AIDS CLINICAL TRIALS ORIENTATION MANUAL FOR NEW RESEARCH STAFF AT KILIMANJARO CHRISTIAN MEDICAL CENTRE

Adapted from the AIDS Clinical Trials Group Orientation Manual

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TERMINOLOGY

Absolute CD4+ count: *The sum of the calculation of* (WBC) x (% of lymphocytes) x (% of CD4+)

Acquired Immunodeficiency Syndrome (AIDS): A manifestation of infection with the human immuno-deficiency virus (HIV) characterized by the presence of one or more diseases as defined by the Centers for Disease Control and Prevention (CDC) and/or the World Health Organization (WHO). These diseases occur following a depression of an individual's immune system function. The affected person becomes susceptible to unusual infections and malignancies. This definition includes all HIV-infected adults and adolescents who have less than 200 CD4+ T-lymphocytes/ml or CD4+ T-lymphocyte percent of total lymphocytes less than 14, or who have been diagnosed with pulmonary tuberculosis, invasive cervical cancer, recurrent pneumonia, or other opportunistic infections.

Antibodies: Proteins in the blood or lymph fluids that identify and help remove or neutralize bacteria, viruses, and other harmful toxins. Antibodies are members of a class of proteins known as immunoglobulins, which are produced and secreted by B-lymphocytes in response to stimulation by antigens.

Antigen: Substance capable of inducing a specific immune response

ART/ARV: Antiretroviral therapy/antiretrovirals

Bias: A point of view that prevents impartial judgment on issues relating to that point of view.

CAB: Community Advisory Board

CD4: Helper cell of the immune system; inducer subset of T-lymphocytes, also known as T4-lymphocyte

CDC: Centers for Disease Control and Prevention

CRF: Case Report Form; form used to capture study data

DNA: (Deoxyribonucleic Acid); the molecular chain found in genes within the nucleus of each cell, which carries the genetic information that enables cells to reproduce.

ELISA: Enzyme linked immunosorbent assay. This is a blood test used to measure the presence of HIV antibodies. The result will either be negative (HIV-) or positive (HIV+).

Fusion Inhibitors: An inhibiting agent that works at the site where the virus attempts to fuse to a healthy CD4 cell. This class of drugs inhibits HIV entry into the cell into the CD4/T4 lymphocyte.

GCRC: General Clinical Research Center

Genotype: The sequence of amino acids that make a viral protein. Genotyping is a test used to determine whether or not HIV has developed mutations in its DNA sequence. This test is used to determine the effectiveness or resistance of antiretroviral treatment.

HAART: Highly Active Anti-Retroviral Therapy – consists of a minimum combination of 3 different drugs, usually of at least two different classes, e.g., combination of 2 NRTI + 1 NNRTI, or 2 NRTI + 1 PI.

Health Care Worker (HCW): Any person (e.g., an employee, nurse, physician, health educator, public-safety worker or volunteer) whose activities involve contact with patients or with blood or other body fluids, in a health care or laboratory setting.

Human Immunodeficiency Virus (HIV): The organism recognized as the agent that causes AIDS. HIV is classified as a lentivirus, of the subgroup retroviruses. HIV infects and destroys CD4 cells, thereby causing progressive damage to the immune system. There are two known types of HIV: HIV-1, common in industrialized, northern countries, and HIV-2, common in sub-Saharan, southern countries.

Immune system: The mechanism of the body that recognizes foreign agents or substances (antigens), neutralizes them, and recalls the response later when confronted with the same challenge.

Immunodeficiency: A breakdown, or inability of the immune system to function, leaving a person susceptible to certain diseases that he/she would not ordinarily develop.

Intent to treat: The term used to account for a subject who has entered into a study, regardless of whether or not a single dose of medication was given.

IRB/IEC: Institutional Review Board/Institutional Ethics Committee – an organization whose primary function is to ensure patient safety and the ethical conduct of clinical trials involving research subjects, before and throughout the conduct of a clinical trial. The IRB/IEC reviews all proposed and ongoing studies involving research subjects for risk to benefit ratio, subject's rights, and all information shared with the participant that helps the subject decide whether or not to participate, or continue to participate in a clinical research study. This process is called informed consent.

Latent: Dormant. Resting. Not active.

Lentivirus: A virus that slowly causes disease.

Lymphocyte: The most prominent cell type in the immune system. B-lymphocytes are one of the two major classes of lymphocytes. During infections, these cells are transformed into plasma cells that produce antibodies specific to the pathogen.

NIAID: National Institute of Allergy and Infectious Diseases

NIH: National Institutes of Health

NIMR: National Institute for Medical Research – the Tanzanian regulatory authority for clinical research taking place in Tanzania, East Africa.

Nucleoside analog: A subunit of nucleic acid, usually a synthetic compound, similar to one of the components used by RNA or DNA early in cell replication.

NRTI: Nucleoside Reverse Transcriptase Inhibitor – a compound, that blocks the nucleic acid site necessary for genetic transcription of HIV viral RNA to viral DNA, thereby inhibiting further viral replication (e.g., zidovudine, stavudine, lamivudine).

Nucleotide analog: A subunit of nucleic acids, closely related to nucleoside analog, but not carrying the phosphate group (e.g., tenofovir).

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor – a compound, similar to a NRTI but blocking a non-nucleic site used by HIV during the replication cycle to change viral RNA into viral DNA (e.g., viramune, efavirenz).

PI: Protease Inhibitors – a compound that works by inhibiting an enzyme used by HIV during the later stage of viral replication cycle, needed for cutting and re-assembly of genetic information into new HIV virons (e.g., lopinavir/ritonavir, nelfinavir, saquinavir).

PCR (Polymerase Chain Reaction): A laboratory process that selects a DNA segment from a mixture of DNA chains and rapidly replicates it. Used to create a large, readily analyzed sample of a piece of DNA. PCR is used in DNA fingerprinting and in medical tests to identify diseases from the infectious agent's DNA. In HIV this test is used to quantify HIV in a person's blood or lymph node (HIV viral load), and sometimes to detect HIV (e.g., primary HIV infections/acute HIV).

Primary HIV Infection (PHI): Also referred to as, "Acute HIV". PHI is the earliest detectable stage of HIV acquisition. Shortly after HIV exposure, HIV replicates unopposed in the body, until the body's natural defense system

is able to form an immune response to the virus. Immune response usually occurs within 3 weeks. At this very early stage of HIV infection, HIV antibody testing is negative, although the person is infected. Viral load testing by HIV PCR reveals a high level of HIV viremia prior to antibody seroconversion. Patients often note a viral-like illness, with fever, malaise, lymphadenopathy, and other non-specific viral symptoms, including sometimes rash. Laboratory tests often reveal thrombocytopenia, elevated transaminases, and leukocytopenia.

Prophylaxis: A preventive intervention intended to preserve health and prevent the initial occurrence of a disease (primary prophylaxis) or to prevent the recurrence of a disease (secondary prophylaxis), (e.g., co-trimoxazole).

Retrovirus: A family of RNA virus that carry the reverse transcriptase enzyme and use a host cells in order to replicate.

