done, and therefore there was a risk of enrolling women whose fetus was abnormal, then might it appear that the study treatment had *caused* the abnormality? Another example: If the woman is already taking ARVs, wouldn't that make it hard to determine whether the treatment worked or didn't work (e.g. if the baby is born HIV-negative, was it the study treatment or another ARV that helped reduce the risk of infection?)
- The final inclusion criteria that is always important to remember for every study: The women could not be enrolled without their *consent*. Women were offered enrollment in the study if they met the inclusion/exclusion criteria, but they were free to decline to participate.

## Slide 23

**PACTG 076:  
schedule of events**

Women and infants  
examined carefully on  
a regular basis to  
check for:

- Side effects
- Signs/symptoms of  
HIV (infants)



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- Because no one had studied any antiretroviral medicines in pregnant women or in HIV-exposed infants, the protocol **Schedule of Events** was intensive. The women and infants had to be examined very carefully on a regular basis. This was to find out if the medicine worked and if the medicine caused any **adverse events** (unwanted/bad side effects).

## Slide 24

## Monitoring

- **Data Safety Monitoring Board (DSMB):** a group of scientists outside the study who monitor the **unblinded** data during the study.



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- Because the study was blinded, the standard practice of having an outside group of scientists look at the data comparing the two groups at regular intervals was put in place for the study.. This group is called the **Data Safety and Monitoring Board, or DSMB**. The DSMB examines the “unblinded” data at regular intervals.

## Slide 25

**PACTG 076: DSMB**

- In the middle of the study, DSMB compared data from ZDV group with placebo group.



**ZDV group**



**Placebo group**

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**Discussion question:**

- There are two reasons for the DSMB to monitor the information collected on the participants during the trial, rather than wait until the end when all of the data has been collected and the study is over. Can you remember why this is? Why is it important for someone to monitor the data during the trial?

**Answer:**

- If the ZDV appears to be effectively protecting infants from HIV infection, it would be important to offer zidovudine to every mother in the study.
- If women or their infants receiving ZDV were experiencing serious side effects and those in the placebo group were not, it would mean that ZDV was not safe and they would have to stop the study.

## Slide 26

### What the DSMB found

- Infants with mothers in ZDV group ***much less likely*** to be diagnosed with HIV infection than infants with mothers in placebo group.



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- The DSMB, in fact, *did* find a difference between the placebo control group and the treatment (ZDV) group.
- On a Friday afternoon, all the research sites got a telephone call to say that the study was being stopped by the DSMB. The DSMB ordered the study to be stopped because it was clear, in examining the unblinded data, that ZDV was effective at lowering the risk of HIV transmission to the infant. The women who were in the ZDV group were less likely than the women who took the placebo to have a baby who became infected with HIV. While infants in the placebo group had about a 25% chance of becoming HIV infected, infants in the ZDV group had about an 8% chance of becoming HIV-positive. This was wonderful news! Many other studies were immediately developed to find better and easier ways to reduce transmission, but this study was very important in proving that it IS possible to reduce infection from mother to child.
- When the study was stopped, all of the data was unblinded so that researchers knew who, among mothers and infants still on the study, was receiving placebo. The mothers still on the study who were receiving placebo (or their baby was receiving placebo) were informed of the results and were offered ZDV.

## Slide 27

**PACTG 076: impact**

- We owe a great debt of gratitude to the women who enrolled in this study.



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Although there is still very much to be done to protect women and their infants, this study was a huge step forward in the science of prevention of mother-to-child transmission. Many women have enrolled in subsequent studies to try to improve PMTCT, and we owe them all a debt of gratitude for their willingness to improve the care of HIV-positive women and their children.

## Slide 28



**Summary**

- Clinical trials are the best way to test the safety and effectiveness of new treatments for HIV. There are stepwise phases of clinical trials.
- The design of a clinical trial is important. A correct design will make sure the study is fair and that the results are scientifically accurate.

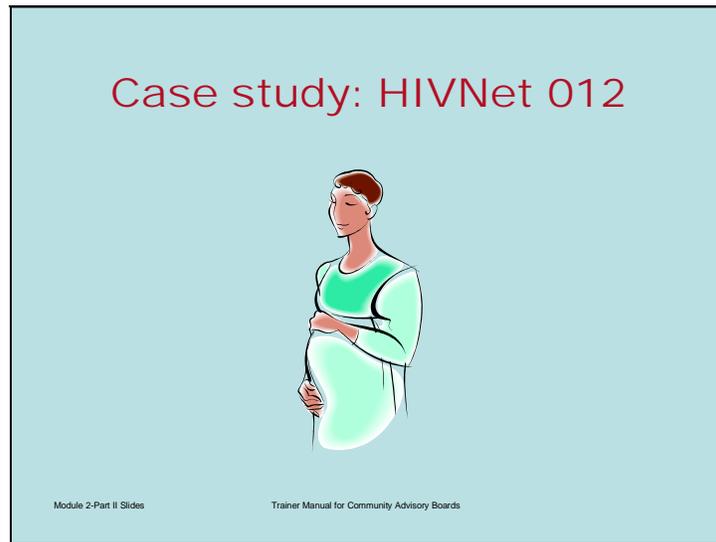
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**To summarize:**

- Clinical trials are the best way to test the safety and effectiveness of new treatments for HIV.
- The correct study design is important to make sure the results are accurate, and the study is safe and unbiased.
- In the best situation, the study design will include randomization, blinding, and a control group.
- A placebo control group is ethical only in certain limited situations.

