

The MTCT-Plus Clinical Manual

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MTCT-PLUS: BRINGING HOPE TO WOMEN, CHILDREN AND FAMILIES IN THE FACE OF AN EPIDEMIC

MTCT-Plus is a major new program designed to link prevention with care and treatment for HIV-infected women and their families in the poorest countries. Based at Columbia University's Mailman School of Public Health and supported by a coalition of foundations, MTCT-Plus will add HIV care and treatment – including treatment with antiretroviral drugs, where indicated – to existing programs to prevent mother-to-child transmission (MTCT) of HIV.

Background. Mothers and children are suffering the heaviest toll in the worldwide battle with HIV/AIDS, particularly in sub-Saharan Africa. Each year, more than 2.5 million women become infected, and more than 500,000 transmit the virus to their infants. Groundbreaking progress has been made in the prevention of MTCT; however, these programs offer no care for the mothers themselves. The tragedy is that many of the children saved by MTCT programs are likely to be motherless by the time they can walk.

Responding to the Challenge. Leaders of private foundations met with United Nations Secretary General Kofi Annan in December 2001 to announce that they and the larger global community of foundations expect to commit \$100 million in new funding for a five-year HIV care and treatment initiative called the **MTCT-Plus Initiative**. The Initiative has already raised \$50 million from a coalition of nine foundations: Bill & Melinda Gates, William and Flora Hewlett, Robert Wood Johnson, Henry J. Kaiser Family, John D. and Catherine T. MacArthur, David and Lucille Packard, Rockefeller, Starr and the UN Foundations, and is under the leadership of Dr. Allan Rosenfield, Dean of Columbia University's Mailman School of Public Health.

MTCT-Plus funds demonstration sites, providing support for the development of family-centered care and treatment programs for infected women and their families. MTCT-Plus provides a package of services that includes education, counseling, psychosocial support, prophylaxis and treatment of HIV complications, and antiretroviral therapy. Support is also provided for community outreach and education to build linkages with local organizations and other resources.

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Introduction to MTCT-Plus



The MTCT-Plus initiative is designed to promote wellness and to improve health care for HIV-infected mothers and their families. By providing a continuum of services, from patient education to HIV-specific treatment, MTCT-Plus builds on successful pMTCT programs to create high-quality HIV care.

In addition to the pMTCT interventions already in place, MTCT-Plus patients will have access to nutritional support, diagnostic testing, prophylaxis of opportunistic infections, and antiretroviral therapy. Multidisciplinary teams will provide psychosocial assistance, patient education, and counseling, adapted by sites to meet the needs of specific cultural environments. MTCT-Plus will also support community outreach and education, and work to build linkages to local organizations and resources.

MTCT-Plus sites are located in a wide range of settings, from urban to rural, across many countries and cultures – and program specifics may vary accordingly. All sites will, however, provide a basic set of clinical services, outlined in this manual. Standardized clinical protocols will enable procurement of drugs and supplies, development of education and training interventions, and collection of outcomes and quality assurance data. The shared protocols will also enable sites to deliver uniformly excellent care.

The Clinical Manual provides an overview of essential MTCT-Plus services, implementation recommendations, clinical guidelines, and treatment algorithms. These are intended to enhance rather than to replace the judgment and expertise of health care workers.

We anticipate that MTCT-Plus protocols will evolve over time. The Clinical Manual will be updated regularly, and is formatted to accommodate frequent changes. Suggestions, comments, and corrections are encouraged, and should be directed to the MTCT-Plus Secretariat at mtctplus@columbia.edu.

Family Care Coordination:

What is family care coordination?

Family care coordination (FCC) is an approach to the care of patients with complex needs, in whom coordination of medical and supportive services is critically important. Evaluation, communication, and advocacy are hallmarks of FCC, allowing patients and providers alike to ensure that care is of the highest quality. Family care coordination also encourages providers to consider the needs of all family members, appreciating that the needs of the individual are intertwined with those of others in their immediate family and community.

Why is family care coordination important?



Experience caring for patients with HIV/AIDS has shown that coordination of medical and supportive services and communication among providers optimizes patient health and well being. Different members of the care team have different “pieces of the puzzle”—a physician may know that the patient is not

thriving; a counselor may know that the patient is having marital difficulties; a social worker may know that the patient lacks resources to feed her family; and a clinic manager may know that a patient is missing appointments. Regular and organized communication among providers can put the pieces of the puzzle together to identify barriers to wellness and to formulate a patient- and family-centered plan of action.

Who should be involved in family care coordination?

There are many successful care coordination models, but all involve the multidisciplinary cooperation of providers of clinical and supportive services. A team approach is recommended; one in which staff providing medical, counseling, outreach and social services meet periodically to discuss specific patients. It is advisable to identify a staff member to play the key coordinating role. This coordinator should lead the FCC meetings described below.

How should family care coordination be done?

At its heart, family care coordination is a patient-oriented, family-focused approach. When done well, it is comprehensive, collaborative, and efficient. FCC includes:

- Initial assessment of a patient’s needs with careful attention to the family setting, social supports, and potential barriers to care
- Development of a care plan for the patient and family

- If multiple members of the family are receiving medical care, regular communication among their providers (with the patients' permission)
- Coordination of the services required to implement the plan
- Patient monitoring to assess the efficacy of the plan
- Periodic re-evaluation and revision of the plan as necessary

Team meetings:

Weekly multidisciplinary team meetings are an ideal way to communicate, exchange information, and develop and monitor a care plan. It is important for both clinicians (physicians, nurses, and medical officers) and non-clinicians (outreach workers, counselors, and health educators) to attend these meetings. These groups are most effective when a team leader, often a nurse, counselor, or social worker, plans the weekly patient list and agenda, distributes it to the team in advance and chairs the meeting.

A common strategy is to discuss a subset of the patients each week (one-fourth, for example) as well as any patients with urgent or emergent issues. Each patient on the list is discussed, a brief update provided and key issues highlighted. Input is solicited from the team, and the team leader confirms and records action items for the week. Notes are taken and become part of the patient record. This structure allows ongoing monitoring and evaluation of care plans, permits team members to efficiently share patient information, and strengthens multidisciplinary collaboration and camaraderie.

Adherence Assessment and Support:

What is adherence?

Adherence is the engaged and accurate participation of an informed patient in a plan of care. It is a broader term than “compliance” – the extent to which patients follow the instructions of their healthcare providers – and implies understanding, consent, and partnership. Adherence includes entering into and continuing in a program or care plan, attending appointments and tests as scheduled, taking medications as prescribed, modifying lifestyle as needed, and avoiding risk behaviors. It includes *adherence to care* and *adherence to medications*, but is usually regarded as more than the sum of its parts.

For patients on antiretroviral (ARV) therapy, medication adherence is critically important to treatment success. Near-perfect pill-taking is required to achieve viral suppression and to avoid the emergence of viral resistance. When patients skip doses and do not take their ARV medications regularly, viral resistance develops and the medicines can stop working. Missing doses is a common problem, and all patients need help to take 100 percent of their medicines as prescribed. The risks of nonadherence are so clear and so large that adherence assessment and support are integral parts of HIV care programs worldwide. Treatment guidelines stress that antiretroviral therapy should not be prescribed in the absence of adherence support.

Why is adherence assessment important?



Studies have shown that healthcare providers are unable to tell which patients are adherent and which are not. Without formal assessment, providers are unlikely to accurately identify adherent and nonadherent patients, missing the opportunity for reinforcement and constructive interventions respectively.

Who should perform adherence assessment?

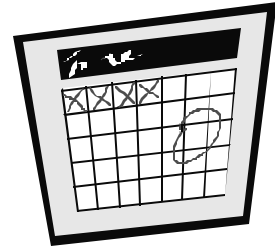
The simple answer is “everyone.” Successful assessment often involves multiple providers. Unless they ask, a clinician may not know that a patient missed a counseling appointment and a counselor may not know that a patient missed a clinical appointment. A patient may be reluctant to inform the person prescribing medications that s/he is not taking her pills, but quite willing to discuss this with another provider of care. A multidisciplinary approach, in which someone other than the clinician conducts a formal adherence assessment, is likely to be the

most successful in elucidating information about adherence to medications.

Adherence to care

How should adherence to care be assessed?

Assessing adherence to care should start with the basics. Does the patient come to all her appointments? Attend the support group meetings? Did he pick up medications at the pharmacy as directed? Complete the tests that were ordered? These are simple questions, but collecting, interpreting and acting on this information requires a robust administrative infrastructure. The system will work best if there is one person clearly designated to supervise adherence to care, such as the clinic administrator or nurse in charge. A list of patients expected at each clinic session should be kept at the registration area—the names of patients who do not appear are then “flagged” and referred to this supervisor following specific protocols. Similarly, if a patient is expected to pick up medications but does not come to the pharmacy, pharmacy staff should notify the supervisor.



How should adherence to care be supported?

The best approach towards maintaining patients in care will clearly vary from patient to patient and setting to setting. However, there are some approaches that are known to be highly effective:

Care setting: A welcoming and comfortable environment is an important motivation for patients to remain in care. Not all patients have experience participating in decisions about their health care. Helping patients to become involved in their care may help them adhere to their treatment plan. Accessible and co-located services, convenient hours, and reimbursement for transportation costs are all inducements to return.

Communication: Establishing good communication with patients builds trust and is essential to effective patient care. Good communication helps to identify patient problems, needs, and barriers to care. Providers should check to make sure patients understand their explanations and instructions, and should provide both written and verbal instructions. They should encourage patients to share information and let them know that they are being heard. It can be difficult for patients to say what they are thinking or are concerned about. Asking specific questions that promote information-sharing rather than “yes” or “no” answers can make this

easier. Restating answers can assure that patients have been understood. And no matter what patients reveal, staff should work to project concern and respect—by what they say, as well as the manner in which they say it.

Patient-provider relationship: Patients are more likely to stay in care if they trust their providers, participate in decision-making, and understand their care plan. While coordination of care, consistency of staff, and provision of patient education programs are all important, a respectful and supportive milieu will go a long way towards encouraging adherence with care.

Confidentiality: Confidentiality should be addressed with all patients upon enrollment into MTCT-Plus. They will need to understand that their participation in the program will be kept confidential and that HIV status will not be disclosed without their approval. However, they should be aware that they may meet individuals from their community who attend the program and who may infer that they are HIV-infected. Patients should be prepared for this eventuality and counseled about the importance of discretion regarding the people they encounter within the MTCT-Plus program.

Patient education and peer support:

- Patient education has many benefits and is discussed at greater length in chapter 7. For the purposes of this chapter, we stress that a patient who understands his/her illness is more likely to be adherent to care and to treatment and that all patients should have access to verbal, written and/or visual information about HIV/AIDS at each visit.
- Peer support groups and one-on-one peer education are powerful tools for health promotion and adherence support.

Outreach and followup: As noted, a robust administrative infrastructure is necessary to rapidly identify patients who miss appointments. Planning ahead for this contingency is a prudent approach and it is important to gather as much contact information about a patient on enrollment as s/he will permit.