Reverse Transcriptase: An enzyme used by a RNA virus to convert viral RNA into viral DNA, allowing viral replication to take place. Once converted to viral DNA, the virus' genetic information integrates itself into the host cell's DNA, and replicates along with the host cell. Towards the end of the viral replication cycle the protease enzyme cuts and re-assembles the virus genetic information, allowing new virons to bud out and incorporate themselves into other CD4 lymphocytes.

RNA: Ribonucleic acid, a nucleic acid found in both the nucleus and cytoplasm of cells, that transmits genetic instructions from the nucleus to the cytoplasm.

SAE: Serious Adverse Event – an immediately life-threatening event, an event that leads to permanent disability, death, or an unplanned or prolonged hospitalization

Seroconversion: The process by which a person's antibody status changes from negative to positive.

SOP: Standard Operating Procedure – the written standards assumed by an operation (organization) that all who work there follow.

Source Documentation: Original medical or office record that serves to verify and collaborate data recorded in the research file or case report form.

STD/STI: Sexually Transmitted Disease/Sexually Transmitted Infection

Treatment Guidelines: Suggestions based on clinical research data that describes when to initiate treatment, what to treat with, and how often to follow and what type of patient follow up is warranted.

VL: Viral Load – the number of virus particles in a milliliter of blood. In HIV this refers to the amount of HIV virus present in an individual infected with HIV's blood. Viral load is reported in copies/mL and logarithms.

Western Blot: One of two tests used in the diagnosis and confirmation of HIV specific proteins. Western blot tests for the presence of HIV antibodies and is reported as the individual protein components present. It is interpreted using bands that are identified with a letter and a number (e.g., p41, p24).

WHO: World Health Organization

PART I - BASICS OF HIV

What is HIV?

HIV (human immunodeficiency virus) is the virus that causes AIDS (acquired immune deficiency syndrome). HIV was initially isolated in 1983 from patients who presented with immune system dysfunction that was unusual for their age and previous health history.

The HIV virus is a retrovirus carrying its genetic information in RNA instead of DNA. RNA is one of the genetic materials that human cells, bacteria, and viruses need in order to make copies of themselves. A RNA virus, like HIV, needs the help of certain living cells in the human body to use as its host cell in order to replicate. Unlike other viruses, HIV uses the cells of the immune system in order to replicate, specifically T-lymphocytes CD4 cells. Not all HIV virus is actively replicating. Some HIV archives in the body, and turns itself off. This is called latent virus. Latent virus can activate as needed in order to keep HIV in the body.

The HIV attaches to a CD4 cell and injects its own genetic material (RNA) into the host cell. The viral enzyme reverse transcriptase is released allowing viral RNA to be converted to DNA and then integrated into the host cells genetic information. This process is called reverse transcription. The infected CD4 will now produce copies of the HIV virus. These new copies enter the bloodstream and lymph fluid and attach to other CD4 cells, continuing the process of viral . replication. During this process CD4 cells are destroyed.

CD4 cells are an important part of the body's immune system. Their main role is to lead the immune system in the fight against infections. A normal CD4 count ranges from 500 to 1,500 cells non HIV-infected individuals. As CD4 cells decline, an HIV-infected individual runs the risk of developing opportunistic infections. Laboratory measurement of CD4 is used:

- To stage HIV: HIV positive (CD4 $\geq$200) or AIDS (CD4 <200)
- As a predictor of that person's risk for developing infections (opportunistic infections)
- As a tool to determine when to initiate antiretroviral therapy and prophylaxis

Another important test used in staging the risk of progression and when to initiate therapy is an HIV viral load by PCR. This is difficult and complex laboratory test that can be easily contaminated. HIV is believed to make millions to billions of new copies of itself every day. The body's immune system controls much of this HIV replication but eventually is unable to keep up with the assault. Viral load provides additional information as to how quickly HIV will progress to AIDS and also whether antiretroviral therapy is working.

Testing to Diagnose HIV Infection

The diagnosis of HIV infection depends on antibody response to the virus. Testing serum for antibodies is the most cost-effective and accurate method of diagnosis. The ELISA (enzyme-linked immunosorbent assay) and Rapid test are the two most common HIV diagnostic tests being used in the Kilimanjaro region. Results are reported as positive, negative, or indeterminate.

- A positive result means antibodies to HIV have been detected and confirmed . Antibodies are formed by the immune system in response to HIV being in the body. Once a person has developed antibodies to HIV, they will have HIV antibodies from there on, irregardless of the amount of HIV in their body, or treatment.
- A negative result means that antibodies to HIV are not present and that this absence of antibodies has been confirmed.
- An indeterminant HIV test results means that some but not adequate antibodies are present in the sample, or confirmation of a test result is not the same.

Both negative and indeterminant test results may mean that at the time of the test there was either no, or inadequate HIV antibodies present to indicate that the individual has been exposed to HIV. In general, the immune system takes 4-8 weeks to form an immune specific response to HIV. Therefore, a negative or indeterminate test result only truly reveal an individuals HIV status as of 2 months back, and not necessarily at present. If the individual has not engaged in unprotected sex or any other HIV associated risk factors over the past two months, a negative test can be read as

truly negative. An indeterminate test should be repeated within 3 months, as should a negative test in an individual continuing to engage in unprotected sex or other HIVassociated risk factors.

The criteria for a positive or negative HIV test result is the combination of two confirmatory results. This can be two ELISA tests or two rapid tests. Both the ELISA and rapid test check for the presence of antibodies to HIV.

False positives are rare but can occur. Conditions that cause indeterminate results include:
- Cross-reacting antibodies from pregnancy
- Infection with HIV-2
- Auto-antibodies with collagen-vascular diseases
- Autoimmune disease
- Certain malignancies

Persons who have participated in an HIV vaccine trial may test positive on the ELISA because the vaccine has stimulated the production of HIV antibodies.

Modes of Transmission

The major transmission routes of HIV are sexual contact, parental exposure to blood and blood products, and perinatal transmission, including mother to child in-utero infection, childbirth, or through breastfeeding.

Body fluids in which high levels of HIV virus may be found, that can cause infection are:
- Blood
- Semen
- Vaginal Secretions
- Breast Milk

An additional small number of persons with HIV/AIDS represent HIV transmissions that occur among health care workers, laboratory employees, or patients in health care settings where needle sticks or other contaminated sharps or body fluid splashes to mucus membranes may occur.

Primary HIV Infection

Primary HIV-1 infection (PHI), also known as acute HIV- I infection or acute seroconversion syndrome, is the earliest detectable stage of the disease. Seroconversion refers to the appearance of HIV- I specific antibodies in plasma and occurs 5 to 10 days after the onset of symptoms associated with PHI. The time from exposure to onset of symptoms is usually 2-4 weeks but the incubation period may be as long as 10 months in rare cases (1). Using a standard serologic test, more than 95% of patient's seroconvert within 5.8 months following HIV transmission (1,2).

The most common symptoms associated with PHI are fever, lymphadenopathy, pharyngitis, malaise, headache, myalgia, and sometimes rash. During this period before the immune system is able to fully launch a response, in the form of antibodies, CD4 cell count transiently decreases as a result of the high level of HIV virus present in the body. PHI diagnosis is infrequently made. HIV RNA testing by PCR helps to make this diagnosis in patients with a negative antibody test, nonspecific viral symptoms, and a history suggestive for PHI. Patients who present with more severe symptoms of PHI have a more rapid progression to AIDS than those with asymptomatic PHI. There is a strong belief that it is critical to identify patients with primary HIV infection since during this period high levels of viremia may increase the risk of transmitting virus to others.