## Slide 29

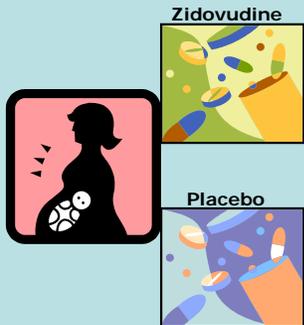


- **Note to trainer:** The notes for the case studies are written with the expectation that you will only be presenting one of the two cases: either PACTG 076 or HIVNet 012.
- The purpose for telling the story of HIVNet 012 is to illustrate the concepts we've been discussing. We hope that discussing a real study will help you to remember what some of the words that have been introduced so far.

## Slide 30

**PACTG 076: the first  
PMTCT ARV clinical trial**

- **Randomized:** ZDV vs. Placebo
- **Double-blind** study
- **Placebo-controlled**

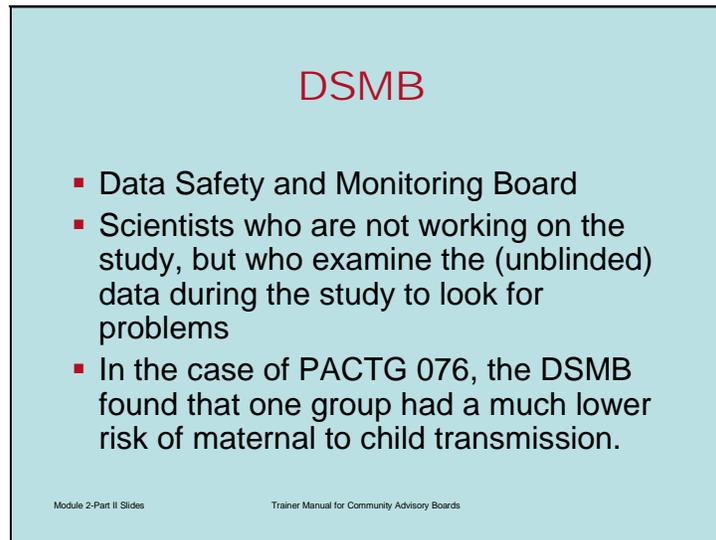


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In order to understand some of the issues related to HIVNet 012, it's helpful to first summarize the state of PMTCT research at the time the study was launched. To summarize:

- In 1994, researchers in the U.S. asked the question: “If you treat a pregnant woman and also treat her baby at birth with an the ARV medicine zidovudine (AZT or ZDV) will the zidovudine lower the risk of the baby getting infected with HIV (also called mother-to-child transmission)? Will the medicine be safe for mom and baby? Will it work? At the time of the study no ARV medicine had been tested in pregnant women to see if the risk of passing HIV from mother to infant could be lowered.
- This study of using antiretroviral medicine to lower the risk of mother-to-child transmission of HIV infection was called ACTG 076. ACTG 076 tested zidovudine given during pregnancy (from 28 weeks), during labor and delivery (intravenously), and to the infant for 6 weeks after birth. Because there was no information on PMTCT with antiretroviral medicine, this study tested the ZDV against a placebo.

## Slide 31

A light blue rectangular box with a black border containing the text for Slide 31. The title 'DSMB' is centered at the top in red. Below it are three bullet points. At the bottom left, it says 'Module 2-Part II Slides' and at the bottom right, it says 'Trainer Manual for Community Advisory Boards'.

**DSMB**

- Data Safety and Monitoring Board
- Scientists who are not working on the study, but who examine the (unblinded) data during the study to look for problems
- In the case of PACTG 076, the DSMB found that one group had a much lower risk of maternal to child transmission.

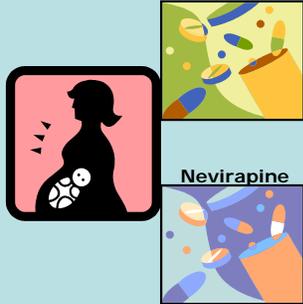
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- The DSMB is a group of scientists who are asked to check the data during a clinical trial to see if any problems are developing. They are looking to see if there are any significant differences between one group or the other in terms of safety or in terms of how they are responding to the medicine.
- In the case of PACTG 076 the study was stopped early by the DSMB because when some of the results were available mid-way through the study, it was obvious that the ZDV was working much better than placebo at lowering the risk of MTCT. Infants born to women in the ZDV group had a much lower chance of being born with HIV infection than infants born to women in the placebo group. The study was stopped and the remaining participants enrolled in the study were all offered ZDV because it was no longer ethical to use a placebo, since it was clear that ZDV worked.
- Because of the success of this trial, ZDV became the standard of care for pregnant women with HIV and their infants in the U.S., and in other countries that could afford this expensive and complicated treatment.

## Slide 32

**HIVNet 012**

- To identify a safe, effective way of PMTCT that would also be convenient and affordable **for resource-limited settings**



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- This left a big problem: The largest number of people infected with HIV were in countries that did not have the health care infrastructure and the resources (money) to implement this long, complex, and expensive treatment. The 076-ZDV treatment regimen was a gift only for those who could afford it. Where there was the greatest need, this ARV regimen was not affordable. Nevertheless, the 076 research was important because it showed that ARV medicine could work for PMTCT. So the next question for researchers to ask was: Could a simpler, less expensive treatment regimen that could be implemented in resource-poor countries also work?
- In 1997, another group of researchers (also funded by the U.S. government) who worked internationally in resource-limited settings designed a new clinical trial using a simple, inexpensive medicine to see if it would lower the risk of mother-to-child transmission of HIV. The study was called HIVNet 012. This clinical trial was conducted in Uganda, where no treatment for HIV or for prevention of mother-to-child transmission was available at all.
- The goal of HIVNet 012 was to identify a safe, effective way to prevent mother-to-infant HIV transmission, which would be convenient and affordable in resource-limited settings like Uganda.