- What contact information should be obtained?
 - Full name, complete address (with map if no street numbers)
 - If available: telephone number (home and/or mobile phone) for patient (or friend or neighbor)
 - Name, address, phone for close family and/or friends
 - Address, phone of places the patient spends time (work, recreation)

- Contact information for the patient's community health worker, if any
 - Document how the patient wishes to be contacted. Has s/he given permission to be called at home? For a home visit? For care providers to contact family and friends?
 - The MTCT-Plus Patient Locator Form can be used to record this information, which should be kept in a locked and secure place.
- What should happen if a patient misses an appointment?
 - If a patient misses an appointment and has not contacted the staff or returned for care within a week, an initial recall should be initiated
 - If there is no response, a home visit should be initiated
 - Never give up on patients who have missed visits and in whom follow-up contact has failed. They may return to the area after traveling, or otherwise re-engage with care. Periodic attempts should be made to contact patients, even if initial outreach attempts are unsuccessful.
 - Missed appointments or change in pattern of visits should be discussed during the family care coordination meetings (see chapter 1).

Adherence to medication

How should medication adherence be assessed?

It is critically important that providers know the following information about each patient:

- Are patients taking medications as prescribed? If not, how many doses are missed?
- What makes it difficult for patients to take medications? Some common problems include side effects, fears about the medication, lack of access to food, and difficulty getting to clinic.
- What helps patients to take medications?

When it comes to assessing adherence to medications, a supportive and nonjudgmental approach is essential. In discussions with their patients, providers should acknowledge that medication adherence is difficult, that there are many barriers to successful pill-taking, and that



it is usual for patients to require assistance and encouragement. As above, a multidisciplinary approach is often the most successful. While there is no gold standard for the assessment of medication adherence, many experts endorse a combination approach. All patients taking

medications (of any sort) should be asked about adherence at each visit. More rigorous assessment (e.g. review of pharmacy records and pill counts) is recommended during ARV initiation.

Patient interview and self report often overestimates adherence, but there are ways that providers can improve the accuracy of this simple type of assessment. Patients should be informed that their providers want them to tell the truth, even if medications have been missed. Similarly, patients on ARV medications should know that if they are going to stop medications, they should stop all their ARVs as instructed by their provider. The use of respectful, nonjudgmental language is vital.

Some examples of questions to assess missed doses include:

- “Many patients taking these medications find it difficult from time to time. Do you ever have trouble taking the pills?”
- “It is hard to take medications every day, and many patients miss a dose now and then. When was the last time you missed a dose of your medications?”
- “How many doses have you missed in the past day? The past two days? The past week?”
- “In an *average* week, how often do you miss your medications?”

Some examples of questions to assess barriers or support strategies include:

- “When is it most difficult to remember your medications?”
- “It’s not easy to take medicine every day. What kinds of problems make it hard to take your pills?” You may need to prompt patients with questions about specific problems such as side effects, forgetting, travel, etc.
- “It’s not easy to take medicine every day. What things help you to take your pills?”

When should medication adherence be assessed?

For patients taking ARV therapy, adherence should be assessed at every visit, as indicated on the MTCT-Plus clinical encounter forms. It is also prudent to routinely assess medication adherence in those patients taking prophylaxis for opportunistic infections or any other medications.

What are barriers to medication adherence?

There are many factors that can create barriers to good adherence, affecting patients’ readiness or ability to take medications regularly as prescribed. Some examples include:

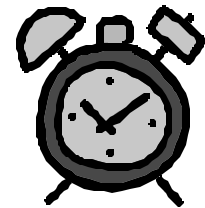
- Cultural beliefs/fears about medication
- Secrecy and stigma regarding diagnosis

- Side effects
- Difficulty swallowing medicines
- Inadequate understanding of the medication regimen
- Competing priorities of day-to-day activities for work, child care, access to food, etc.
- Forgetfulness/lack of support to remember medicines
- Travel/ being away from home

How can medication adherence be supported?

Experience with HIV care has highlighted that adherence support is essential. Successful interventions include:

- Patient education and practical counseling:
 - Personalizing education and advice to specific aspects of the patient’s lifestyle
 - Careful instruction about how to take medications (timing, food restrictions, drug interactions)
 - Tips about how to remember medications (daily cues, reminders, partners)
 - Information about toxicity—which adverse effects should patients look out for and what should they do if they occur?
- Easy access to an uninterrupted supply of medication
 - Ensuring that patients understand where, when and how to obtain medications
 - Providing on-site pharmacies where possible
 - Avoiding “stock outs”
 - Helping patients plan for safeguarding medicines
- Streamlined regimens minimizing the number of pills and the number of doses/day
- Prefilled pill boxes, routinely checked by clinic staff
- Medication “reminders” linking to daily activities, watches, timers, beepers, alarm clocks
- Referrals to support groups
 - Access to a community of peers, who can assist medication adherence with practical and emotional support
- Medication partners/“buddies”/accompagneurs
 - Providing patients with a medication partner – a peer, friend, family member or outreach worker who learns about the medications along with the patient and who takes responsibility for assisting the patient. In some cases this medication “buddy”



might contract to observe the therapy, in others to provide reminders and/or assist with refills.

- Modified directly observed therapy
Observing some doses at home or in the clinic. Observing daily medication at the clinic can be cumbersome, but using a medication partner in the community to observe at least one dose a day has been quite successful in some settings.
- Addressing barriers to adherence
Healthcare providers can support adherence by identifying barriers and providing interventions that address them. Barriers to adherence should be discussed during the Family Care Coordination meetings, as should current or looming crises in the patient's life.

Adherence in children

Adherence to medications for children can be particularly difficult. Pediatric formulations are often poorly palatable and formulations are not always suited for administration to young children. Furthermore, many children are in the care of more than one caretaker, some of whom may not know the child's diagnosis. In this setting, administration of medication to children can be compromised. Assessing adherence can also be difficult. Often, the individual bringing the child to the clinic is not the individual responsible for administering medications. As children age, they are often given responsibility for taking their medications and they may not be able to accurately report upon their adherence.



Caregivers for children on therapy should be questioned about missed doses, problems administering medication, and potential side effects. If the child is old enough, it may be worthwhile to include them in the discussion about their medications as well as in the discussion about adherence. Adherence supports listed above are generally useful for children as well as adults, but may need to be modified for liquid formulations and to address the needs of the child receiving the medications as well as the adult administering the medications.

Other strategies to help support medication adherence in children:

- Prepare the family about bad tasting medications and how to mask their taste.
- Prepare the family for common side effects and what to do if they occur. Many families stop medicines when faced with unexpected side effects.

- Teach families about young children's need for ritual, consistency and supervision in medicine taking.

What is psychosocial support?

HIV/AIDS has profound effects on the physical, emotional, social and economic well-being of infected and affected individuals and families. Thus, addressing these dimensions of the lives of those infected and those of their families is an integral part of HIV care. Provision of comprehensive psychosocial care and support for persons living with HIV/AIDS must take into account a broad range of issues, such as the assessment and treatment of mental health problems related to HIV, management of stigma, maintenance of economic stability, and mobilization of community, social and spiritual supports.

Psychosocial interventions may consist of a range of activities, such as (but not limited to) individual, family, and group counseling, home-based counseling, family education groups, respite for parents and caregivers, developmentally-appropriate community and recreational activities for children, school or daycare placements for children, vocational counseling, linkages with permanency planning support services, or referral for legal advice.

Why is psychosocial support important?

When confronted with a chronic and serious illness like HIV/AIDS, fear of disability, dependency or death, stigma, social isolation, and lack of access to medical and educational resources can be great sources of suffering for some individuals. People with HIV/AIDS, like those with other chronic illnesses, frequently experience symptoms of depression and anxiety as they struggle to normalize their lives and often require coordination of numerous supports and services. In many regions, the AIDS pandemic has a multigenerational impact on families – on their ability to sustain themselves economically and on their emotional resources. Providers equipped to enable patients and families to express their concerns and to find solutions to the problems they pose are a critical resource. Lack of attention to psychosocial support systems, psychiatric symptoms, economic concerns, stigma and/or the need to plan for the future of dependents may lead to increased emotional distress, potentially detracting from clinical care and patient progress.



Who should perform psychosocial assessment?

The psychosocial assessment for families affected by HIV requires the evaluation of individual, household, and extended family strengths, resources, and needs. In order to meet these needs, an assessment of community-based spiritual/religious, social service, and legal resources should also be conducted.

Any trained provider may conduct the psychosocial assessment. In many settings the assessment may be multidisciplinary, with each type of clinician focusing on his or her area of expertise. Specific issues, such as psychiatric symptoms, may lend themselves to evaluation by trained clinicians. Others, such as economic issues, may trigger evaluation by other members of the care team. All providers should be familiar with the psychosocial issues associated with HIV disease and the local resources available to meet families' needs.

When should the need for psychosocial support be assessed?

A comprehensive assessment of psychosocial needs should be conducted during the initial visits. At each follow-up visit, a more focused assessment should be performed, guided by the areas of need identified at baseline. Since the psychosocial assessment is part of the comprehensive program of care, it is critical that the provider who conducts this assessment is fully aware of all aspects of the patient's treatment, including illness stage and readiness for or adherence to antiretroviral medication. Missed visits or new symptoms/problems should trigger reassessment, and all issues should be discussed and prioritized at the regular team meetings (see chapter 1).

How should psychosocial needs be assessed?

Providers and patients should develop a respectful relationship that will facilitate a collaborative alliance. The following guidelines will aid this process.¹

- Maintain a supportive approach and avoid being judgmental.
- Inquire about the patient's family/household situation, financial status, relationship status, and support systems.
- Assess the individual's understanding of HIV/AIDS transmission, treatment options, and illness stage. When working with couples and families, it will be necessary to work with both partners regarding their individual illness status as well as their concerns regarding infected and affected children.
- Evaluate how the patient is coping with the HIV/AIDS diagnosis. Note that the patient may experience grief reactions upon

¹ McDaniel JS, Chung JT, Brown L et al. Practice guidelines for the treatment of patients with HIV/AIDS. *Am J Psychiatry* 2000; 157:11.

receiving the diagnosis, and may already have experienced multiple losses due to HIV/AIDS.

- Explore cultural beliefs around HIV illness. In many settings, HIV/AIDS continues to be cloaked in mystery, and myths about the illness abound. The patient and family may have culturally specific ideas about how HIV/AIDS is contracted, the meaning of infection, or how HIV/AIDS is “cured.” The provider should work to elicit these beliefs and to examine them with the patient. If the patient espouses beliefs that are potentially harmful, these should be explored non-judgmentally and corrected.
- Explore other services utilized by the patient (e.g. traditional healers, mental health providers, and other supportive services) and the role these practitioners may play in the care process.
- Ensure that the patient understands the treatment plan, whom to contact with questions or problems, and what to do in the case of emergencies.

How should psychosocial welfare be supported?

Providers should work to maximize psychological function:

- Identify local social and community-based services. Develop a network of social service providers.
- Assess the patient’s social supports including family, close friends, community, faith-based (church, spiritual, and/or other religious resources), and social service agencies.
- Evaluate readiness and desire to disclose HIV status to appropriate members of support network.
- Make referrals to support groups (if none exist, one should be established).
- Diagnosis of psychiatric disorders such as depression and anxiety is important, and management will be highly dependent on local treatment resources. Where possible, providers should become familiar with the diagnosis and treatment of mood disorders. Referrals may be made to on-site mental health services, off-site services such as those at a nearby hospital or community program, and/or to other local services as appropriate.
 - Review psychiatric history
 - Screen for depression, being sensitive to the fact that some patients will present somatic complaints that may be indicative of depressed mood. Inquiring about hopefulness for the future and ability to take pleasure in activities can assist to clarify the clinical picture.
 - Screen for anxiety
 - Screen for suicidal ideation
 - Screen for substance abuse

- When there is a history of psychiatric intervention, gather information on providers, services, and support systems utilized.