AIDS

The first AIDS surveillance case definition was published in 1982 (Centers for Disease Control, 1982) and included a group of conditions that were moderately indicative of a defect in cell-mediated immunity [such as *Pneumocystis carinii* pneumonia (PCP) or Kaposi's sarcoma] and that occurred in persons with no known causes for diminished immune function. When HIV was identified as the causative agent and the HIV-antibody test became available in 1985, the surveillance case definition was expanded to include additional conditions less closely associated with

immune suppression in persons found to be HIV-antibody positive (Centers for Disease Control, 1985). These conditions included disseminated histoplasmosis, chronic isosporiasis, and certain non-Hodgkin's lymphomas. In 1987 the CDC again expanded this definition was to include HIV wasting syndrome, HIV encephalopathy and extrapulmonary tuberculosis. In addition, the expansion allowed for presumptive as well as definitive diagnoses to accommodate changing diagnostic practices. In 1993, the CDC expanded the AIDS surveillance case definition to include (a) all HIV-infected persons with CD4 counts under 200cells/microliter or a CD4 percentage of total lymphocytes of less than 14 and (b) three additional clinical conditions: pulmonary tuberculosis (TB), recurrent pneumonia, and invasive cervical cancer (Centers for Disease Control and Prevention, 1992b).

- Not all HIV-infected persons have been tested.
- Anonymous testing programs do not always report results
- The use of home testing kits is not recorded in public health surveillance programs

Thus, the CDC estimates that there may have been as many as one million HIV and AIDS cases in the U.S. by the end of 2002, with at least 25% not even knowing they were infected (Fleming et al, 2002). Global estimates are even more staggering. UNAIDS reported 5 million new cases annually and estimated that as many as 40 million people worldwide were infected by the end of 2003 (UNAIDS 2003).

Regional HIV/AIDS Prevalence

The World Health Organization (WHO) and United Nations AIDS Programme, (UNAIDS) report HIV/AIDS prevalence in Tanzania as of 2003, (reported January 2005) as 8.8% of the adult population (15 years of age and up). Women are significantly more infected than men, and account for more than 60% of new infections reported in youth, age 15-24 years. HIV prevalence among pregnant women in Tanzania ranges from 4.2% to 32.1%. Some 100,000 children are infected, and AIDS orphans are estimated to be 2 million. People living with HIV/AIDS (PLWA) are estimated to occupy more than half of the available hospital beds in Tanzania.

Of 1,242 HIV/AIDS hospital admissions to Kilimanjaro Christian Medical Centre (KCMC) between 1997 and 2001, the following diagnosis were assigned: 21% tuberculosis (TB), 14% malaria, 12% gastroenteritis/diarrhoea, 10% non-tubercular pulmonary infection, 9% oral candidiasis, 6% anaemia, 6% central nervous system (CNS) disease, 4% dermatitis, 4% meningitis, 4% Karposi Sarcoma (KS), 4% extrapulmonary TB, and the remaining ranging from 1-3% were cardiac or renal disease, malignancy, urinary tract infection, lymphoma, septicemia, soft tissue infection, sexually transmitted disease, intra-abdominal infection, crytococcosis, and otitis media. 11% of HIV/AIDS admissions diagnoses were unclassified.

Malaria and tuberculosis have been shown to increase HIV viral load in patients who are co-infected. Effective treatment for these co-infections is essential, and may decrease mortality and viral burden, which when high may allow HIV to be transmitted more easily to others.

HIV Infection in Health Care Workers

As of June 2000, the CDC had received voluntary reports of 56 confirmed cases of health care workers (HCW) in the United States who had occupationally-acquired HIV infection, documented by seroconversion after specific exposure to infected blood, body fluids of other laboratory solutions containing HIV. An additional 138 cases are considered possible occupationally acquired HIV infections. These workers had a history of occupational exposure to blood, other infectious body fluids, or laboratory solutions containing HIV, and no other risk for HIV infection was identified, but seroconversion after a specific exposure could not be documented. Of the 56 confirmed cases:

- The major occupations were nurses and laboratory technicians
- All transmissions involved blood or bloody body fluid except for three involving laboratory workers-exposed to HIV viral cultures
- To date there have been no confirmed seroconversions in surgeons associated with operating on patients HIV infected patients, and no confirmed seroconversions with exposures to a suture needle.

Blood is unquestionably the body fluid associated with the greatest risk for occupational infection. Potential sources of exposure to HIV are blood, bloody body fluids, semen, vaginal secretions, cerebrospinal, pleural, peritoneal, pericardial, synovial and amniotic fluid, tissue or viral cultures).

In December 1991, the U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) promulgated their final rule governing occupational exposure to blood borne pathogens, which became effective in March 1992. OSHA updated these regulations in January 2001, to comply with the Needlestick Safety and Prevention Act of November 2000. The January 2001 regulations are still in effect. This standard endeavors to eliminate or minimize occupational exposure to HIV, hepatitis B virus, and other blood borne pathogens by encouraging the use of:

- Combination of engineering and work practice controls such as hand washing facilities, sharp containers, safer medical device or equipment, plastic bags, splashguards, resuscitation mask and bio-safety cabinets.
- Personal protective equipment such as gloves, mask, protective eyewear, gowns whenever potential body fluid contact is anticipated.
- Training
- Medical Surveillance
- Hepatitis B Vaccination
- Signs and labels identifying hazards

The standard also mandates universal precautions for infection control and requires employers to develop a written exposure control plan and to provide post-exposure evaluation and testing for all employees who have exposure incidents. Universal precautions means treating all potential contact with body fluids as infectious material.

Primary prevention of blood exposure is the main focus of preventing occupational transmission of HIV and other blood borne pathogens. The OSHA standard supports the concept that engineering controls, in conjunction with safer work practices and personal protective equipment, will minimize or even eliminate exposure.

A specific plan for post-exposure management must at minimum follow KCMC policy, and include a procedure for immediate, confidential, medical evaluation and follow up. Appropriate documentation of the route of exposure, the circumstances surrounding the exposure incident, and test results of the health care worker and the source of the exposure are necessary.

If accidental exposure to HIV occurs:

- Give immediate treatment: skin should be washed with soap and water; mucous membranes should be flushed with water for a minimum of five minutes.
- Assessment: Source should be evaluated for HIV, HBV, and HCV.
- Follow Public Health Services and Institution's recommendations for Post-Exposure Prophylaxis (PEP)
- Always refer to your institution's policy/guidelines.

If indicated, PEP is available to all exposed KCMC HIV/AIDS research staff. Immediate reporting and follow up to the KCMC HIV/AIDS Director (or delegate during times of absence) is essential to evaluate and initiate prophylaxis in a timely manner.

Considerations that influence the rationale and recommendations for Post-Exposure Prophylaxis (PEP), include: the pathogenesis of HIV Infection, particularly the time course of early infection; the biologic plausibility that infection can be prevented or ameliorated by using antiretroviral drugs and direct or indirect evidence of the efficacy of specific agents used for prophylaxis; and the risk/benefit of PEP to exposed HCW.