## Slide 33

### Discussion questions

- What do you think about the ethics of including a placebo group in this trial vs. not including one?
- The standard of care in Uganda at the time was no ARVs available.
- The standard of care in wealthier countries was ARV prophylaxis for PMTCT.

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**Review:**

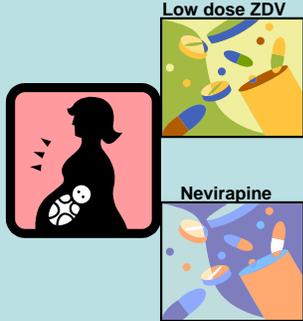
- Placebos are considered acceptable for testing a new medication when the standard of care for the problem/disease is “no treatment”
- A placebo was used in PACTG 076 because there was no known treatment for PMTCT, and the standard of care was “no treatment” for PMTCT before this study was done
- When HIVNet 012 was designed, the results of PACTG 076 were available, so researchers knew that ZDV could reduce the risk of MTCT.
- However, the 076 ZDV regimen was not available in Uganda. The standard of care for PMTCT in Uganda was “no treatment”.

**Discussion:** Should the researchers test Nevirapine against a placebo, or must they provide all participants with ZDV? (This question is also discussed at length in the Research Ethics module, so you may want to limit or skip this discussion here)

## Slide 34

**HIVNet 012**

- ZDV: Short acting medicine
- NVP: Longer-acting medication



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- At the time, there was a lot of controversy and concern and discussion about the ethics the study if a placebo were to be used.
- In the end, a placebo was NOT used. The simple and inexpensive regimen of interest to the researcher, nevirapine (a single dose to the mother and a single dose to the infant) was tested against ZDV. However, the ZDV was not the same regimen that was used in the clinical trial 076. ZDV was given in a lower and simpler dose than was used in 076 so that if successful, it could also be a choice for resource-poor countries.
- People were very hopeful that the simple nevirapine regimen would work. Nevirapine is a longer-lasting medicine than zidovudine---it stays in the blood stream for several days. Since most transmission of HIV from mother to infant takes place at the time of delivery, there was hope that the single dose before delivery to the mother, and a single dose after delivery to the infant, would work. The single-dose regimen would be much easier to implement in countries where the health care infrastructure is weak, and where more complicated and expensive regimens were not affordable.

## Slide 35

**Study design**

- Randomized
- Open label
- Comparison trial: Low dose ZDV compared with single-dose nevirapine (one dose each to mother and infant)

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Let us talk about the study design:

- Researchers randomized the women to the ZDV or NVP group
- Both the participant and the researcher knew the group assignment (This was necessary because women assigned to the NVP group were given the NVP tablet to take home, with instructions to take the tablet at the onset of labor).
- Because there was no control group of women assigned to a standard medicine, the trial was called a **comparison trial**. We say there was no “control group” because neither group of women were receiving a standard treatment. Neither treatment was known to work or not work.....This made the study unusual.
- Another important difference between PACTG 076 and HIVNet 012 was that the babies in HIVNet 012 were breastfed, while in 076 the infants were bottle fed. HIV transmission to the infant can happen from breastfeeding, so it would be expected that some infants born HIV-negative would become HIV positive from breast milk during the study.

## Slide 36

**Study design**

- Participants
  - HIV-infected pregnant women
  - No active serious disease or other infection
  - Not taking any other ARV medicine
  - Older than 18 years of age
  - At least 32 weeks pregnant
  - Attending the antenatal clinic

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**Discussion:** Can you tell me what the inclusion criteria for the study are? Exclusion criteria?

Inclusion: HIV-infected, at least 32 weeks pregnant, over age 18, attending antenatal clinic

Exclusion: active serious illness or other infection, taking ARV medicine, not HIV-infected, under age 18, fewer than 32 weeks pregnant, not attending antenatal clinic

**Discussion:** Why do you think that taking other ARV medicine is a reason to exclude women from this study?

(Because taking other ARVs will make it impossible to tell if the study treatment works or not.)

- The final inclusion criteria that is always important to remember for every study: The women could not be enrolled without their *consent*. Women were offered enrollment in the study if they met the inclusion/exclusion criteria, but they were free to decline to participate.

## Slide 37

## Schedule of events

- Babies were examined carefully on a regular basis.
- Checked for
  - side effects
  - signs or symptoms of HIV infection



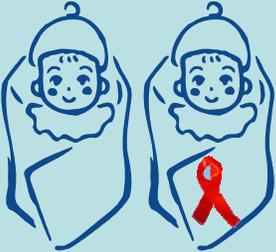
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- NVP had never been tested in pregnant women or infants, and the experience with using ZDV during pregnancy and for infants was relatively limited. Therefore, infants were examined carefully on a regular basis according to the **Schedule of Events** in the protocol (schedule of clinic visits and tests). This was to find out if there were any side effects from the medicine, and to check for any signs or symptoms of HIV infection in the infant.