Providers should explore the role of religion/spirituality:

- Inquire about spiritual beliefs and religious faith.
- Assess the use of traditional/ complimentary health systems and explore this as a possible source of support.

Providers should explore concerns regarding stigma and isolation. HIV/AIDS continues to be highly stigmatized, and fear of rejection can influence a person's decision to disclose her status, seek treatment, or engage in strategies for risk reduction. Discrimination against people with HIV/AIDS can compromise job security as well as safety and security in the home.

- Allow patients to enumerate fears as well as to describe any actual experiences of discrimination.
- Enable patients to identify trusted sources of support in the family or community.
- Assist in provision of emotional and social resources for those who have experienced discrimination.
- Providers should also explore their own ideas and fears that may contribute to the patient's experience of stigma. Some providers will be infected with HIV themselves, and may share the concerns of their patients. Others may hold beliefs and attitudes of the larger society that lead to subtle rejection of patients. Continuing education regarding HIV/AIDS and purposeful examination of stigmatizing attitudes can assist providers to develop and strengthen a compassionate approach to patient care.

Providers should assess disclosure status. The issues will vary depending upon whether patients are disclosing to partners, children, or other family and friends:

- Ask patients if they have disclosed their diagnosis to anyone. Learn about the reactions from their support system.
- Determine concerns about disclosure
 - To partner
 - To children
 - To family and friends
- Assess readiness to disclose and to whom.
- Develop a plan for disclosure that is appropriate to the patient's level of readiness.
- Assess social supports and needs. Assess any changes in social activity level since diagnosis, concerns about stigma.
- Refer to support groups as appropriate.

Providers should be prepared to manage issues of disability, death and dying:

- Assess permanency plans for children. Explore family and community norms regarding placement of orphaned children. Assist with the development of custody plans for children as needed.
- Provide counseling, support, and assistance with emotional distress.
- If available, provide referrals for home care and palliative care as needed.

Where appropriate, providers should give advice to the patient's family regarding sources of care and support

- With the patient's consent, invite the family to collaborate in care.
- Refer family members to support groups as needed.

What is nutritional assessment?

Malnutrition is common in HIV/AIDS, occurring as both protein-energy malnutrition (PEM) and micronutrient malnutrition. Protein-energy malnutrition is usually measured in terms of body size, such as weight, height, body fat, and muscle mass. Micronutrient malnutrition - such as iron, vitamin A, and iodine deficiencies - is more difficult to measure. It has been called “hidden hunger” because it is difficult to recognize until it becomes severe. While malnutrition is easy to spot in some patients, in others it is more subtle. Nutritional assessment, a systematic evaluation of current nutritional status and adequacy of diet, is an important component of care.

Why is nutritional assessment important?



HIV and malnutrition create a vicious cycle in which HIV compromises a patient’s nutritional status and malnutrition exacerbates the effects of HIV. HIV and opportunistic infections may impair absorption and increase catabolism. Experts suggest that HIV-infected adults may be in a hypermetabolic state, requiring more calories and considerably more protein than those without HIV. The nutritional requirements of HIV-infected women who are pregnant or nursing are even higher, as are those of HIV-infected children. Identifying and treating malnutrition can help to strengthen the immune system, prevent or reverse weight loss, and delay HIV progression, dramatically improving health and well being. Assessment can identify specific treatable symptoms that contribute to malnutrition, such as nausea, difficulty swallowing, or diarrhea. Nutritional counseling can also prevent food-borne illness by promoting hygiene and food and water safety.

Who should perform nutritional assessment?

Ideally, a trained clinical nutritionist or dietician performs nutritional assessment. In the absence of specialized nutrition personnel, other clinical and supportive staff can be trained to perform this type of assessment. Simple questions such as “have you lost weight?” “tell me what you ate yesterday” or “do you get hungry?” can elicit extremely useful information. Each member of the MTCT-Plus team can contribute to this assessment. Clinical providers can screen for acute illness, odynophagia, anorexia and other barriers to nutrition. Social

workers can ask if food is available in the home. Outreach workers can assess access to food and cooking supplies on home visits. The information should be shared at the Family Care Coordination meetings (see chapter 1).

How should nutrition be assessed?

Subjective nutritional assessment is performed by interviewing the patient in a supportive and private environment. Access to food should be carefully explored, as should the presence of symptoms that impede intake or absorption (nausea, vomiting, diarrhea, constipation, lack of appetite, difficulty chewing or swallowing, abdominal pain and/or early satiety). Patients should also be asked about food and water safety and hygiene.

Objective information includes weight, and height, which should be recorded at every clinical visit. Body mass index, calculated from height and weight, is also a useful measurement (see Appendix 4-1 for non-pregnant adult BMI tables). Infants' head circumference and weight and height should be followed carefully, as should children's weight, height and BMI; these should be routinely plotted on growth curves. Children's growth curves from the U.S. Centers for Disease Control and Prevention are included as Appendix 4-2; these may not be appropriate for all settings. Basic laboratory tests which can be used to confirm suspicions of malnutrition include albumin, cholesterol, glucose, electrolytes, and hemoglobin. Studies of renal and hepatic function may also be of assistance.

At all stages of nutritional assessment, ongoing communication with the care team is essential. If available, the nutritionist/dietician should attend team meetings and work closely with providers of supportive services.

How often should nutritional assessment be conducted?

All HIV-infected patients should receive a baseline nutritional assessment and specific nutritional counseling. Weight should be measured at each clinical visit, and weight loss (or, in the case of children, failure to gain weight) should be regarded as a "red flag" that triggers in-depth nutritional assessment. Even patients whose weight is stable may benefit from routine, periodic re-assessment.

How can nutrition be supported?

Nutritional education and counseling is an integral part of the care and support of HIV-infected individuals and should be provided for every patient in MTCT-Plus. Counseling may be supplemented by flyers with written and pictorial information. Sometimes peer support works well if a particularly food/cooking adept patient is willing to share ideas.

Demonstrations in community settings and/or the patient's house are also an excellent way to communicate information about food. For example, if a certain food such as a roasted soybean is identified as available and appropriate, a meal preparation demonstration could show how the soybean can be ground into foods being prepared. Patients should learn the importance of adequate nutrition, the basics of food and water safety, hygiene interventions that reduce the risk of infections (particularly infectious diarrhea), and how to manage common symptoms such as diarrhea and nausea. Specific examples of foods that help bulk the stool or resolve diarrhea can be given. Physical activity and weight-bearing exercise, where appropriate and when energy requirements can be met, can help increase energy, stimulate appetite, and preserve or build lean body mass.



Patients should also be familiar with any *food restrictions* imposed by their medications – such as the need to take didanosine (ddI, Videx) on an empty stomach. While the first-line agents used in MTCT-Plus do not have stringent dietary rules, patients taking some second-line medications will need to follow specific guidelines with regard to the timing of medicines and food. More details are available in Table 4-1 and in Chapter 10.

Table 4-1: Drug-food interactions

ARV	Dietary advice
Zidovudine (ZDV)	No food restrictions
Lamivudine (3TC)	No food restrictions
Didanosine (ddI)	Take on an empty stomach at least ½ hour before or 2 hours after food.
Stavudine (d4T)	No food restrictions
Abacavir (ABC)	No food restrictions
Nevirapine (NVP)	No food restrictions
Efavirenz (EFV)	Do not take with high-fat meals
Nelfinavir (NLF)	Take with food (meal or snack)

Nutritional supplementation can be as simple as multivitamins, which will be provided to all patients in MTCT-Plus. However, additional support in the form of food assistance may also be required and linkages to community-based organizations that provide food, give away vegetable/fruit seeds, teach gardening skills or income-generating projects will be very important. Ensuring appropriate infant feeding is an essential component of care, and each pMTCT program within MTCT-Plus has preexisting guidelines regarding infant feeding.

Appendix 4-1:

Calculated Body Mass Index (abbreviated table): Adults and adolescents

Height		Weight (round to the closest number in the table)																
		Kg	35	37.5	40	42.5	45	47.5	50	51	52	53	54	55	56	57	58	59
Cm	In	Lb	77	82.5	88	93.5	99	104.5	110	112.2	114.4	116.6	118.8	121	123.2	125.4	127.6	129.8
150	59		15.6	16.7	17.8	18.9	20	21.1	22.2	22.7	23.1	23.6	24	24.4	24.9	25.3	25.8	26.2
152	59.8		15.1	16.2	17.3	18.4	19.5	20.6	21.6	22.1	22.5	22.9	23.4	23.8	24.2	24.7	25.1	25.5
154	60.6		14.8	15.8	16.9	17.9	19	20	21.1	21.5	21.9	22.3	22.8	23.2	23.6	24	24.5	24.9
156	61.4		14.4	15.4	16.4	17.5	18.5	19.5	20.5	21	21.4	21.8	22.2	22.6	23	23.4	23.8	24.2
158	62.2		14	15	16	17	18	19	20	20.4	20.8	21.2	21.6	22	22.4	22.8	23.2	23.6
160	63		13.7	14.6	15.6	16.6	17.6	18.6	19.5	19.9	20.3	20.7	21.1	21.5	21.9	22.3	22.7	23
162	63.8		13.3	14.3	15.2	16.2	17.1	18.1	19.1	19.4	19.8	20.2	20.6	21	21.3	21.7	22.1	22.5
164	64.6		13	13.9	14.9	15.8	16.7	17.7	18.6	19	19.3	19.7	20.1	20.4	20.8	21.2	21.6	21.9
166	65.4		12.7	13.6	14.5	15.4	16.3	17.2	18.1	18.5	18.9	19.2	19.6	20	20.3	20.7	21	21.4
168	66.1		12.4	13.3	14.2	15.1	15.9	16.8	17.7	18.1	18.4	18.8	19.1	19.5	19.8	20.2	20.5	20.9
170	66.9		12.1	13	13.8	14.7	15.6	16.4	17.3	17.6	18	18.3	18.7	19	19.4	19.7	20.1	20.4
172	67.7		11.8	12.7	13.5	14.4	15.2	16.1	16.9	17.2	17.6	17.9	18.3	18.6	18.9	19.3	19.6	19.9
174	68.5		11.6	12.4	13.2	14	14.9	15.7	16.5	16.8	17.2	17.5	17.8	18.2	18.5	18.8	19.2	19.5
176	69.3		11.3	12.1	12.9	13.7	14.5	15.3	16.1	16.5	16.8	17.1	17.4	17.8	18.1	18.4	18.7	19
178	70.1		11	11.8	12.6	13.4	14.2	15	15.8	16.1	16.4	16.7	17	17.4	17.7	18	18.3	18.6
180	70.9		10.8	11.6	12.3	13.1	13.9	14.7	15.4	15.7	16	16.4	16.7	17	17.3	17.6	17.9	18.2
182	71.6		10.6	11.3	12.1	12.8	13.6	14.3	15.1	15.4	15.7	16	16.3	16.6	16.9	17.2	17.5	17.8
184	72.4		10.3	11.1	11.8	12.6	13.3	14	14.8	15.1	15.4	15.7	15.9	16.2	16.5	16.8	17.1	17.4
186	73.2		10.1	10.8	11.6	12.3	13	13.7	14.5	14.7	15	15.3	15.6	15.9	16.2	16.5	16.8	17.1
188	74		9.9	10.6	11.3	12	12.7	13.4	14.1	14.4	14.7	15	15.3	15.6	15.8	16.1	16.4	16.7
190	74.8		9.7	10.4	11.1	11.8	12.5	13.2	13.9	14.1	14.4	14.7	15	15.2	15.5	15.8	16.1	16.3