The following basic precautions should be taken to minimize the likelihood of exposure to HIV in the event of a contaminated blood, body fluid or laboratory solution spill:

- Obtain necessary supplies for cleanup (rags, paper towels, appropriate disinfectant, wt floor sign, etc)
- Never pick up contaminated glass or sharp objects with the hands. Use a dustpan and brush, clamps, or other device for this purpose.

- Dispose of sharp materials, such as a broken vacutainer tube or syringe, in a sharps container.
- Absorb liquid material with rags or paper towels and dispose of in the appropriate receptacle (linens in a soiled linen bag, paper towels in a biohazard bag, etc).
- Apply appropriate disinfectant to spill area. Let set for at least ten minutes.
- Wipe over areas with a cleaning solutions or water to complete the cleaning process.
- Dispose of contaminated cleaning solutions and articles in the appropriate container.
- WASH HANDS.

When to Initiate Antiretroviral Therapy

Antiretroviral therapy targets various stages of the HIV replication cycle. Guidelines developed together by the World Health Organization and local health authorities describe when to initiate antiretroviral therapy, but are not absolute and continue to be refined. A summary of current standards are listed in the following table:

HIV Status - ADULTS	TREATMENT GUIDELINES	ARV REGIMEN
Severe HIV disease/AIDS (WHO stage IV) manifesting with HIV wasting defined as >10% normal body weight loss, chronic diarrhea lasting > 1 month, unexplained chronic fever lasting > 1 month, or any AIDS defining opportunistic infection, CD4 count < 200 cells/mm^2	Start ARV. Start prophylaxis and treatment for opportunistic infections as available.	First line – Triomune =d4T+3TC+NVP Alternatives: ZDV+3TC+NVP, or ZDV+3TC+EFV, or D4T+3TC+EFV Second line – ABC=ddI+LPV/RTV ABC+ddI+SQV/RTV
Moderately symptomatic HIV disease (WHO stage III) manifesting with HIV wasting defined as >10% normal body weight loss, chronic diarrhea lasting > 1 month, unexplained chronic fever lasting > 1 month, oral candidiasis, pulmononary tuberculosis, severe bacterial infections, >CD4 ≤ 350 cells/mm^2	Start ARV treatment.	As above
Mildly symptomatic HIV disease (WHO stage II) manifesting with weight loss < 10% of normal body weight, minor mucoutaneous manifestations, herpes zosters, recurrent upper respiratory infections, CD4 > 350 cells/mm^2	Do not start ARV. Monitor CD4 count and symptoms for change/progression of disease.	None
Asymptomatic HIV disease (WHO stage 1), CD4 count >350 cells/mm^2	Do not start ARV. Monitor CD4 count and symptoms for change/progression of disease.	None
HIV Status – PEDIATRIC	TREATMENT GUIDELINES	
Severe HIV disease/AIDS (WHO stage III) manifesting with AIDS defining opportunistic infection, progressive encephalopathy, malignancy, recurrent septicemiaor pneumonia, or failure to thrive (HIV	Start ARV. Start prophylaxis and treatment for opportunistic infections as available.	First line – ZDV+3TC+NVP ZDV+3TC+EFV (children > 5 yrs) Second line – ABC+ddI+NFV

wasting) in the absence of known etiology. Children >18 months old with CD4% <15%, infants <18 months old with CD% <20%		
Moderate HIV (WHO stage II), manifesting with chronic diseases > 30 days, severe persistent or recurrent oral candidiiasis outside of the neonatal period, weight loss or failure to thrive in absence of known etiology, recurrent severe bacterial infections other than septicemia or meningitis. CD4 percent > 15% in children other than 18 months or >20% in infants < 18 months.	Do not start ARV. Monitor CD4 % and symptoms for change/progression of disease	None
Mild HIV (WHO stage I), asymptomatic, CD4 percent > 15% in children other than 18 months or >20% in infants < 18 months.	Do not start ARV. Monitor CD4 % and symptoms for change/progression of disease	None
HIV Status – other	Start ARV for pregnant women - PMTCT	NVP plus - as indicated

Treatment Options Available

Treatment guidelines represent a synthesis of nearly 15 years of clinical and pre-clinical antiretroviral research. Effective treatment for HIV/AIDS centers on a combination of one NNRTI or PI combined with 2 NRTIs. This powerful combination is referred to as highly active antiretroviral therapy or HAART. Both the NNRTI and PI class may interact with other medications. Potential drug interactions can greatly change drug levels, effectiveness, and the safety of a regimen. Interactions should be checked prior to initiating any new medications. Treatment options, including available therapies and formulations continue to change and will not be detailed here for that reason.

ANTIRETROVIRAL AGENTS FOR HIV

NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS (NRTI): NRTI's are incorporated into the DNA of the HIV virus by the enzyme reverse transcriptase during RNA to DNA viral genetic transcription, thereby stopping further virus replication. The resulting DNA is incomplete and cannot create new virus. Following is a list of NRTIs currently approved for use in Tanzania:

- Abacavir (ABC, Ziagen®)
- Didanosine (ddI, Videx®)
- Lamivudine (3TC, Epivir®, Lamivir®)
- Stavudine (D4T, D4T-XR, Zerit®, Stavir®)
- Zidovudine (ZDV or AZT, Retrovir®)
- Co-formulation of Lamivudine + Stavudine + Viramune (Triomune®)
- Co-formulation of Lamividine + Zidovudine (Combivir®, Zidovex-L®, Duovir®)

These drugs may be combined in co-formulated pills.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI): NNRTIs stop HIV production by binding directly to reverse transcriptase and preventing the conversion of RNA to DNA. These drugs are called non-nucleoside inhibitors because even though they work at the same stage as nucleoside analogues, they act in a completely different way. The currently available NNRTs in Tanzania are:

- Efavirenz (EFV, Stocrin®)
- Nevirapine (NVP, Nevirex®)

- Triomune (A generic co-formulation of Lamivudine + Stavudine + Viramune)

PROTEASE INHIBITORS (PI): PIs work at the last stage of the virus reproduction cycle. They bind directly to the protease enzyme, preventing assembly of complete and functional viral particles that can be released to infect new CD4 cells. The following is a list of PIs currently approved for use in Tanzania:

- Lopinavir + Ritonavir (LPV/r, Kaletra®)
- Nelfinavir mesylate (NFV, Viracept®)
- Ritonavir (RTV, Norvir®)
- Saquinavir (SQV, Invirase ®)
- Indinavir (IDV, Crixivan®, Indivan®)

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As ARTs work at specific targets in the HIV replication cycle, latent virus is not effected by these therapies. It is for this reason that even when virus is fully suppressed, drug pressure, in the form of continuing ART is necessary.

PROPHYLAXIS

Prophylaxis is the prevention of disease from occurring, or preserving health. Post exposure prophylaxis (PEP) refers to preventing HIV infection from occurring in known HIV exposure. In existing HIV infection, prophylaxis refers to preventing disease from occurring once significant immune damage (AIDS) has occurred. Patients with AIDS are at risk for various types of infections, including pneumocystis carnii pneumonia, disseminated mycobacterium avium complex (MAC) disease, cytomegalovirus, toxoplasmosis, and crytosporidiosis. Prophylaxis should be used in immunosuppressed adults and children living with HIV/AIDS, and is also recommended for perinatally exposed infants. The following is a list of prophylaxis currently approved for use in Tanzania:

- Co-trimoxazole (Septrin)

Co-trimoxazole is recommended for all adults with symptomatic HIV disease, CD4 count < 200, including all symptomatic pregnant women after the first trimester and before 37 weeks of pregnancy. All children born to HIV+ women from age 6 weeks of age and those identified as being HIV+ within their first year of life should be given Co-trimoxazole until proven to be HIV negative, intolerant of this medication, or CD4 percent increases to >15%.