## Slide 38

**HIVNet 012 results**

- Infants from the NVP group were much less likely to be born with HIV infection than infants from the group who received ZDV.



**NVP group    ZDV group**

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- The study results showed that both ZDV and NVP were safe. There were few side effects, and these were mostly very mild and reversible.
- You can see on the slide that more infants were HIV infected in the ZDV group than in the NVP group. NVP was significantly better than ZDV at PMTCT, and significantly better than no treatment at all for PMTCT.
- NVP reduced the rate of transmission by 47% at 14-16 weeks of age, and by 41% at 18 months of age. (Remember, infants were breastfeeding.) What does this mean? For example, if the rate of HIV transmission from mother to child is about 30%, that means that 30 out of every 100 infants born to HIV+ women will be HIV-infected. However, if NVP treatment is given, reducing the rate of infection by 47% would mean that about 15 infants out of every 100 would be HIV-positive, instead of 30 infants infected if no treatment were given.
- NVP treatment is simple, safe, effective and affordable, and was adopted as the standard of care in many resource-limited countries worldwide. There are more effective treatments for PMTCT, but the sad reality is that they are not available to all HIV-positive pregnant women and their infants.

## Slide 39

## Discussion question

- How do you think research might help to address the disparity in mother to child transmission between rich and poor countries?
- Can you think of research questions to be asked?

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- There is still a large difference between the effectiveness of treatments available in resource-rich settings and treatments available in resource-poor countries. In the US and Europe, HIV-infected pregnant women can be treated with 3-drug HAART regimens to prevent transmission, and the transmission rate has dropped below 2% (from about 25% with no ARV treatment). Women in these countries bottle feed because formula and clean water are readily available.
- How do you think research might help to address the difference in mother-to- child transmission in rich and poor countries? Can you think of research questions to be asked? (Examples: ARVs to prevent breast milk transmission; simple, less expensive ARVs as effective as NVP; vaccine to protect infants from HIV)

## Slide 40



**Summary**

- Clinical trials are the best way to test the safety and effectiveness of new treatments for HIV. There are stepwise phases of clinical trials.
- The design of a clinical trial is important. A correct design will make sure the study is fair and that the results are scientifically accurate.

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**To summarize:**

- Clinical trials are the best way to test the safety and effectiveness of new treatments for HIV.
- The correct study design is important to make sure the results are accurate, and the study is safe and unbiased.
- In the best situation, the study design will include randomization, blinding, and a control group.
- A placebo control group is ethical only in certain limited situations.

# CASE STUDIES: PACTG 076 AND HIVNET 012

## Module 2

### Trainer Instructions

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#### Time Frame *(45-60 minutes)*

#### Purpose

- To illustrate research concepts introduced during this training in the context of a case study

#### Materials needed

- Slides with trainer notes and discussion questions
- Flipchart or blackboard/chalk for noting key concepts (if desired)
- Participants are provided with a list of the questions for discussion, and copies of the slides.

#### Instructions

- In advance of the training, read through the slides and discussion questions (provided in the slide trainer notes).
- This exercise is meant to be a group interactive exercise. If you have a large group of participants (more than 20), it may be easier to “discuss” the case study in smaller groups. In this case, present the study “story” first, and then have the smaller groups work on the discussion questions on their own (20-30 minutes), followed by returning to the larger group to present their responses.
- Explain that the purpose of the exercise is to reinforce understanding of the concepts covered in the training by describing “real” studies that have been done.
- Explain that the case study exercise will be a discussion, and that you want participants to answer the questions raised during the case study.
- Follow the slides and trainer notes as they are (alternating between describing the study and pausing for discussion and review of concepts). The trainer notes are on the slides, but are also provided here in the following pages.
- If desired, write some of the key points brought up in the discussion on the blackboard or flip chart.

## CASE STUDY: PACTG 076

### Module 2

### Slide Notes

- In 1994, researchers asked the question: “If you treat a pregnant woman and also treat her baby at birth with an ARV medicine, will the medicine lower the risk of the baby getting infected with HIV (also called mother-to-child transmission)? Will the medicine be safe for mom and baby? Will it work?”
- At the time of the study no ARV medicine had been tested in pregnant women to see if the risk of passing HIV from mother to infant could be lowered. Many people were worried about this study and whether ARVs were safe for pregnant women and infants. They said, “How can you give an ARV medicine to a pregnant woman?” (ZDV and other ARVs were approved and licensed medications, but were untested in terms of pregnancy)
- In fact, women who agreed to participate in the study were brave. For many of them, the decision was very difficult and frightening. Many women decided not to enter the study because they feared the medicine would harm their baby.
- PACTG 076 was
  - Randomized: women were randomly assigned to one of the two groups. Neither the woman nor the researcher could pick which group to be in. A computer makes the assignment in order to reduce the risk of bias. Use of a control group and randomization ensures that the differences in the results between the two groups are not due to chance alone, rather than the treatment given. For example, if all women in the study were given ZDV, and there was a slightly lower rate of HIV transmission to their infants, do you know that the ZDV caused the difference? Could it be chance?
  - Placebo-controlled: because there was no medicine known to lower the risk of mother-to-child transmission, this clinical trial was designed to test the effectiveness of zidovudine (ZDV) against a placebo (pill that looks like the medicine but contains no medicine). The control in this study was a placebo; this type of study is called a “placebo-controlled” study. Pregnant women with HIV infection who agreed to participate in this study received either the medicine (ZDV) or a placebo.
  - Double-blind: neither the women nor the researchers knew which women were getting ZDV and which were getting placebo. This is called a “double-blind” study. The moms took the pills during the last trimester of pregnancy and during labor and delivery, and they gave their infants the medicine every day for 6 weeks after birth.
  - At the time this study was designed, there was no known method for PMTCT. No one knew whether giving ARV medicine would reduce the risk of HIV in the infant. No one could know for certain if ARV medicine could harm the fetus or cause a problem such as premature delivery. The standard of care for pregnant women with HIV infection prior to this study’s completion was no HIV treatment (or PMTCT treatment)