Calculated Body Mass Index (abbreviated table): Adults and adolescents page 2

Height		Weight (round to the closest number in the table)																
		Kg	60	61	62	63	64	65	66	67	68	69	70	72.5	75	77.5	80	82.5
Cm	In	Lb	132	134.2	136.4	138.6	140.8	143	145.2	147.4	149.6	151.8	154	159.5	165	170.5	176	181.5
150	59		26.7	27.1	27.6	28	28.4	28.9	29.3	29.8	30.2	30.7	31.1	32.2	33.3	34.4	35.6	36.7
152	59.8		26	26.4	26.8	27.3	27.7	28.1	28.6	29	29.4	29.9	30.3	31.4	32.5	33.5	34.6	35.7
154	60.6		25.3	25.7	26.1	26.6	27	27.4	27.8	28.3	28.7	29.1	29.5	30.6	31.6	32.7	33.7	34.8
156	61.4		24.7	25.1	25.5	25.9	26.3	26.7	27.1	27.5	27.9	28.4	28.8	29.8	30.8	31.8	32.9	33.9
158	62.2		24	24.4	24.8	25.2	25.6	26	26.4	26.8	27.2	27.6	28	29	30	31	32	33
160	63		23.4	23.8	24.2	24.6	25	25.4	25.8	26.2	26.6	27	27.3	28.3	29.3	30.3	31.2	32.2
162	63.8		22.9	23.2	23.6	24	24.4	24.8	25.1	25.5	25.9	26.3	26.7	27.6	28.6	29.5	30.5	31.4
164	64.6		22.3	22.7	23.1	23.4	23.8	24.2	24.5	24.9	25.3	25.7	26	27	27.9	28.8	29.7	30.7
166	65.4		21.8	22.1	22.5	22.9	23.2	23.6	24	24.3	24.7	25	25.4	26.3	27.2	28.1	29	29.9
168	66.1		21.3	21.6	22	22.3	22.7	23	23.4	23.7	24.1	24.4	24.8	25.7	26.6	27.5	28.3	29.2
170	66.9		20.8	21.1	21.5	21.8	22.1	22.5	22.8	23.2	23.5	23.9	24.2	25.1	26	26.8	27.7	28.5
172	67.7		20.3	20.6	21	21.3	21.6	22	22.3	22.6	23	23.3	23.7	24.5	25.4	26.2	27	27.9
174	68.5		19.8	20.1	20.5	20.8	21.1	21.5	21.8	22.1	22.5	22.8	23.1	23.9	24.8	25.6	26.4	27.2
176	69.3		19.4	19.7	20	20.3	20.7	21	21.3	21.6	22	22.3	22.6	23.4	24.2	25	25.8	26.6
178	70.1		18.9	19.3	19.6	19.9	20.2	20.5	20.8	21.1	21.5	21.8	22.1	22.9	23.7	24.5	25.2	26
180	70.9		18.5	18.8	19.1	19.4	19.8	20.1	20.4	20.7	21	21.3	21.6	22.4	23.1	23.9	24.7	25.5
182	71.6		18.1	18.4	18.7	19	19.3	19.6	19.9	20.2	20.5	20.8	21.1	21.9	22.6	23.4	24.2	24.9
184	72.4		17.7	18	18.3	18.6	18.9	19.2	19.5	19.8	20.1	20.4	20.7	21.4	22.2	22.9	23.6	24.4
186	73.2		17.3	17.6	17.9	18.2	18.5	18.8	19.1	19.4	19.7	19.9	20.2	21	21.7	22.4	23.1	23.8
188	74		17	17.3	17.5	17.8	18.1	18.4	18.7	19	19.2	19.5	19.8	20.5	21.2	21.9	22.6	23.3
190	74.8		16.6	16.9	17.2	17.5	17.7	18	18.3	18.6	18.8	19.1	19.4	20.1	20.8	21.5	22.2	22.9

Clinical Care of Adults:

The goal of MTCT-Plus is to promote health and prevent illness in patients with HIV/AIDS. The counseling and supportive services described in other chapters are essential components of care and are needed to ensure that patients are able to utilize available clinical services. This chapter will focus on clinical issues including the recommended schedule and types of assessments, clinical guidelines for the prophylaxis of opportunistic and other infections, and the provision of ARV therapy. As noted, these are intended to assist sites to provide essential elements of care, not to supplant the judgment and expertise of treating clinicians. Program sites should utilize their usual procedures for providing clinical care and for linkages to their local resources:

- *Management of acute illness:* Patterns of acute illness will vary from place to place, and sites will continue to follow local and national guidelines for diagnosis and management. Referral procedures should be explicit—when are patients referred to the local hospital? How is medical information transferred? How is follow-up arranged? How is detailed information about hospitalizations retrieved? For patients receiving preventive or ARV drugs, it will be important to distinguish between an intercurrent illness and an adverse effect to medication; careful and systematic follow-up and documentation will be required. Effective communication between MTCT-Plus providers and those responsible for inpatient care will be essential.
- *Linkages to local resources:* Resources for patient care and support will differ from site to site, influencing diagnostic, management, and referral protocols. One example is that of mental health services which, if available, will be an important resource for MTCT-Plus patients. A periodic inventory of local care services is strongly recommended.

Assessment

At enrollment, each MTCT-plus patient will undergo a comprehensive assessment, including clinical, laboratory, and psychosocial evaluation. Non-clinical assessments are described in other chapters of this manual, and include the socio-demographic information needed to complete the MTCT-Plus enrollment forms. The information gathered from the comprehensive baseline assessment will guide the patient's individual/family care plan (see chapter 1), which will be modified over time based on periodic reassessments.

Baseline Assessment Information gathered during the baseline assessment will dictate the frequency and intensity of follow-up, as well as the provision of specific medical and supportive services. Clinical and laboratory information, particularly medical history, physical examination, and CD4 count, will assist providers to place patients in one of three categories:

- *Asymptomatic, CD4 count > 500:* Care of these patients will focus on counseling, patient education and other supportive services for the individual and for her family. Multivitamins will be provided, INH prophylaxis assured (if indicated), and patients will return for periodic assessment. Adherence to care and retention in the program will be an important focus for these patients.
- *Asymptomatic, CD4 201-500:* In addition to the services above, these patients may receive cotrimoxazole prophylaxis at some sites. They will require more frequent return visits and reassessment.
- *Symptomatic and/or CD4 \leq 200:* In addition to the services and medications above, these patients are eligible for antiretroviral (ARV) therapy. They will be seen weekly while ARVs are initiated and monthly thereafter.

Clinical Monitoring All patients should return for routine clinical visits on a schedule determined by disease stage and outlined in Appendices 5-1 and 5-2. At each visit, a structured evaluation via symptom checklist (Appendix 5-5) and targeted physical examination will be performed. The symptoms include those associated with common complications associated with HIV disease (e.g. tuberculosis) and those that may indicate adverse reactions to medications that the patient is taking. Patients should be informed of early symptoms of illness and encouraged to seek care in the interval between scheduled visits if needed.

Laboratory Monitoring The frequency of laboratory monitoring will be determined by clinical stage (see Appendix 5-2). Additional testing will be performed at the discretion of the provider.

Prophylaxis

Cotrimoxazole:

Prophylaxis of *Pneumocystis carinii* pneumonia is strongly endorsed in resource-rich settings, where it has a demonstrated mortality benefit. Although PCP is not known to be a major cause of HIV-related illness in Africa, most country guidelines and those developed by WHO recommend its use. This is due in part to the suspicion that PCP may be under diagnosed in resource-constrained settings, and in part to the fact that

cotrimoxazole may have benefits other than the prevention of PCP. Based on studies conducted in Cote d'Ivoire, there has been considerable interest in the use of cotrimoxazole to prevent bacterial infection. WHO has provisionally adopted recommendations to use cotrimoxazole prophylaxis in all HIV-infected patients with CD4 < 500 (or total lymphocyte count < 1200) and several country guidelines also endorse this approach. Some experts question these recommendations, however, noting that there is insufficient evidence of benefit.

MTCT-Plus will support the provision of cotrimoxazole (or Dapsone in the case of allergy) to all patients with advanced disease, and will defer to local and national guidelines regarding the use of cotrimoxazole in patients with more than 200 CD4 cells, providing prophylaxis to these patients at the discretion of the site medical director.

Recommendation:

Cotrimoxazole DS tabs daily or thrice weekly (or Dapsone 100 mg daily for patients with cotrimoxazole intolerance) for all adult patients with:

- Symptomatic HIV disease (WHO stage 3 or 4)
 - Previously diagnosed PCP
- Asymptomatic HIV disease and CD4 \leq 200
- Asymptomatic patients with CD4 201-500 at the discretion of site medical director.

Isoniazid:

Tuberculosis is a leading cause of morbidity and death among HIV-infected patients, and WHO/UNAIDS guidelines² support treatment of latent TB infection (LTBI) for persons dually infected with HIV and *M. tuberculosis*. Treatment of latent TB infection should only be given after active tuberculosis has been excluded via symptom checklist and, if needed, sputum examination or radiologic testing.

Recommendation:

In most circumstances, local protocols will govern screening for and treatment of LTBI and site medical directors will make the final decisions in this regard. We recommend baseline and annual tuberculin skin testing (TST) using PPD (5 units) in HIV-infected patients to identify those eligible for isoniazid (INH) treatment of LTBI. In areas with high rates of latent TB infection or high TB prevalence, sites may choose to provide INH treatment of LTBI for all HIV-infected patients. INH should not be given to patients who have previously received INH prophylaxis, were previously treated for TB, have contraindications to INH, or are suspected of having active tuberculosis.

² WHO 1999. Preventive therapy against tuberculosis in people living with HIV. Weekly Epidemiological Report 1999;74:385-400.

- Baseline and annual tuberculin skin testing (unless previously treated for tuberculosis)
- Treatment of LTBI for the following:
 - If positive (≥ 5 mm), exclude active TB as per local and national guidelines, then:
 - INH 5 mg/kg/day (max 300 mg/day) plus pyridoxine 50 mg/day for 6 months
- Or: INH 5 mg/kg/day (max 300 mg/day) plus pyridoxine 50 mg/day for 6 months to all HIV-infected adults at the discretion of site medical director.