All HIV+ persons should be assessed for exposure to tuberculosis (TB). The risk of activation or symptomatic TB in HIV+ patients is greatly increased, as compared to HIV negative persons. Patients with HIV and TB coinfection have an up to 10 times greater mortality rate. HIV+ patients with a positive TB test should be assesed for active versus inactive disease. Patient with inactive TB should initiate TB prophylaxis. Those with active TB disease should receive appropriate treatment. The following is a list of prophylaxis currently approved for use in Tanzania for this indication:

- Isoniazid (INH)

RESISTANCE

HIV constantly changes, or mutates during cycles of replication. HIV viral replication occurring in the presence of antiretroviral medications will eventual lead to drug resistance of the medications in the system. Not all mutations cause drug resistance. HIV virus free of mutations is called wild type virus. Wild type virus is the hardiest virus, most able to reproduce readily in the absence of antiretroviral therapy. However, if antiretroviral medications are in the system, the virus is not able to reproduce and given an opportunity, tries to find a way around the medications.

Clinical studies suggest that viral drug resistance is correlated both with failure of current therapy and with poor virologic response to new therapies. The reasons for failure can include:

- Prior use of suboptimal therapies

- Poor adherence to the regimen
- Poor tolerability of the regimen
- Interactions with medications being prescribed for other conditions which may affect drug levels
- Variations in drug bioavailability from one individual to the next
- Infection with HIV containing drug-resistant virus

There are three types of resistance:

- Clinical resistance – HIV continues to multiply rapidly even though the patient is taking HAART, as evidenced by decreasing CD4 count and deteriorating clinical picture.
- Increase in amount of HIV virus present while on HAART
- Phenotypic resistance- HIV multiplies in the test tube even when exposed to specific antiretroviral drugs.
- Genotypic resistance- the genetic code of a strain of HIV has mutations in it, as compared to wild type, and these mutations are linked to drug resistance.

Laboratory tests have been developed to measure phenotypic and genotypic resistance. These tests require a high level of training and sophisticated laboratory equipment. Samples are usually sent to one of a few commercial laboratories in the world that perform these test. Due to the expertise and cost requirements to perform these tests, phenotypic and genotypic testing are not currently available in Tanzania, but may be performed on archived study samples, especially in treatment failures or PMTCT.

When a phenotype is performed, a sample of a patient's HIV is cultured and a dose of antiretroviral drugs is added to the cultures, one at a time. The affect of each drug on the growth rate of the strain being tested is compared to data from wild type virus. If the patient's sample grows more than wild type, it is considered resistant to the drug being tested. Measurements of resistance are reported as a "fold" change. If the patient's virus grows ten times as fast as the wild type, it has 10-fold resistance. A phenotype has the advantage of being a direct measure of HIV resistance to drugs. However, it does not take into account that pharmacokinetic factors (absorption, distribution, metabolism, elimination) vary from person to person, drug interactions, and the possibility that drug levels can by manipulated by strategies such as boosting with a protease inhibitors, e.g., SQV/RTV, LPV/RTV.

It may be possible to achieve suppression of a virus that reportedly is resistant to a certain drug by reaching high enough blood levels of that drug. Each of the antiretroviral medications has a cutoff, or specific fold change, above which the drug would not work. Generally, though, a five-fold change or greater is indicative of drug resistance.

Genotype testing involves actually mapping the genome of a patient's strain and comparing it to the genomic map of wild type viruses. Specific mutations have been identified that correspond to the development of resistance to each of the antiretroviral medications. The pattern of mutations is then used to predict which of the drugs most likely will not work. Phenotype and genotype can be thought of as culture and sensitivity (respectively) test.

Recently, the virtual phenotype has been relied on to determine drug effectiveness. This test combines some elements of genotyping and phenotyping. A patient's virus is genotyped and the results compared to other samples in a database with similar genotype results and known phenotype results. This procedure predicts how the patient's strain will react in the presence of certain drugs, compared to what has happened in other patients with similar genotypes. The virtual phenotype is faster and less expensive but not necessarily as accurate as performing an actual phenotype.

For accurate as possible results, phenotypes and genotypes require that patients have viral loads of at least 500 to 1000 copies/ml and must be taking medications at the time the tests are done. Otherwise, the results may be misleading, inaccurate or reflect the genotype/phenotype of minority subpopulations of the virus (less than 20% of the total viral population) as compared to the dominant strain that the current antiretroviral regimen has been selected to treat.
The following table summarizes the advantages and disadvantages of genotyping and phenotyping:

	Advantages	Disadvantages
Genotype	May improve virologic outcome. Less expensive than phenotype Quicker turnaround time on results Well standardized	May not measure minority subpopulations Unreliable if viral load is <1000 Indirect measure of resistance Results open to interpretation

	Good reproducibility	
Phenotype	May improve virologic outcome Direct measure of resistance Interpretation more straightforward. Provides drug levels needed to treat resistant virus (thresholds)	May not measure minority subpopulations Unreliable if viral load is <1000 Very expensive Slower turnaround on results Detects resistance to a single medication but not combinations Thresholds do not always account for PK boosting with RTV.

Adherence

The success of an antiretroviral regimen lies in its ability to suppress viral replication. Studies have found that near perfect adherence (>95%) is necessary to achieve and maintain viral suppression. Even a minor drop in adherence from 95% to 90% over time can result in drug resistance and viral rebound.

Many factors can impact on a patient's ability to adhere to a medication regime. These factors can be divided into three categories proven to impact adherence:

Clinic/Provider characteristics, include:

- Trust
- Consistency
- Clear explanations
- Full disclosure
- Accessibility
- Scope of services

Patient characteristics, include:

- Level of motivation
- Social support
- Belief systems
- Satisfaction with regimen
- Coping skills
- Mental state

Therapy characteristics, include:

- Total number of pills per day (pill burden)
- Dosing frequency
- Diet restrictions
- Side effects
- Pill size
- # of copays
- # of refills
- # of prescriptions
- # of bottles
- Bedtime dosing

Many of these factors are difficult to alter, especially patient characteristics. However, through long-term community education and communication, changes may come little by little. For example, a community may believe that certain medications are poison or cause harm and reject treatment as a result. Other factors that may not be as easily altered, are the size of a capsule, dosing frequency, or available therapies.

Tailoring a medication regimen to the patient's daily routine is essential to successful treatment. Linking every day events together with dosing can improve adherence. When a patient begins or changes antiretroviral therapy, adherence counseling can be improved by the discussion of proper administration, what to do about missed or late doses, the risk of drug resistance with each missed dose, any food restrictions, drug interactions, side effects, and proper storage. Adherence counseling should be a continuous process and assessed at each patient encounter.

In addition to counseling, other recommendations in order to improve drug adherence, includes:

- Multi-disciplinary interventions, including pharmacist-based interventions
- Use of reminders such as cell phone or watch alarms and pillboxes
- Education aids such as medication pictures, calendars or stickers.