**Discussion question:**

- Do you think it was ethical (fair) to use a placebo control group in this study? Why or why not? (Note to trainer: There is an entire module devoted to ethics in clinical trials, and the use of placebos is covered extensively within that module. If there is a lot of reaction to this question, let participants know that we understand that the issue is very complex, and that there will be other opportunities to discuss placebo use and ethics.)
- The inclusion and exclusion criteria for this study were as follows:
  - **Inclusion:** HIV-infected, 14-34 weeks pregnant CD4 count above 200, normal sonogram
  - **Exclusion:** Taking ARV medicine, not HIV-infected, CD4 count below 200, Life threatening problems for the fetus (based on sonogram), ARV treatment for the woman indicated based on her own health

**Discussion question:**

- Can you think why some of these criteria are important?
- For example, if sonograms were not done, and therefore there was a risk of enrolling women whose fetus was abnormal, then might it appear that the study treatment had caused the abnormality? Another example: If the woman is already taking ARVs, wouldn't that make it hard to determine whether the treatment worked or didn't work (e.g. if the baby is born HIV-negative, was it the study treatment or another ARV that helped reduce the risk of infection?)
- The final inclusion criteria that is always important to remember for every study: The women could not be enrolled without their consent. Women were offered enrollment in the study if they met the inclusion/exclusion criteria, but they were free to decline to participate.
- Because no one had studied any antiretroviral medicines in pregnant women or in HIV-exposed infants, the **Schedule of Events** in the protocol said the women and infants had to be examined very carefully on a regular basis. This was to find out if the medicine worked and if the medicine caused any **adverse events** (unwanted/bad side effects).
- Because the study was blinded, the standard practice of having an outside group of scientists look at the data comparing the two groups at regular intervals during the study. This group is called the **Data Safety and Monitoring Board**, or **DSMB**. The DSMB examines the "unblinded" data.
- Discussion question:
- There are two reasons for the DSMB to monitor the information collected about the participants during the trial, rather than wait until the end when all of the data have been collected and the study is over.
  - Can you remember why this is?
  - Why is it important for someone to monitor the data during the trial?

**Answer:**

- If the ZDV appears to be effectively protecting infants from HIV infection, it would be important to offer zidovudine to every mother in the study.
- If women or their infants receiving ZDV were experiencing serious side effects and those in the placebo group were not, it would mean that ZDV was not safe and they would have to stop the study.
- The DSMB, in fact, did find a difference between the placebo control group and the treatment (ZDV) group.
- On a Friday afternoon, all the research sites got a telephone call to say that the study was being stopped by the DSMB. The DSMB ordered the study to be stopped because it was clear, in examining the unblinded data, that ZDV was effective at lowering the risk of HIV transmission to the infant. The women who were in the ZDV group were less likely than the women who took the placebo to have a baby who became infected with HIV. While infants in the placebo group had about a 25% chance of becoming HIV infected, infants in the ZDV group had about an 8% chance of becoming HIV-positive. This was wonderful news! Many other studies were immediately developed to find better and easier ways to reduce transmission, but this study was very important in proving that it IS possible to reduce infection from mother to child.
- When the study was stopped, all of the data was unblinded so that researchers knew who, among mothers and infants still on the study, was receiving placebo. The mothers still on the study who were receiving placebo (or their baby was receiving placebo) were informed of the results and were offered ZDV.

Although much remains to be done to protect women and their infants, this study was a huge step forward in the science of prevention of mother-to-child transmission. After PACTG 076, many women have enrolled in studies to try to improve PMTCT, and we owe them all a debt of gratitude for their willingness to improve the care of HIV-positive women and their children.

## CASE STUDY: HIVNET 012

### Module 2

### Slide Notes

- The purpose of telling the story of HIVNet 012 is to illustrate the concepts we've been discussing. We hope that talking about a real study will help you remember some of the words that have been introduced so far.

#### Discussion question:

- Who can tell me what any of them mean?

#### Review answers:

- Randomized: Women were randomly assigned to one of the two groups. Neither the woman nor the researcher could pick which group to be in. A computer makes the assignment in order to reduce the risk of bias.
- Placebo-controlled: Because there was no medicine known to lower the risk of mother-to-child transmission, this clinical trial was designed to test the effectiveness of zidovudine (ZDV) against a placebo (pill that looks like the medicine but contains no medicine). The control in this study was a placebo; this type of study is called a "placebo-controlled" study. Pregnant women with HIV infection who agreed to participate in this study received either the medicine (ZDV) or a placebo.
- Double-blind: Neither the women nor the researchers knew which women were getting ZDV and which were getting placebo. This is called a "double-blind" study. The moms took the pills during the last trimester of pregnancy and during labor and delivery, and they gave their infants the medicine every day for 6 weeks after birth.
- In 1994, researchers in the U.S. asked this question: "If you treat a pregnant woman and also treat her baby at birth with an the ARV medicine zidovudine (AZT or ZDV) will the zidovudine lower the risk of the baby getting infected with HIV (also called mother-to-child transmission)? Will the medicine be safe for mom and baby? Will it work? At the time of the study no ARV medicine had been tested in pregnant women to see if the risk of passing HIV from mother to infant could be lowered.
- This study, which looked at using antiretroviral medicine to lower the risk of mother-to-child transmission of HIV infection was called PACTG 076. PACTG 076 tested zidovudine given during pregnancy (from 28 weeks), during labor and delivery (intravenously), and to the infant for 6 weeks after birth. Because there was no information on PMTCT with antiretroviral medicine, this study tested the ZDV against a placebo
- The Data Safety Monitoring Board (DSMB) is a group of scientists who are asked to check the data during a clinical trial to see if any problems are developing. They are looking to see if there are any significant differences between one group or the other in terms of safety or in terms of how they are responding to the medicine.