Table 5-1: Prophylaxis

Intervention	Why	For whom	Dose
Cotrimoxazole	PCP prophylaxis	Strongly recommended for: <ul style="list-style-type: none"> - Patients with CD4 ≤ 200 - Patients with symptomatic HIV disease (stage 3 or 4) 	One DS tab daily or One DS tab thrice weekly
	and Prevention of bacterial infection	May be provided for patients with CD4 201–500 at discretion of site medical director	
Dapsone	PCP prophylaxis	In the case of cotrimoxazole intolerance, recommended for: <ul style="list-style-type: none"> - Patients with CD4 ≤ 200 - Patients with symptomatic HIV disease (stage 3 or 4) 	100 mg daily
INH	Prevention of tuberculosis	Patients with positive (≥ 5 mm) TST <i>or</i> all HIV-infected adults in high-prevalence areas. Except those with: <ul style="list-style-type: none"> - Previous INH prophylaxis - Previous TB treatment - Contraindication to INH - Suspicion of active TB 	INH 5 mg/kg (max 300 mg) daily x 6 months <i>plus</i> Pyridoxine 50 mg daily x 6 months
Fluconazole	Prevention of cryptococcal meningitis	If indicated by country guidelines	
Insecticide treated bed nets	Prevention of malaria	As per country guidelines	
Intermittent malaria treatment		For pregnant patients as per country guidelines	

Malaria treatment:

Malaria/HIV coinfection is of particular concern in areas where both diseases are endemic. Preliminary studies suggest that HIV may heighten vulnerability to malaria, especially among pregnant women. While there are no MTCT-Plus-specific guidelines for the prevention or treatment of malaria, we note the multi-pronged approach endorsed by WHO and encourage sites to formalize site-specific guidelines.

Recommendation:

As per WHO guidelines,³ in high-endemic areas:

- Insecticide-treated bed nets
- Intermittent treatment during pregnancy

Antiretroviral Therapy

Basic principles of antiretroviral use

The introduction of highly active antiretroviral therapy (HAART) has transformed the HIV/AIDS epidemic. In every setting in which HAART has been used, death rates have dropped, as have hospitalizations and the incidence of opportunistic infections. Despite their immense benefit to patients with advanced disease however, the medications are not without risk, including drug toxicity and viral resistance. Years of experience with HAART have taught providers the central role of informed patient participation, the need for meticulous medication adherence, the complexity of drug interactions, and the importance of regular monitoring.

- **Patient readiness:** Medical guidelines determine which patients are eligible for ARV therapy. In order for treatment to be successful however, patients must also be ready to take medications every day for the rest of their lives. In some cases, this requires little preparation. In others, a significant amount of patient support is needed before ARV therapy can be prescribed. There is no substitute for patient participation in this type of decision making, and patient education and adherence programs should be part of any HIV/AIDS care initiative.
- **Minimizing viral resistance:** Providers can play an important role in delaying the occurrence of HIV resistance by assisting patients to achieve adherence (see chapter 2) and through good prescribing practices. These include:
 - Never prescribe ARV medication in the absence of adherence counseling and support.
 - Work with patients to minimize barriers to medication adherence.
 - Pay meticulous attention to other medications and treatments and their potential to interact with ARVs.
 - Never prescribe monotherapy or dual therapy for treatment of chronic HIV infection (these may be used for pMTCT or for post-exposure prophylaxis).
 - Never add a single drug to a failing regimen.
 - If ARV medications are to be discontinued, stop the entire regimen.

³ WHO Expert Committee on Malaria, Twentieth Report. Technical report series, No. 872. Geneva, Switzerland, 2000.

- **Drug-drug interactions:** ARV agents, particularly, protease inhibitors have multiple interactions with other medications and should not be prescribed without a careful review of each patient's regimen, including herbal and traditional agents. (See chapter 10).
- **Drug-food interactions:** While the first-line agents used in MTCT-Plus do not have stringent dietary rules, patients taking some second-line medications will need to follow specific guidelines with regard to the timing of medicines and food. (See Appendix 5-4).
- **Special considerations in patients with tuberculosis:**

At most MTCT-Plus sites, the local TB program will treat active tuberculosis as per local and national protocols. Communication between providers of anti-TB therapy and providers of HIV care is critical, both to avoid drug-drug interactions that may threaten successful therapy, and to heighten awareness of the potential for immune reconstitution syndromes

 - Drug-drug interactions: As noted above, protease inhibitors and the non-nucleoside reverse transcriptase inhibitor nevirapine interact with rifampin, and co-administration of these drugs is contraindicated. One alternative is to change the ARV regimen to one that avoids PIs and nevirapine, such as a triple-nucleoside or efavirenz-containing combination. Another choice is to use non-rifamycin-based TB therapy, or dose-adjusted rifabutin. We recommend the establishment of specific treatment protocols for co-infected patients, as well as formal linkages to providers of TB treatment. In circumstances where an ARV regimen compatible with antituberculous therapy cannot be provided, ARVs should be initiated once antituberculous therapy has been completed.
 - Immune reconstitution: With vigorous immune reconstitution due to ARV therapy, some HIV-infected patients may develop HIV-related complications in the first few months after initiation of ARVs. Thus, patients need to be followed carefully after ARVs are started, both to ensure adherence and to determine the occurrence of adverse reactions as well as these early complications.

Patients with TB who are receiving ARVs may experience a transient, paradoxical worsening of TB symptoms in this context. These reactions are difficult to differentiate from those that might be associated with TB symptoms or TB treatment failure. Thus, it is prudent to carefully evaluate the patients via clinical reassessment and repeated sputum studies. In most cases, supportive therapy, such as nonsteroidal anti-inflammatory agents, is sufficient, although short-course steroids are occasionally indicated. Providers

should be familiar with this “immune reconstitution syndrome,” and patients should be counseled to report early symptoms.

- ***Special considerations for pregnant patients taking ARVs:***

Several medications in the MTCT-Plus formulary are known teratogens, most notably efavirenz (EFV, Sustiva), which should never be prescribed to a pregnant woman. The combination of didanosine (ddl, Videx) and stavudine (d4t, Zerit) is not teratogenic but should be used only when absolutely necessary in pregnant women due to the increased risk of lactic acidosis—and then only with additional counseling and monitoring. When prescribing these medications to patients who may *become* pregnant, meticulous attention to counseling and documentation is required; at a minimum, women should be asked if they might be pregnant and if they are using contraception at every clinical visit. WHO guidelines note that EFV should not be used in women for whom effective contraception cannot be assured. Clinicians who choose to prescribe efavirenz to women of child-bearing age are strongly encouraged to prescribe injectable contraceptives as well as condoms, to regularly ask about possible pregnancy, and to consider routine pregnancy testing (as teratogenic effects occur during the first trimester before many patients know that they are pregnant).

When to initiate ARVs

As above, patient education and adherence counseling are essential components of ARV therapy. ARV medications should never be prescribed to patients who have not made the informed decision to take them consistently and correctly or in settings where ongoing drug supply is not assured; irregular use of ARVs carries more risk than benefit.

Following WHO guidelines, MTCT-Plus will provide ARVs for adult patients with:

- WHO stage IV HIV disease (clinical AIDS) irrespective of CD4 cell count
- WHO stage II or III HIV disease and CD4 of 350 or less
- WHO stage I – IV and CD4 of 200 or less

Initial ARV regimens

The ARV regimens selected by MTCT-Plus are all highly active and all have been shown to be effective in multiple studies. The program suggests the first-line regimens and alternatives listed below, all of which are consistent with WHO guidelines. We prioritize the use of zidovudine/lamivudine and nevirapine, a highly active regimen with a low pill count, tolerable side effect profile, and lack of evidence for teratogenicity. In special circumstances and based on discussions between site director and Secretariat staff, alternate regimens may be

selected. Specific information about each drug can be found in Chapter 10.

Recommended initial regimen: zidovudine/lamivudine + nevirapine

Zidovudine (ZDV, Retrovir)/lamivudine (3TC, Epivir) (Combivir) + nevirapine (NVP, Viramune)

Alternate regimens:

Lamivudine + stavudine + nevirapine

Lamivudine (3TC, Epivir) + stavudine (d4T, Zerit) + nevirapine (NVP, Viramune)

Zidovudine/lamivudine + abacavir

Zidovudine (ZDV, Retrovir)/lamivudine (3TC, Epivir)/abacavir (ABC, Ziagen) (Trizivir)

Zidovudine/lamivudine + nelfinavir

Zidovudine (ZDV, Retrovir)/lamivudine (3TC, Epivir) (Combivir) + nelfinavir (NLF, Viracept)

Detailed algorithms for ARV initiation can be found in Appendix 5-3. In general, providers should ask themselves the following questions:

- **Does the patient have a medical indication for antiretroviral therapy?**
As above, this includes WHO stage IV disease (irrespective of CD4 count), WHO stage II or II disease and $CD4 \leq 350$, or WHO stage I and $CD4 \leq 200$.
- **Is there a medical contraindication to the planned first-line regimen?**
The next step after identifying a patient who is eligible for antiretroviral therapy is to exclude medical contraindications to the specific first-line regimen selected by the site medical director. These contraindications are defined in table 5-2. In general, severe neutropenia, anemia, and/or thrombocytopenia will preclude the use of zidovudine. Severe renal and hepatic insufficiency may preclude the use of antiretroviral agents altogether, although diagnostic evaluation may reveal a reversible etiology and should be conducted according to local guidelines. Prior use of antiretroviral therapy (other than for pMTCT) or intolerance to ARVs may require expert consultation, as will current use of anti-TB medication.
- **Is the patient pregnant?**
As noted, the use of efavirenz (EFV) is absolutely contraindicated during pregnancy. The combination of didanosine (ddl) and stavudine (D4T) is discouraged. There are minimal data regarding the use of abacavir (ABC) during pregnancy.
- **Is there a non-medical contraindication to antiretroviral use?**
Not every patient with a medical indication for antiretroviral therapy is ready to begin treatment immediately. One purpose of multidisciplinary,

psychosocial, and adherence assessments is to exclude “non-medical” contraindications to ARV use, and to confirm that a patient is prepared and empowered to take ARVs consistently and correctly. While many patients will be ready to begin treatment, identifying modifiable barriers to adherence such as ongoing substance abuse (e.g. alcoholism), severe psychiatric illness, or an unstable social situation, will enable providers to intervene for others, deferring ARVs until the barrier is addressed.