Part II

Overview of Clinical Research

Overview of Clinical Research

What is research?

Research is a deliberate study directed towards fuller scientific understanding or knowledge.

What is a clinical trial?

A clinical trial, also called clinical research, is a systematic investigation that involves human volunteers in order to answer specific health questions. Carefully conducted clinical trials are the fastest and safest way to find new treatments that work in people, and ways to improve health. A specific question(s), criteria for participation, management and evaluations are formed prior to initiating a study and written into a protocol that specifies all aspects of the clinical trial period to be followed by all sites participating in the clinical research study.

There are different types of clinical research. An interventional trial is one that determines whether an experimental treatment or new indication of a known therapy is safe and effective, under a controlled environment. An observational trial addresses health issues in large groups of people or populations in natural settings.

What are the phases of clinical trials?

Clinical trials are conducted in different phases. Each phase has a specific purpose and helps scientists answer different specific questions. The less known about a drug and its safety picture, the less human subjects are enrolled. Prior to initiation of phase I clinical trials where the experimental agent is used in human subjects with the disease or criteria being studied, experimental agents are developed and tested in the laboratory, animals and healthy volunteers. Approval for use in human subjects must be obtained prior to any phase of clinical research. Below is a brief outline of each phase:

Phase I clinical trials: In phase I clinical trials, research scientists test a new drug or treatment in a small group of people (20-80) for the first time to evaluate safety , determine a safe dosage range, and identify side effects.

Phase II clinical trials: In phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

Phase III clinical trials: In phase III clinical trials, the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

Phase IV clinical trials: In phase IV clinical trials, post-marketing studies continue to gather additional information about the drug's risks, benefits, and optimal use.

Randomization

Clinical research trials utilizing more than one treatment option in order to demonstrate non-inferiority or superiority to an approved treatment do so by random treatment assignment of study subjects called randomization. This is a method based on chance. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatments are better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant Study subjects who have met all criteria to enter a clinical trial are thereby randomized in an unbiased fashion. This is usually achieved via a computerized system or sealed envelope.

Types of controls or “blinds”

A randomized trial is considered “blinded” if the participant is not told which treatment assignment or arm he is on. Blinded randomization is sometimes also referred to as “masked”. Various degrees of blinds exist:

Single-Blind Study: One party, either the investigator or participant, is unaware of what medication the participant is taking; also called single-masked study. The research pharmacist is aware of which treatment this subject has been assigned .

Double-Blind Study: Neither the study participant nor the study staff know which treatment arm the participant is receiving. Double-blind trials are thought to produce objective, unbiased results, since the expectations of the doctor and the participant do not affect the outcome. This is also called a double-masked study.

Partially Blinded Study: In some protocols, some of the study medications are blinded and while other are not.

Studies without treatment blinds are called open-label**.**

Inclusion vs. Exclusion

All clinical trials have guidelines about who can and cannot participate. Using inclusion/exclusion criteria is an important principle of medical research that helps to produce reliable results. The factors that allow someone to participate in a clinical trial are called "inclusion criteria" and those that disallow someone from participating are called "exclusion criteria". These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Before joining a clinical trial, a participant must qualify for the study. Some research studies seek participants with illnesses or conditions to be studied in the clinical trial, while others need healthy participants. It is important to note that inclusion and exclusion criteria are not used to reject people personally, but instead are used to identify appropriate participants and keep them safe. The criteria help ensure that researchers will be able to answer the questions they plan to study.

Screening, Baseline, Treatment and Post Treatment Periods

Also known as clinical trial evaluations, every study participant must come for each scheduled evaluation throughout the study in order to continue to participate**. Screening** is the initial evaluation of a participant in which information about the clinical trial is reviewed and consent obtained. Review must include the purpose, risks, and benefits of the clinical research trial. Potential study participants must have the opportunity to ask questions and have these thoroughly answered prior to obtaining written consent. After written consent is obtained, study specific laboratory, clinical and records assessments to confirm inclusion/exclusion criteria may be initated.

Pre-Entry is sometimes required by a protocol. Pre-entry evaluations are performed after screening but before entry/randomization. Most of these evaluations are to confirm safety labs (i.e., chemistries, full blood pictures) within 14 –30 days prior to entry.

Once the participant has successfully passed all required lab tests and is found to meet all eligibility criteria, he/she is enrolled into the clinical research study. This visit is referred to as **baseline** (or entry/day 1) visit, or sometimes **randomization**. It is at this visit that the participant will receive study drug if it is a treatment trial. Sometimes randomization occurs prior to baseline in order to allow for sufficient time to access open label treatments or to allow for shipping of randomized medications.

Depending on the clinical trial, the study participant continues with periodically evaluations for laboratory and clinical assessments. Frequency or intensity of the visit schedule may vary from daily, weekly, monthly, etc. depending on the design of the study, including, phase of development, or duration of the study and visits already performed.

Placebo

A placebo is an inactive pill, liquid, or powder that looks the same as the active research agent but has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness in an unbiased manner. In some studies, the participants in the control group will receive a placebo instead of an active drug or treatment. Treatment study designs must meet standard of care criteria. Most studies compare what is considered the standard of care + new drug vs. the standard of care + placebo.

Good Clinical Practice

Good Clinical Practice (GCP) is an international ethical and scientific quality standard that outlines design, conduct, recording and reporting of clinical trials that involve human subject participations. This orientation manual does not intend to provide adequate training of GCP within this resource. Research staff are referred to KCMC site GCP manual and Duke IRB Research Ethics training for more detailed discussion and training.

PART III

NIH / DAIDS and ACTG

B) The National Institute of Allergy and Infectious Diseases

Introduction
The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. For more than 50 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world.

Expanded NIAID Research Portfolio
The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as:

- bioterrorism
- emerging and re-emerging infectious diseases including:
    - acquired immunodeficiency syndrome (AIDS)
    - severe acute respiratory syndrome (SARS)
    - West Nile virus
    - malaria
    - tuberculosis
- the increase in asthma prevalence among children in this country

The growth of NIAID programs also has been driven by unprecedented scientific opportunities in the core NIAID scientific disciplines of:

- microbiology
- immunology
- infectious diseases

Advances in these key fields have led to a better understanding of the human immune system and the mechanisms of infectious and immune-mediated diseases.

Vaccine Research
Vaccine research has long been a cornerstone of NIAID research. Effective vaccines have contributed enormously to improvements in public health worldwide, and research supported by NIAID has led to new or improved vaccines for a variety of serious diseases, including:

- rabies
- meningitis
- whooping cough
- hepatitis A and B
- chickenpox
- pneumococcal pneumonia

NIAID is committed to improving global health through the rigorous pursuit of effective vaccines for human diseases.

Vaccine Research Goals
NIAID has three broad goals in vaccine research:

- identifying new vaccine candidates to prevent diseases for which no vaccines currently exist
- improving the safety and efficacy of existing vaccines
- and designing novel vaccine approaches such as new vectors and adjuvants

Vaccine Development Challenges
One of the important challenges for the 21st century is the development of safe and effective vaccines for the three greatest microbial killers worldwide:

- HIV/AIDS
- malaria
- tuberculosis

These three diseases account for one-third to one-half of healthy years lost in less-developed countries. NIAID has a robust portfolio of vaccine research and development for these and other diseases of global importance, including agents of bioterrorism.