- In the case of PACTG 076 the study was stopped early by the DSMB because when some of the results were available mid-way through the study, it was obvious that the ZDV was working much better than placebo at lowering the risk of MTCT. Infants born to women in the ZDV group had a much lower chance of being born with HIV infection than infants born to women in the placebo group. The study was stopped and the remaining participants enrolled in the study were all offered ZDV because it was no longer ethical to use a placebo, since it was clear that ZDV worked. Because of the success of this trial, ZDV became the standard of care for pregnant women with HIV and their infants in the U.S., and in other countries that could afford this expensive and relatively complicated treatment.
- But there was a problem: The highest number of people infected with HIV were in countries that did not have the health care infrastructure and the resources (money) to implement this long, complex, and expensive treatment. The 076-ZDV treatment regimen was a gift only for those who could afford it. Where there was the greatest need, this ARV regimen was not affordable. Nevertheless, the 076 research was important because it showed that ARV medicine could work for PMTCT. Could a simpler, less expensive treatment regimen that could be implemented in resource-poor countries also work?
- In 1997, another group of researchers (also funded by the U.S. government) who worked internationally in resource-limited settings designed a new clinical trial using a simple, inexpensive medicine to see if it would lower the risk of mother-to-child transmission of HIV. The study was called HIVNet 012. This clinical trial was conducted in Uganda, where no treatment for HIV or for prevention of mother-to-child transmission was available at all.
- The goal of HIVNet 012 was to identify a safe, effective way to prevent mother-to-infant HIV transmission, which would be convenient and affordable in resource-limited settings like Uganda.

**Review:**

- Placebos are considered acceptable for testing a new medication when the standard of care for the problem/disease is “no treatment”
- A placebo was used in PACTG 076 because there was no known treatment for PMTCT, and the standard of care was “no treatment” for PMTCT before this study was done
- When HIVNet 012 was designed, the results of PACTG 076 were available, so researchers knew that ZDV could reduce the risk of MTCT.
- However, the 076 ZDV regimen was not available in Uganda. The standard of care for PMTCT in Uganda was “no treatment”.
- The first question the researchers asked when designing the study was: Can we test nevirapine against a placebo, or must we provide all participants with some antiretroviral therapy
- At the time, there was a lot of controversy and concern and discussion about the ethics the study if a placebo were to be used.
- In the end, a placebo was NOT used. The simple and inexpensive regimen of interest to the researcher, nevirapine (a single dose to the mother and a single dose to the infant)

was tested against ZDV. However, the ZDV was not the same regimen that was used in the clinical trial 076. ZDV was given in a lower and simpler dose than was used in 076 so that if successful, it could also be a choice for resource-poor countries.

- People were very hopeful that the simple nevirapine regimen would work. Nevirapine is a longer-lasting medicine than zidovudine---it stays in the blood stream for several days. Since most transmission of HIV from mother to infant takes place at the time of delivery, there was hope that the single dose before delivery to the mother, and a single dose after delivery to the infant, would work. The single-dose regimen would be much easier to implement in countries where the health care infrastructure is weak, and where more complicated and expensive regimens were not affordable.
- Researchers randomized the women to the ZDV or NVP group
- Both the participant and the researcher knew the group assignment (This was necessary because women assigned to the NVP group were given the NVP tablet to take home, with instructions to take the tablet at the onset of labor. Women randomly assigned to receive ZDV were given ZDV when they arrived at the hospital in labor).
- Because there was no control group of women assigned to a standard medicine, the trial was called a comparison trial. We say there was no “control group” because neither group of women were receiving a standard treatment. Neither treatment was known to work or not work.....This made the study unusual.
- Another important difference between PACTG 076 and HIVNet 012 was that the babies in HIVNet 012 were breastfed, while in 076 the infants were bottle fed. HIV transmission to the infant can happen from breastfeeding, so it would be expected that some infants born HIV-negative would become HIV positive from breast milk during the study.
- The inclusion and exclusion criteria for HIVNet 012 were as follows:
  - **Inclusion:** HIV-infected, at least 32 weeks pregnant, over age 18, attending antenatal clinic
  - **Exclusion:** active serious illness or other infection, taking ARV medicine, not HIV-infected, under age 18, fewer than 32 weeks pregnant, not attending antenatal clinic

**Discussion question:**

- Why do you think that taking other ARV medicine is a reason to exclude women from this study?

**Answer:**

- Because taking other ARVs will make it impossible to tell if the study treatment works or not.
- The final inclusion criterion that is always important to remember for every study: the women could not be enrolled without their consent. Women were offered enrollment in the study if they met the inclusion/exclusion criteria, but they were free to decline to participate.