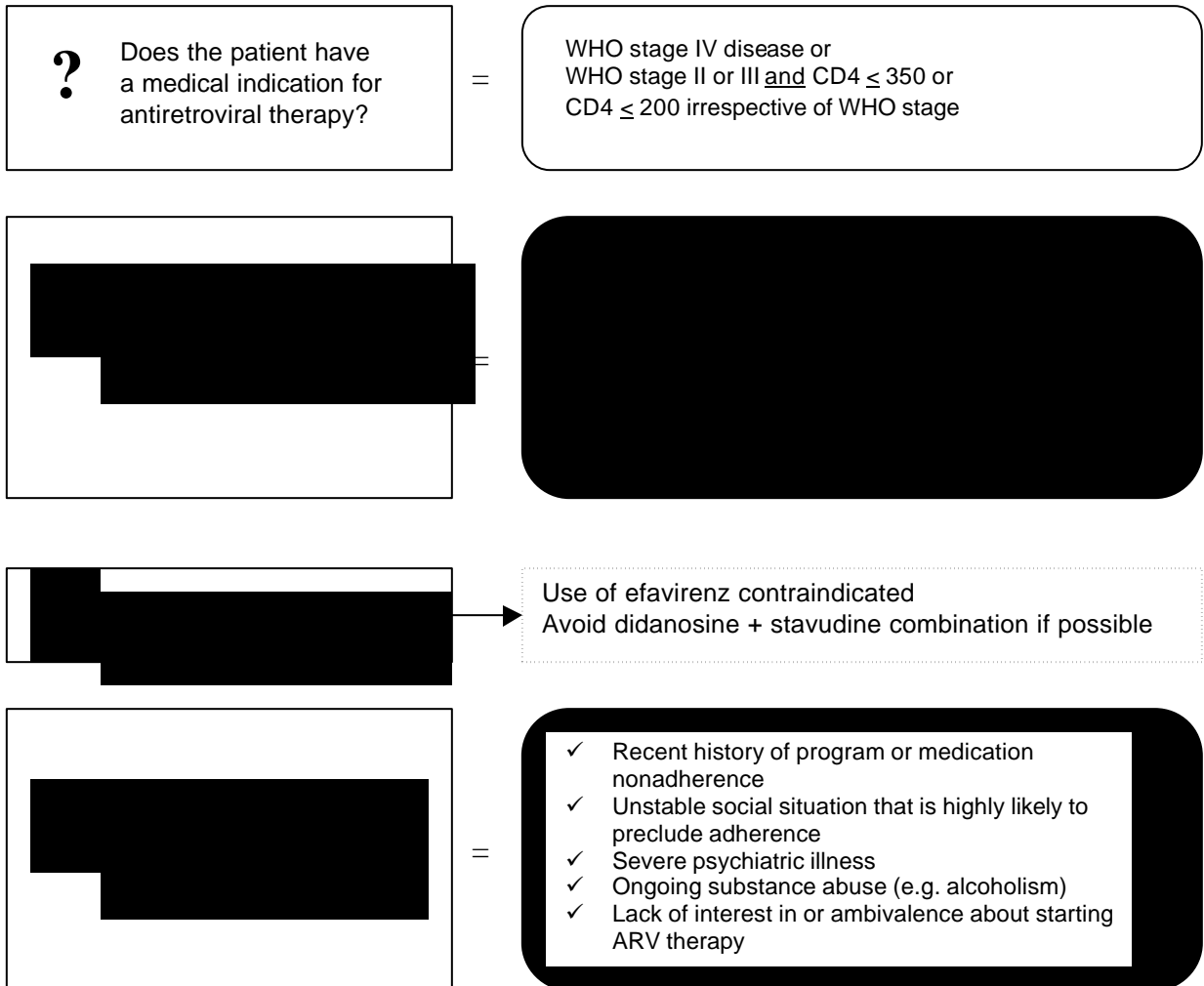


Table 5-2: Medical contraindications to initiation of first-line ARV regimen

Contraindication	Definition	Comments	Recommendation
Severe Anemia	Hb \leq 6.9 g/dL	Contraindication to use of zidovudine	Use alternate first-line regimen: Lamivudine/stavudine/nevirapine
Severe thrombocytopenia	platelets \leq 49,999 mm ³	Contraindication to use of zidovudine	Use alternate first-line regimen: Lamivudine/stavudine/nevirapine
Severe neutropenia	ANC \leq 749 mm ³	Contraindication to use of zidovudine	Use alternate first-line regimen: Lamivudine/stavudine/nevirapine
Severe renal insufficiency	Creatinine > 3 times normal	Contraindication to ARV use	Patient not currently eligible for ARVs. Conduct diagnostic evaluation as per local guidelines and reassess for ARV eligibility if renal function improves
Severe hepatic insufficiency	LFTs > 5 times normal	Contraindication to ARV use	Patient not currently eligible for ARVs. Conduct diagnostic evaluation as per local guidelines and reassess for ARV eligibility if hepatic function improves.
History of prior ARV intolerance	If intolerant of zidovudine, use lamivudine + stavudine + nevirapine. If intolerant of nevirapine, consider zidovudine + lamivudine + efavirenz.* Other substitutions may require expert advice.		
History of prior ARV use (other than pMTCT)	Use of any ARV for more than four weeks	Potential for ARV resistance	Expert management required. Consult local expert or Secretariat for case-by-case advice.
Current use of anti-TB medications	Use of rifampin	Drug-drug interactions with nevirapine	See text. If CD4 count high, consider deferring ARV use until completion of TB therapy. If not, consider use of alternate first-line regimen, e.g. zidovudine/lamivudine/efavirenz.*

*N.B. efavirenz is a potent teratogen and should not be used during pregnancy or if access to effective contraception cannot be assured.

Table 5-3: Drug-specific dosing for Adults and Adolescents

Drug class/drug	Dose
Nucleoside RTIs	
Zidovudine (ZDV)	300 mg twice daily
Stavudine (d4T)	40 mg twice daily (30 mg twice daily if <60 kg)
Lamivudine (3TC)	150 mg twice daily
Didanosine (ddI)	400 mg once daily (250 mg once daily if <60 kg)
Abacavir (ABC)	300 mg twice daily
Non-nucleoside RTI	
Efavirenz (EFV)	600 mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily

Protease Inhibitors	
Nelfinavir (NLF)	1250 mg twice daily

How to monitor patients on ARVs

In addition to the clinical and laboratory monitoring performed for all participants in the MTCT-Plus program (see above), additional monitoring is required for those taking ARVs. Careful monitoring is an essential component of effective ARV use, permitting early detection of adverse effects, ongoing reinforcement of patient adherence, and periodic assessment of treatment efficacy. The type and frequency of monitoring will be somewhat dependent on local resources. The following are monitoring recommendations for patients receiving ARVs in the MTCT-Plus program; these represent *minimal* monitoring requirements and should be modified for individual patients at their clinicians' discretion.

- **ARV-specific clinical monitoring:**

As patients initiate ARV therapy, weekly visits are recommended for the first 8 weeks. An alternate scheme is to alternate bi-weekly clinical visits with bi-weekly home visits. These "initiation" visits should focus on adherence assessment and support, and on assessing adverse events or ARV toxicity via structured symptom checklist (appendix 5-5). Common early symptoms of toxicity depend on the ARV regimen used and may include rash, nausea, diarrhea, headache and fatigue; see chapter 10 for details. Several of these symptoms—headache and fatigue, for example—often resolve over time. In addition, some patients may develop symptoms early after initiation of ARV (e.g. cough, fever, prominent lymphadenopathy) which may indicate an underlying infectious process that has become evident due to a vigorous immunologic reconstitution. Appropriate management of these symptoms and conditions should be instituted as per usual site procedures.

After the initial 8-week initiation period, patients should be seen monthly for clinical monitoring. At each visit an interval medical history and symptom checklist should be reviewed. Women should be asked about contraceptive use and if they might be pregnant. A targeted physical exam should be performed; asymptomatic patients should have, at a minimum, measurement of temperature and weight and examination of the oropharynx, lungs, and abdomen. Adherence assessment and support should be a part of every visit and patients should be referred for psychosocial assessment and supportive services as indicated.

- **ARV-specific laboratory monitoring:**

At a minimum, baseline laboratory testing for patients initiating ARV therapy in MTCT-Plus should include measurement of renal function

(serum creatinine and blood urea nitrogen level) and liver function (serum alanine and/or aspartate aminotransferase level), a complete blood count, and CD4 enumeration.

- Baseline labs: CBC, renal function, liver function, CD4 counts
- Labs every 6 months: CD4 count
- Interval labs as indicated by symptoms and signs and at the discretion of the treating clinician

When to change ARVs

The first ARV regimen should be both potent and durable. If adherence is adequate, clinical and immunologic benefits should be long lasting. Changing ARV medications should be done with caution. Resistance and cross-resistance are important considerations, and ARV sequencing can have important therapeutic impact. In addition, premature changes risk exhausting future ARV options available to that patient. There are two settings in which ARVs should be changed. In the case of **toxicity**, a single drug substitution may be indicated (Table 5-4). In the case of **therapeutic failure**, the entire regimen should be changed (Table 5-7).

Changing ARVs due to toxicity:

ARV-associated adverse events may be detected by symptoms or by laboratory investigation. Some symptoms are mild and/or transient, while others require supportive therapy (such as antiemetics or antimotility agents) or more frequent clinical monitoring. Severe side effects may require interruption of HAART. When serious toxicity appears to be caused by a specific ARV, a single-drug substitution can be made. In some cases, however, the entire regimen will need to be changed. Tables 5-4 and 5-5 detail criteria for changing ARVs due to toxicity and table 5-6 indicates which drugs to substitute.

Zidovudine is generally well-tolerated, although headache, nausea, and fatigue can occur in up to five percent of patients. These symptoms are often transient, and ZDV should not be discontinued unless they are severe (see Table 5-5). Bone marrow suppression can also occur; anemia usually occurs within four to six weeks and neutropenia is often seen within the first six months. Anemia should, thus, be considered in patients who develop fatigue, shortness of breath or weakness while on zidovudine, although routine assessment of blood counts in asymptomatic patients is not required. Macrocytosis is almost universal and is not an indication to switch agents or to conduct further diagnostic evaluation. Less common toxicities include hepatitis, myopathy and lactic acidosis.

Lamivudine is an extremely well-tolerated agent with minimal toxicity.

The most common toxicity in adults receiving nevirapine is rash, which is more frequent in women than in men and which may develop in up to 20 percent of those taking the drug, often within two to eight weeks after initiation. Skin manifestations are generally mild to moderate, but five to seven percent discontinue therapy because of this side effect. Rash can be minimized by introducing drug at a reduced dose for the first 14 days and then increasing to the full dose; this “dose escalation” is the standard of care in MTCT-Plus. The usual prescription is for one 200-mg tablet once a day for 14 days, increasing to one 200-mg tablet twice a day if no side effects are seen. Once at full dose, nevirapine treatment should be continued for grade 1 and 2 toxicities, but discontinued for grade 3 or greater (or for rash and systemic symptoms).⁴

Nevirapine treatment can also result in hepatotoxicity, which, like rash, is most common in the first weeks to months after initiation. Fatal hepatic failure has been reported. Liver function will be monitored at the discretion of the treating clinician; patients whose baseline liver function tests are abnormal may benefit from periodic reassessment even if asymptomatic. If liver dysfunction is detected once nevirapine has been initiated, diagnostic assessment should follow local guidelines; nevirapine should be permanently discontinued if Grade 3 or greater toxicity develops (transaminases \geq 5 times upper limit of normal). Efavirenz has been successfully substituted when nevirapine has been associated with liver dysfunction, although this switch should be made with caution and in the context of careful clinical and laboratory monitoring.

Of note, nevirapine interacts with estrogen-containing oral contraceptives, markedly reducing their efficacy; alternate forms of contraception should be substituted. Other drug-drug interactions are outlined in chapter 10.

Abacavir hypersensitivity:

Fever	Cough
Rash	Shortness of breath/dyspnea on exertion
Headache	Diarrhea
Malaise	Abdominal pain
Fatigue	Myalgia
Nausea/vomiting	Arthralgia

While abacavir is usually well-tolerated, clinicians must be familiar with the hypersensitivity syndrome that is seen in three to five percent of patients taking the drug, usually within six weeks of initiation. Characterized by fever, generalized erythematous rash, headache, nausea, fatigue and multi-organ involvement, the syndrome requires immediate and

⁴ Grade 1 = erythema, pruritis. Grade 2 = diffuse maculopapular rash or dry desquamation. Grade 3 = vesiculation or moist desquamation or ulceration. Grade 4 = any one: mucous membrane involvement, suspected Stevens -Johnson (TEN), erythema multiforme, necrosis, or exfoliative dermatitis.

permanent discontinuation of abacavir. Symptoms are generally reversible once abacavir is stopped, but ongoing treatment or reintroduction can be fatal. There is no one diagnostic test for this hypersensitivity syndrome; if it is suspected based on patient symptoms, abacavir should be discontinued immediately and NEVER restarted.