HIV/AIDS
Despite recent progress in treatment and prevention, human immunodeficiency virus (HIV) disease and AIDS continue to exact an enormous toll throughout the world. Estimates on the scope of the HIV/AIDS pandemic are profoundly sobering. As of the end of 2003, an estimated 40 million people worldwide are living with HIV/AIDS, 5 million people worldwide were newly infected with HIV, and 3 million people with HIV/AIDS died. More than 95 percent of these infections and deaths have occurred in developing countries, most of which also are burdened by other significant health challenges.

HIV/AIDS Research Collaborations
To help turn the tide of the global HIV/AIDS pandemic, NIAID has established research collaborations with international colleagues in more than 50 countries to develop comprehensive approaches to the HIV pandemic, encompassing vaccine development and other prevention activities, therapeutics and care of the HIV-infected person. These collaborations already have yielded important results, notably in developing methods to reduce mother-to-child transmission of HIV.

NIAID-sponsored Research Efforts
NIAID-sponsored researchers have made critical discoveries about the basic biology of HIV and the immune response to HIV infection, which in turn have led to the development of therapies that suppress the growth of the virus in the body. Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication, why the host immune response fails to control the infection, and how reservoirs of virus persist in the body despite highly active antiretroviral treatment (HAART).

NIAID continues to search for more scientific information about how the virus attacks the body and how the body defends itself, which is critical for identifying additional targets for therapeutic interventions and vaccines.

Immune System Research
An important NIAID research focus is the immune system, the complex network of cells, tissues, and organs that work together to defend the body against attacks by foreign invaders such as bacteria, viruses, parasites and fungi. Because the human body provides an ideal environment for many microbes, they try to break in. It is the immune system's job to keep them out or, failing that, to seek out and destroy them. When the immune system hits the wrong target or is crippled, however, it can unleash a torrent of diseases, including asthma and allergy diseases, arthritis, or AIDS.

NIAID-funded Research in Basic and Clinical Immunology
NIAID-funded research in basic and clinical immunology has led to many promising approaches for treating individuals with immunologic conditions such as multiple sclerosis, type 1 diabetes, and asthma. For example,

researchers are developing novel ways of selectively blocking inappropriate or destructive immune responses while leaving protective immune responses intact, an area of research known as tolerance induction.
The NIAID-supported Immune Tolerance Network (ITN) is an international consortium consisting of approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. The ITN has 18 approved clinical protocols that are enrolling patients, or will do so soon, in areas such as islet transplantation for type 1 diabetes, kidney transplantation, autoimmune diseases, and asthma and allergic diseases

Conclusion
We still have much to discover about many infectious and immune-mediated diseases, and how best to diagnose, treat and prevent them. However, with a strong research base, talented investigators in the United States and abroad, and the availability of powerful new research tools, we fully expect that our basic and applied research programs will provide the essential elements to enhance our defenses against those who would attempt to harm us with bioterrorism, to develop new tools in the fights against HIV/AIDS and other infectious diseases, and to improve therapies and management of immune-mediated diseases.

Website for NIAID:

www.niaid.nih.gov

Adult AIDS Clinical Trials Group International Research Agenda

Over the past several years, the impact of the AIDS epidemic in resource-limited setting has become increasingly apparent. This recognition has led to a greatly increased commitment to focus clinical care resources on the epidemic in these settings. Although the basic principles of therapy developed for more heavily resourced setting will likely apply to the management of HIV infection in these setting, it is highly likely that differences in demographics, genetics, co-morbid conditions and resource limitations will contribute to significant differences in the optimal management of the disease in resource limited settings. Given the scale of the proposed investment in clinical care in these settings and the unforgiving nature of the virus when the disease is inappropriately managed, it is critical that the investment in care be accompanied by a rigorous research and evaluation program that can maximize the impact of theses interventions.

Community Advisory Board

Mission Statement

The mission of the Community Advisory Boards (CABs) of the AIDS Clinical Trials Group (ACTG) is to integrate community involvement in the AIDS Clinical Trials Units (ACTUs) in order to advance HIV/AIDS research.

Purpose

CAB's provide an opportunity for affected communities, especially clinical trials participants to:

- understand the clinical research process;
- voice concerns regarding specific clinical studies, their development, implementation and outcomes;
- give assistance concerning issues related to the accrual and retention of trial participants;
- give clinical trial participants necessary advocacy;
- forge a viable partnership that will lead to improved knowledge of HIV/AIDS disease;
- give a means to address grievance issues; and

- promote ethical research purposes and practices.

Clinical Site Monitoring

This Clinical Site Monitoring Project contract will provide services currently performed by PPD Pharmaco, Inc. Among other activities, the contract will provide for:

1. Monitoring of clinical research studies in therapeutics, vaccines and other prevention strategies;

2. Initiating and monitoring of sites and pharmacies conducting DAIDS/NIH-supported clinical research in the United States and abroad;

3. Monitoring of laboratory facilities and procedures for obtaining, testing and storing clinical research specimens, when requested as a special assignment;

4. Training site personnel on good clinical practice and on the policies and procedures to conduct clinical research established by DAIDS, the Food and Drug Administration (FDA), the Office for Protection from Research Risks (OPRR), and the collaborative research groups;

5. Training and evaluation of behavioral counselors in the HIV Vaccine and Prevention Trials Networks (HVTN and HPTN) to assure the appropriateness of behavioral counseling and the integrity of behavioral intervention trials;

6. Auditing of the monitors' work to ensure its consistency and quality;

7. Timely maintenance of a database of monitoring reports, monitoring findings and problem resolution, and training activities;

8. Communication and coordination with DAIDS and DAIDS-supported collaborative research groups to enhance the quality of the clinical research; and

9. Capacity to rapidly intensify the monitoring effort for the HVTN or the HPTN in the event that more promising vaccine or prevention candidates become available for large-scale efficacy trials in the United States and internationally, or that other related vaccine/prevention trials programs are established.

The contractor's monitors will visit sites conducting active protocols as follows:

a. Monitor main sites every three months;

b. Monitor subsites every six months; and

c. Conduct extra visits as directed by the Project Officer, e.g., to sites experiencing significant problems conducting research, carrying an unusually high subject load, or performing complex or high-priority protocols

The contractor's monitors will review subject records in accordance with a monitoring assignment the contractor shall develop each quarter for each research group. The Project Officer will review and approve each assignment prior to its implementation.

Site visits shall routinely include the following tasks:

a) Full chart reviews: For a sample of subjects on active protocols, verify that all reportable data have been accurately captured on case report forms (CRFs) and serious adverse event (SAE) forms as appropriate, and that adequate source documentation is maintained.

b) Special protocol assignments: Review specified subject records to verify endpoints, adverse events or other specific data items, as requested by the assignment.

c) Assess the site's compliance with the requirements of the protocols being conducted and maintenance of clinical records including:

* adherence to inclusion and exclusion criteria;

* reporting of serious adverse experiences;

* reporting of protocol violations;

* registry of protocol exemptions approved by the protocol team;

* documentation of objective findings such as clinical endpoints and adverse reactions; and

* the adequacy of source documents, the recording of data onto CRFs, and its accurate entry into the central computer database.

d) Assess the site's compliance with the policies and procedures of DAIDS and the pertinent research group, and Federal and local regulations.

e) Assess the various components of the implementation of the clinical studies including:

* the procedures for requesting and obtaining biological samples;

* the procedures for requesting and obtaining laboratory and diagnostic reports and other clinical records;

* the site personnel's knowledge of specific protocols being conducted at the site; and

* the site personnel's knowledge of pharmacy procedures.

f) Follow up to verify correct handling of past site visit issues or findings.