- NVP had never been tested in pregnant women or infants, and the experience with using ZDV during pregnancy and for infants was relatively limited. Therefore, infants were examined carefully on a regular basis according to the **Schedule of Events** in the protocol (schedule of clinic visits and tests). This was to find out if there were any side effects from the medicine, and to check for any signs or symptoms of HIV infection in the infant.
- The study results showed that both ZDV and NVP were safe. There were few side effects, and these were mostly very mild and reversible.
- You can see on the slide that more infants were HIV infected in the ZDV group than in the NVP group. NVP was significantly better than ZDV at PMTCT, and significantly better than no treatment at all for PMTCT.
- NVP reduced the rate of transmission by 47% at 14-16 weeks of age, and by 41% at 18 months of age. (Remember, infants were breastfeeding.) What does this mean? For example, if the rate of HIV transmission from mother to child is about 30%, that means that 30 out of every 100 infants born to HIV+ women will be HIV-infected. However, if NVP treatment is given, reducing the rate of infection by 47% would mean that about 15 infants out of every 100 would be HIV-positive, instead of 30 infants infected if no treatment were given.
- NVP treatment is simple, safe, effective and affordable, and was adopted as the standard of care in many resource-limited countries worldwide.
- There is still a large difference between the effectiveness of treatments available in resource-rich settings and treatments available in resource-poor countries. In the US and Europe, HIV-infected pregnant women can be treated with 3-drug HAART regimens to prevent transmission, and the transmission rate has dropped below 2% (from about 25% with no ARV treatment). Women in these countries bottle feed because formula and clean water are readily available.
- How do you think research might help to address the difference in mother-to-child transmission in rich and poor countries? Can you think of research questions to be asked? (Examples: ARVs to prevent breast milk transmission; simple, less expensive ARVs as effective as NVP; vaccine to protect infants from HIV)
- At this point in time, the World Health Organization recommends that countries implement additional ARV treatment for PMTCT treatment if resources allow for it. Although NVP is effective at lowering the risk of transmission, we now know that using two or three medicines together for PMTCT is significantly more effective at reducing the rate of transmission than using a single medicine like NVP. The rate of transmission in resource-rich countries is very low because women are receiving multi-drug ARV regimens. This reduces the rate of transmission below that which can be achieved with single dose of nevirapine, or even with extensive treatment with ZDV. Sadly, not all women and infants are benefiting from the knowledge we now have about PMTCT.

# PARTICIPANT EVALUATION FORM

## Module 2 Part I

### Introduction to Clinical Trials

#### INSTRUCTIONS:

- Your opinion is important to us.
- There are no RIGHT or WRONG answers.
- Your answers are private. You do not need to put your name on this form.
- Please answer ALL the questions to help us improve this training.
- For questions 1 - 5, please rate the *effect* the training has had on your understanding of the following:

0= No effect, 1= Some effect, 2= Much effect	No Effect	Some Effect	Much Effect
1. What clinical trials are and how they are developed	0	1	2
2. The purpose of clinical trials	0	1	2
3. The definition of a protocol	0	1	2
4. How researchers look at the data (information) collected during the study	0	1	2
5. For increasing your understanding of HIV clinical trials, the <b>ACTIVITY- Clinical Trials HIV 1-2-3</b> exercise had...	0	1	2



## PARTICIPANT EVALUATION FORM

### Module 2 Part II

#### Introduction to Clinical Trials

#### INSTRUCTIONS:

- Your opinion is important to us.
- There are no RIGHT or WRONG answers.
- Your answers are private. You do not need to put your name on this form.
- Please answer ALL the questions to help us improve this training.
- For questions 1 - 7, please rate the *effect* the training has had on your understanding of the following:

0= No effect, 1= Some effect, 2= Much effect	No Effect	Some Effect	Much Effect
1. Phases of clinical trials	0	1	2
2. Randomization of trial participants	0	1	2
3. Definition of a “control group”	0	1	2
4. Definition of a “treatment group”	0	1	2
5. Group discussions during the slide presentation	0	1	2
6. Double-blind studies	0	1	2
7. Placebos	0	1	2
For the last 2 questions, 0= not useful, 1= useful, 2= very useful			
8. The materials in the training manual	0	1	2
9. This module as a whole	0	1	2

*Please continue on the next page.*

*Please answer the following questions to the best of your ability:*

After this training, what help might you need to apply this information?

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What changes would you suggest to make the training more useful?

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What part of this training did you find the **most useful**?

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What other training programs do you feel are important for CAB members?

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Other comments:

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***Thank you for your comments!***

## TRAINERS' ASSESSMENT: POST-TRAINING

### Module 2

#### Introduction to Clinical Trials

*Please help us evaluate the training for this module by telling us about the level of improvement you observed in the participants' knowledge of **Clinical Trials**.*

	NO IMPROVEMENT	SOME IMPROVEMENT	MAJOR IMPROVEMENT
1. What clinical trials are and how they are developed	0	1	2
2. The purpose of clinical trials	0	1	2
3. Definitions of <ul style="list-style-type: none"> <li>• Control group</li> <li>• Treatment group</li> <li>• Double-blind</li> <li>• Placebo</li> </ul>	0	1	2

What changes would you suggest to make the training more useful?

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What part of this training did you find the **most useful**?