The most common toxicity seen with nelfinavir is diarrhea or loose stools, seen in up to 30 percent of patients. While often mild, two percent of patients may need to discontinue therapy, and many more require antimotility agents; some clinicians routinely prescribe such agents for all patients initiating nelfinavir. Hyperglycemia, hyperlipidemia, and hepatitis can be seen with nelfinavir, as with all protease inhibitors.

Lactic acidosis can be seen with any of the non-nucleoside antiretroviral agents, although it may be more common in patients treated with stavudine (D4T). Symptomatic lactic acidosis is rare (less than 0.1 percent), but up to five percent of asymptomatic patients on NNRTIs may have elevated lactic acid levels. Although uncommon, the syndrome should be familiar to providers because of its potential severity. Symptoms include fatigue, abdominal pain, nausea/vomiting, and weight loss and laboratory investigation reveals elevated serum lactate with or without metabolic acidosis. An elevated anion gap, creatinine phosphokinase (CPK), transaminases, and lactate dehydrogenase may also be seen. The most important response is to stop the offending antiretroviral agent; lactic acidemia often resolves over a period of three to six months. Restarting ARVs will often require expert consultation, as the safety of reintroducing NNRTIs in this setting has not been firmly established.

Table 5-4: Laboratory indications to change ARVs due to toxicity

Parameter	Grade 3 toxicity
Hematology	
Hemoglobin	< 6.9 g/dL
Absolute neutrophil count	< 749 mm ³
Platelets	< 49,999 mm ³
Chemistries	
Sodium	≤ 122 meq/L or ≥ 159 meq/L
Potassium	≤ 2.4 meq/L or ≥ 6.6 meq/L
Bilirubin	≥ 2.5 x upper limits of normal
Creatinine	≥ 3 x upper limits of normal
Glucose	< 39 mg/dL or > 251 mg/dL (fasting in nondiabetics)
Liver function tests	
AST (SGOT)	≥ 5x upper limits of normal
ALT (SGPT)	≥ 5x upper limits of normal
Alkaline phosphatase	≥ 5x upper limits of normal
Pancreatic enzymes	

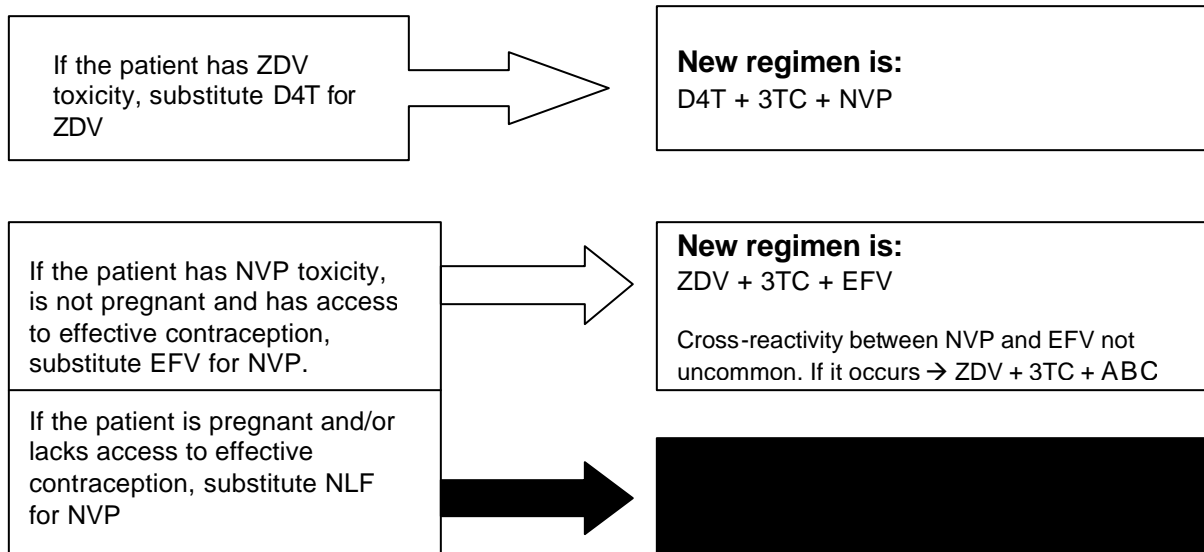
Amylase, lipase	> 2x upper limits of normal
-----------------	-----------------------------

Table 5-5: Clinical indications to change ARVs due to toxicity

Symptom	
Nausea	Severe discomfort or minimal intake for ≥ 3 days
Vomiting	Severe vomiting of all foods/fluids in 24 hours or orthostatic hypotension or IV therapy required
Diarrhea	Orthostatic hypotension or IV therapy required
Fever	Unexplained fever of ≥ 39.6 C (103 F)
Headache	Severe or requires narcotic therapy
Rash	Moist desquamation, ulceration, or mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis, or necrosis requiring surgery
Allergic reaction	Generalized urticaria, angioedema or anaphylaxis
Peripheral neuropathy	Severe discomfort, objective weakness, loss of 2-3 previously present reflexes or absence of 2-3 previously present sensory dermatomes
Fatigue	Normal activity reduced $> 50\%$

Table 5-6a: Recommended ARV changes for patients with early toxicity

If the initial regimen is zidovudine (**ZDV**) + lamivudine (**3TC**) + nevirapine (**NVP**):



If the initial regimen is lamivudine (3TC) + stavudine (D4T) + nevirapine (NVP):

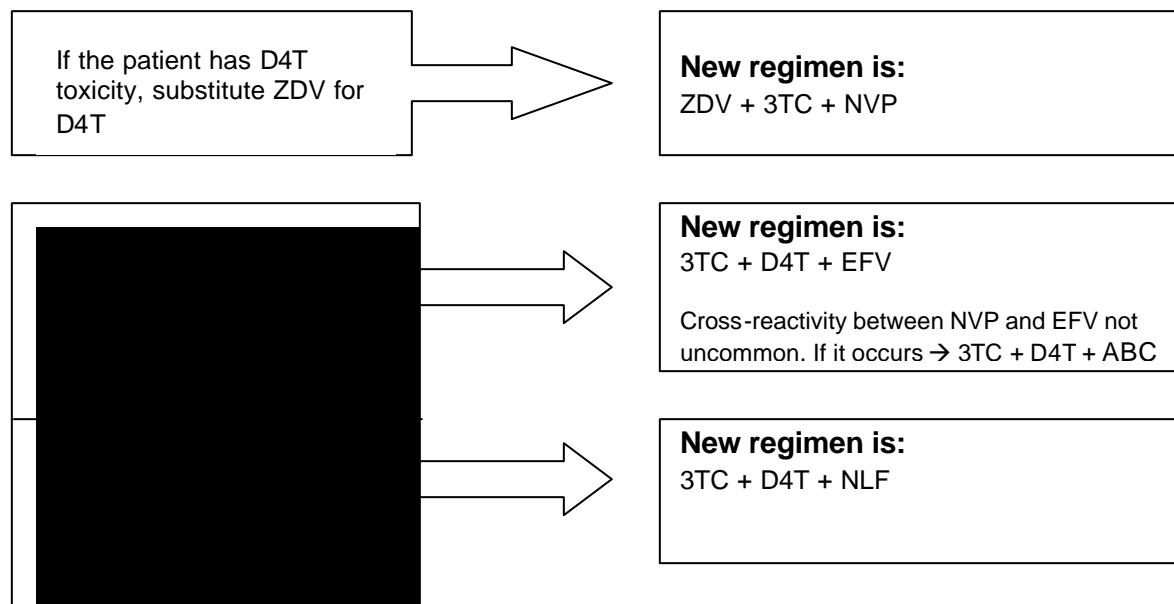


Table 5-6b: Single-drug substitutions for early toxicity (continued)

Primary regimen:	Single-drug substitution for toxicity
ZDV+3TC+NVP	
	<i>If ZDV toxicity: D4T + 3TC + NVP</i>
	<i>If NVP toxicity: ZDV + 3TC + EFV</i>
	<i>If subsequent EFV toxicity: ZDV+3TC+ABC</i>
Primary regimen:	Single-drug substitutions for toxicity
D4t+3TC+NVP	
	<i>If D4T toxicity: ZDV + 3TC + NVP</i>
	<i>If NVP toxicity: D4T + 3TC + EFV</i>
	<i>If subsequent EFV toxicity: D4T+3TC+ABC</i>

Changing ARVs due to therapeutic failure:

Successful ARV therapy leads to clinical and immunologic improvements with associated suppression of HIV replication. It is reasonable to expect a symptomatic patient to show clinical improvement within three months of initiating ARVs. Within six months, CD4 counts generally rise by at least 50 cells/mm³, although the magnitude of the rise in CD4+ cell count is dependent on the baseline value. Therapeutic failure is most commonly associated with nonadherence (see Adherence and Case Management

chapters), and it is critical to evaluate adherence with ARV prior to changing medications.

The entire ARV regimen should be changed if therapeutic failure is determined based on the following:

- Clinical failure to improve or worsening (change in WHO stage) after 3 months on ARVs
- CD4 failure to improve (by ~ 50 cells/mm³) or worsening at 6 months. If a patient has made marked clinical improvement, the initial ARV regimen should be continued despite a rise of < 50 CD4 cells/mm³
- A subsequent fall in CD4 count of 30 percent or more from the peak value or a return to or below the pre-therapy baseline.

Secondary ARV regimens:

As noted, ARV agents should not be changed casually. Secondary ARV regimens should only be used in the case of therapeutic failure, as defined above. The choice is based on expected resistance patterns that occur with specific agents and takes into account the need for replacement of a specific regimen with another with minimal potential for cross resistance. The following sequencing suggestions are based on settings where providers and patients lack ready access to viral load or viral resistance testing.

Table 5-7: Secondary ARV regimens

If the failing regimen is...	Then switch to ...	Unless...
ZDV + 3TC + NVP	ddl + D4T* + NLF	If patient has already been on D4T and switched due to toxicity, switch to: ddl + ABC + NLF
D4T + 3TC + NVP	ddl + ZDV + NLF	If patient has already been on ZDV and switched due to toxicity, switch to: ddl + ABC + NLF
ZDV + 3TC + EFV	ddl + D4T* + NLF	If patient has already been on D4T and switched due to toxicity, switch to: ddl + ABC + NLF
ZDV + 3TC + ABC	ddl + D4T* + NLF	
D4T + 3TC + ABC	ZDV + ddl + NLF	
* As noted in text, the combination of ddl and d4T during pregnancy should be used only when absolutely necessary and only in the context of additional laboratory and		

Adherence support

Adherence support is an essential component of ARV use, and expert guidelines emphasize that ARVs should not be prescribed without it. Suggestions for adherence assessment and support are detailed in chapter 2.