The contractor's monitors shall be responsible for these additional tasks which shall be incorporated into regularly scheduled site visits at the intervals specified at sites involved in active protocols:

a) Site operations assessment: On an annual basis, describe the various components of the operation and management of each clinical site including:

* the site personnel and their roles, including staff responsible for day-to-day management of the site, oversight of subsites, outreach/recruitment, internal quality management, and maintenance of regulatory files;

* communication channels among site staff and between the site and its subsites;

* adequacy of the facilities and study equipment;

* availability of a secured area for storing confidential information (e.g., signed informed consents, research records); and compliance with specified procedures to protect confidentiality; and

* documentation of the site’s implementation of periodic internal quality management activity.

b) Specific-protocol oriented investigational drug audit: On a semi-annual basis, perform an audit of each site pharmacy or drug management area for a sample of active protocols including, but not limited to, evaluation of:

* the pharmacy’s procedures to ensure that the treatment regimens are being dispensed in accordance with the protocol and DAIDS guidelines;

* subject records, treatment assignment lists and accountability documents, to ensure that their confidentiality is maintained; and

- the proper management of the study to ensure that procedures are being followed to prevent diversion of investigational drugs. This will include performing inventories of investigational agents physically present and reconciliation with accountability records.

c) Regulatory audits: On at least an annual basis, perform an audit to ensure that the site's regulatory-related procedures and files are in order. The site should have on file a current FDA Form 1572, the latest protocols and consents along with IRB-approvals, current laboratory certifications, current investigator's brochures, documentation of annual IRB renewals, and all safety reports issued.

PART IV

AIDS RESEARCH PHARMACY

Research Pharmacy

One component of an AIDS Clinical Trials Unit is the research pharmacy. This pharmacy is established to provide care and medications specifically for the clinical trials and its study patients. Although the pharmacist's role within the AIDS Clinical Trial Unit may vary from site to site, the operation procedures for randomization, investigational medication ordering, storage, dispensing and accountability are standardized. The pharmacy must practice according to the guidelines established by the Pharmaceuticals Affairs Branch of the Division of AIDS. Adherence to these guidelines are ensured by annual monitor visits.

Pharmacist

Each site has a designated research pharmacist who is responsible for following pharmacy operational procedures as specified in the Pharmacy Guidelines and Instructions for AIDS Clinical Trials Group manual. This manual is provided to each site by the Pharmaceutical Affairs Branch and should be located in the site pharmacy. An additional copy may be located in the Study Coordinator's files, In addition to this manual, the site pharmacist is responsible for maintaining a site specific policies and procedures manual.

Responsibilities of the site pharmacist include maintaining accurate and detailed information of all medications ordered, received, dispensed, and returned for each study. The site pharmacist also makes necessary dosing adjustments as defined by protocol (e.g. dose by weight, reductions secondary to toxicities, CrCl, etc). The pharmacist is required to write a dispensing procedure for each protocol in the vent he/she is unavailable, enabling a designated backup pharmacist to enroll patients and dispense medications.

The pharmacist's role, however, goes beyond maintaining the daily operations as mentioned above. He/she maintains the integrity of a blinded trial to prevent the patient, care giver and research staff from becoming biased. The pharmacist serves as a drug information resource. He/she is available to identify potential drug interactions, sides effect and help avert possible adverse reactions, especially in situations where a patient is taking multiple concurrent medications. The site pharmacist provides patient counseling as well as education tools and information in an effort to enhance patient adherence, thereby allowing the patient to get the most benefit from a clinical trial while providing the most accurate data.

C. Medication Accountability/Quality Control and Inventory Control

The NIAID Clinical Research Products Management Center (CRPMC) provides study medications to all ACTU sites. Sample Order, Return and Transfer Forms are available in the ACTG pharmacy manual. Only designated ACTU pharmacists are permitted to order, receive, return and handle the medications. All medications must be kept in a secured area separate from regularly dispensed non-study medications. All study information and records must also be kept in a secured area, readily available for inspection by site monitors.

Each protocol has its own separate medication supply and study specific drug accountability/inventory control logs, order and return logs. Individual medication dispensing logs (e.g., patient profile) should be maintained on each patient. The pharmacist is also responsible for the accounting and returning of all used and unused study medications. More detailed information regarding handling of study medications can be found in the ACTU pharmacy manual.

D) Pharmacy Enrollment Procedures

When a site becomes registered for a study, the pharmacist is notified by either the site ACTU or via facsimile. The CRPMC sends the drug supply statement to the pharmacist. This statement informs the pharmacist of the medication(s) provided for the study and necessary ordering information. The pharmacist is then responsible for placing an initial order using the appropriate forms.

The site pharmacist also receives a randomization list. This list contains the study identification numbers (SID) specific for that site which are assigned to patients at the time of randomization. The pharmacist refers to this list every time a patient is enrolled in a study. In a situation where a study is partial or double blinded, the pharmacist must take measures to ensure the patient's medication remains blinded.

The site pharmacist should be notified by the ACTU staff prior to enrolling a study patient as well as all study visits which required medications to be dispensed. This will allow the pharmacist time to complete the necessary paperwork (e.g. order forms, accountability records, patient education materials, etc) and order medications. Conversely, the site pharmacist should notify the ACTU staff as soon as study medications and SID lists are available so patients can be enrolled.

At the time of study enrollment, the pharmacist will need the patient's name, weight/BSA/CrCl (if medications are dosed based on these parameters), patient and study identification numbers (PID and SID), and a copy of the signed informed consent. The pharmacist then dispenses enough medication to reach the next study visit. Just as in outpatient and hospital pharmacies, a written prescription is required for each study patient when medication is needed. The prescription must be signed by the Principal Investigator or another physician listed on Form 1572 of the study registration documents. During the enrollment visit, the pharmacist may meet with the patient to review the study medications, dosing schedule, potential side effects and answer questions.

PART V

Role of Home Based Care Workers within AIDS RESEARCH UNIT

Role of the Home-based Care Worker within AIDS Research Unit

The Home-based care worker (HBCW) primary responsibility is to ensure that study subjects attend study follow up visits. As a clinical research team member, HBCW assess, evaluate and intervene to meet the psychosocial needs, of the patient and/ or family who is adjusting to a change in medical status. The HBCW served as liaison with patient and family to other health professionals for the purpose of clarification of health needs and psychosocial issues. HBCW demonstrate an understanding of human behavior and the relationship to disease entities and work as advocates for the patient, family, and significant other when other advocates are not available, or they are unable to advocate for themselves. HBCW demonstrate the ability to engage, assess, evaluate, formulate goals, initiate planning, implement plans with patients, their families, and/or significant others. HBCW maintain a list or knowledge of community resources, agencies, and/or services available to assist patients and their families.