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Trainer Name:	Signature:	Date:
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**Please use the back of this form for additional comments and suggestions.**





# **Module 2**

# **Appendix**





# APPENDIX

## SAMPLE CASE REPORT FORM



06-06-05  
PE4821(P1026S)/09-13-04

### COMPREHENSIVE SIGNS AND SYMPTOMS

NIAID PEDIATRIC AIDS CLINICAL TRIALS GROUP

Page 1 of 2

Patient Number	<input type="text"/>	<input type="text"/>	<input type="text"/>	Date of Patient Visit	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Protocol Number	<input type="text" value="P"/>	<input type="text" value="1"/>	<input type="text" value="0"/>	<input type="text" value="2"/>	<input type="text" value="6"/>	<input type="text" value="S"/>	Institution Code		<input type="text"/>	<input type="text"/>
Form Week	<input type="text"/>	<input type="text"/>	<input type="text"/>	* Seq No.	<input type="text"/>	** Step No.	<input type="text"/>	Key Operator Code	<input type="text"/>	<input type="text"/>

\* Enter a "1" if this is the first of this form for this date. Designate subsequent forms on the same date with a 2, 3, etc.  
\*\*Enter the subject's current study step number. Enter '1' if the study does not have multiple steps.

**INSTRUCTIONS:**

- Record all signs or symptoms that are new, ongoing or have resolved since the last evaluation regardless of relationship to a diagnosis.
- Record each episode of the same sign or symptom separately. If a sign or symptom has a change in grade, report the previous grade as resolved and the new grade as a separate episode.
- Always use the same terminology to describe the same sign or symptom.
- Estimate date(s) according to "Date Conventions" if complete date is not known.
- Use "-1" for the dates of ongoing signs/symptoms.
- **DO NOT USE "-1" except where specifically indicated.**

**For Protocol P1026S: Record all signs/symptoms ≥ Grade 2.**  
**For infants born to mothers on ATV: Report any evidence of jaundice.**

**CODE REFERENCES:**

<sup>1</sup> **Symptom Code** - Refer to the Master CRF Appendices Notebook or the DMC Web Site (<http://www.fstrf.org>) for Appendix 29. Symptoms in "700" series require a site code.

<sup>2</sup> **Site Code** - Refer to the Master CRF Appendices Notebook or the DMC Web Site (<http://www.fstrf.org>) for Appendix 28. "-1 = Not applicable," may only be used for symptoms in the "800" series.

<sup>3</sup> **Grade** - Refer to DAIDS Toxicity Tables for grading the severity of Adult and Pediatric AE's.

**If not listed, use:**

- 1 - Mild
- 2 - Moderate
- 3 - Severe
- 4 - Life-threatening

<sup>4</sup> **Status**  
1 - New  
2 - New and Resolved  
3 - Ongoing/change in treatment relationship  
4 - Ongoing/no change in treatment relationship  
5 - Resolved/change in treatment relationship  
6 - Resolved/no change in treatment relationship

<sup>5</sup> **Date of Onset/Date of Resolution This Grade**  
Use "-1"s for the 'date of onset/resolution at this grade' for ongoing signs/symptom. Estimate date if complete 'onset/resolution date' is not known.

<sup>6</sup> **Diagnosis Related?**  
Is this Sign or Symptom associated with a diagnosis reported on the COMPREHENSIVE DIAGNOSES form?

<sup>7</sup> **Diagnosis Code**

If the Sign or Symptom is associated with a reported diagnosis, enter the five digit diagnosis code from the COMPREHENSIVE DIAGNOSES form. When a sign or symptom could be associated with more than one diagnosis, up to two codes may be entered. If there is only one diagnosis, use "-1" in the second diagnosis code box.

<sup>8</sup> **EVALUATION FORM COMPLETED**

If more than one code applies to the same sign/symptom, use the lowest numbered applicable code listed below.

- 1 - Yes, signs/symptoms included on an evaluation form with a related diagnosis.
- 2 - Yes, signs/symptoms included on an evaluation form with related signs/symptoms.
- 3 - Yes, signs/symptoms included on an evaluation form with a related laboratory results.
- 4 - Yes, evaluation form completed for a singular event not related to a diagnosis, signs/symptoms or laboratory results.
- 5 - Not completed, evaluation form not required.

An EVENT EVALUATION - PART A form should be completed for a singular event OR a group of related events under the following circumstances:

- ◊ To evaluate any new ≥ Grade 3 signs/symptoms.
- ◊ To evaluate a change in relationship to treatment of a previously reported sign/symptom.
- ◊ To evaluate any signs or symptoms of a grade which causes a treatment modification ( stopping, decreased dose, etc.)
- ◊ To evaluate any sign or symptom which requires an SAE report.

COMPREHENSIVE SIGNS AND SYMPTOMS

Pt. No.       \* Seq. No.  \*\* Step No.   Date        
 mmm dd yyyy

1. Has the subject experienced any new, ongoing or resolved signs and/or symptoms since the last evaluation? ..... (1-Yes, 2-No, 3-Not evaluated)   
**If No or Not evaluated, STOP.**  
**If Yes, continue. Use the Tab Key after the last entry. All references and codes are on page 1.**

Symptom Code	Site if Required <sup>2</sup>	Grade <sup>3</sup>	Status <sup>4</sup>	Date of Onset/Date of Resolution This Grade <sup>5</sup> (mmm/dd/yyyy)	Diagnosis Related? <sup>6</sup> (1-Yes, 2-No)	If Yes, Diagnosis Code	Eval. Form? <sup>8</sup> (codes 1-5)
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b.	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>
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