Care of Pregnant Patients

The majority of MTCT-Plus participants will be women who are, have been, or may become pregnant. In general, care will be dictated by community guidelines, and women should be encouraged to adhere to the local schedule of MCH visits. Additional considerations for pregnant HIV-infected women include:

Nutrition: Pregnant and breastfeeding women have increased calorie and protein requirements and careful attention to nutrition is even more important in pregnant women who are HIV-infected. Provision of multivitamins and referral to local supportive services (if needed) are strongly recommended.

Teratogenicity: As noted, efavirenz (EFV, Sustiva) is a known teratogen and must never be prescribed to pregnant patients; it should also be avoided in women who may become pregnant and who lack access to effective contraception. Nelfinavir, which can be used during pregnancy, may cause hyperglycemia and additional monitoring of blood glucose levels during pregnancy is prudent.

Other issues: The combination of didanosine (ddl, Videx) and stavudine (d4t, Zerit) should be used only when absolutely necessary in pregnant women due to the potential increased risk of lactic acidosis. If it is necessary to use this regimen during pregnancy, additional counseling and laboratory monitoring is warranted. There are minimal data regarding the use of abacavir (ABC) during pregnancy.

pMTCT: All sites have robust programs for the prevention of mother-to-child transmission and pregnant women should be offered care as per site guidelines. Some pregnant women, however, will meet guidelines for ARV therapy based on clinical or laboratory criteria and some women receiving ARV therapy will likely become pregnant while on treatment. Most clinicians recommend postponing the initiation of therapy until after the first trimester unless the clinical need for treatment is pressing. For women who become pregnant while on treatment, one can consider discontinuing

therapy during the first trimester. This will lower the risk of early teratogenicity, but may potentially increase the risk of mother-to-child transmission. These decisions should be made in collaboration with the obstetrics provider, the MTCT-Plus provider, and the woman and her family.

Women receiving ARV therapy during pregnancy are likely to have enhanced clinical and immune status as well as virologic control, and the risk of MTCT should be diminished. However, unless complete virologic control is achieved, the risk of perinatal transmission is likely to persist. Therefore, it may be necessary to use additional treatments during the intrapartum and neonatal period. This will be especially important for women who are receiving chronic therapy with nevirapine.

Malaria treatment. As above, malaria coinfection is likely to pose an increased risk to HIV-infected pregnant women. Preliminary data suggest that HIV infection may increase a pregnant patient's susceptibility to malaria, while malaria may accelerate HIV progression. In areas where both diseases are endemic, WHO guidelines recommend the use of insecticide-treated bed nets, intermittent preventive treatment (IPT) during pregnancy, and case management of malaria illness.

Care of Adolescents

It is expected that adolescents will enroll in the MTCT-Plus program. Young women are likely to be referred through pMTCT programs while others may be identified as HIV-infected household members. It is appropriate for pregnant and postpartum teens to receive care with other adults according to adult guidelines. For those identified as household members, age and developmental status may better determine the site of care. For young teens, dosing of medications should follow pediatric guidelines until Tanner V staging⁵ has been reached, at which time adult dosing guidelines can be used. Independent of setting, the care of teens often requires special expertise and a careful consideration of the complex needs of young people as they enter adulthood. An understanding of developmental needs, emerging sexuality, the role of the individual within the household, the presence of supportive relationships, and the special considerations of maintaining adherence will facilitate successful engagement of adolescents in a strong therapeutic relationship.

⁵ Tanner V staging: adult distribution of pubic hair, adult size penis/testes or mature breast (nipple elevated, areola contour continuous with breast).

Appendix 5-1:

WHO Staging System for HIV Infection and Disease in Adults and Adolescents

<p>Clinical Stage I:</p> <ol style="list-style-type: none">1. Asymptomatic2. Persistent generalized lymphadenopathy (PGL) <p><i>Performance scale 1: Asymptomatic, normal activity</i></p>
<p>Clinical Stage II:</p> <ol style="list-style-type: none">3. Weight loss, $\leq 10\%$ of body weight4. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)5. Herpes zoster within the last 5 years6. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis) <p><i>And/or Performance scale 2: Symptomatic, normal activity</i></p>
<p>Clinical Stage III:</p> <ol style="list-style-type: none">7. Weight loss $> 10\%$ of body weight8. Unexplained chronic diarrhea > 1 month9. Unexplained prolonged fever (intermittent or constant) > 1 month10. Oral candidiasis (thrush)11. Oral hairy leukoplakia12. Pulmonary tuberculosis within the past year13. Severe bacterial infection (i.e. pneumonia, pyomyositis) <p><i>And/or Performance scale 3: bed-ridden $< 50\%$ of the day during the past month</i></p>
<p>Clinical Stage IV:</p> <ol style="list-style-type: none">14. HIV wasting syndrome⁶15. Pneumocystis carinii pneumonia16. CNS toxoplasmosis17. Cryptosporidiosis with diarrhea > 1 month18. Extrapulmonary cryptococcosis19. Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes20. Herpes simplex virus (HSV) infection, mucocutaneous > 1 month, or visceral any duration21. Progressive multifocal leukoencephalopathy (PML)22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)23. Candidiasis of the esophagus, trachea, bronchi or lungs24. Disseminated atypical mycobacterium25. Non-typhoid Salmonella septicemia26. Extrapulmonary tuberculosis27. Lymphoma28. Kaposi's sarcoma (KS)29. HIV encephalopathy⁷ <p><i>And/or Performance scale 4: bed-ridden $> 50\%$ of the day during the last month</i></p>

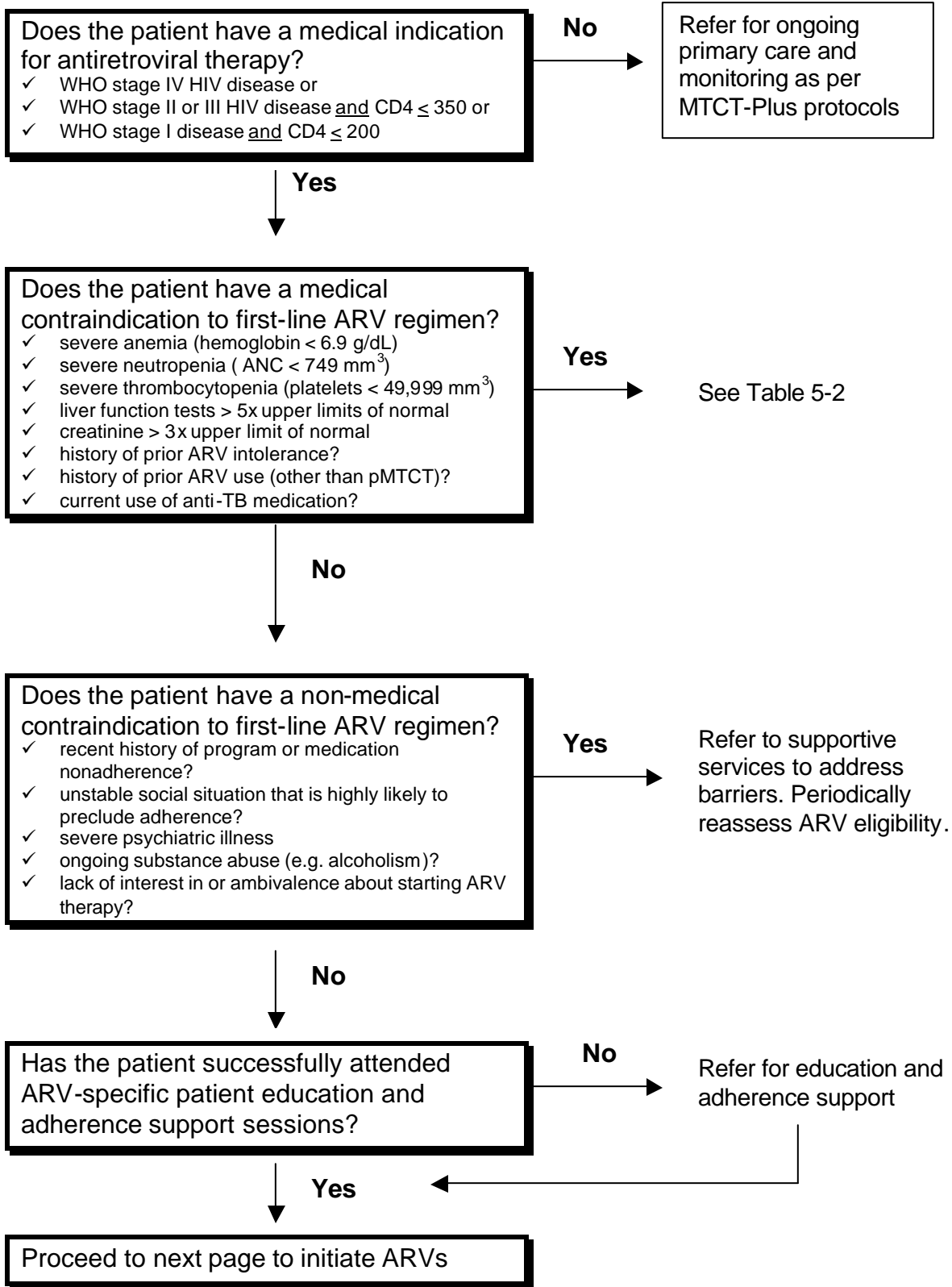
⁶ HIV wasting syndrome: weight loss of $> 10\%$ body weight, plus either unexplained chronic diarrhea (> 1 month), or chronic weakness and unexplained prolonged fever (> 1 month).

⁷ HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings)

Appendix 5-2: Follow-up visits for asymptomatic adults

Month	CD4 \leq 200	CD4 201–500	CD4 > 500
1	Medical history (acute illness) Post-partum check Supportive services as needed Cotrimoxazole prophylaxis If PPD+, ensure INH Other prophylaxis as needed Multivitamins	Medical history (acute illness) Post-partum check Supportive services as needed Cotrimoxazole (as per site) If PPD+, ensure INH Multivitamins	Medical history (acute illness) Post-partum check Supportive services as needed If PPD+, ensure INH Multivitamins
	Antiretroviral initiation visit: - Adherence counseling - Medication prescription - Weekly visits		
2	Continued weekly visits if on ARVs (8 weeks minimum) - Adherence assessment/support - Psychosocial assessment - Supportive services as needed - Symptom checklist	- History (acute illness) - Symptom checklist - Targeted physical exam - Psychosocial assessment - Supportive services - If PPD+, ensure INH - Cotrimoxazole (as per site) - Multivitamins	
3	Monthly visits for pts on ARVs - History (acute illness) - Symptom checklist - Targeted physical exam - Adherence assessment/support - Psychosocial assessment - Supportive services as needed - Cotrimoxazole - If PPD+ ensure INH - Multivitamins		3-month visit - History (acute illness) - Symptom checklist - Targeted physical exam - Psychosocial assessment - Supportive services - If PPD+, ensure INH - Multivitamins
4	Monthly visits for pts on ARVs - History (acute illness) - Symptom checklist - Targeted physical exam - Adherence assessment/support - Psychosocial assessment - Supportive services as needed - Cotrimoxazole - If PPD+ ensure INH - Multivitamins	4-month visit - History (acute illness) - Symptom checklist - Targeted physical exam - Psychosocial assessment - Supportive services - If ppd+, ensure INH - Cotrimoxazole (as per site) - Multivitamins	
5	Monthly visits for pts on ARVs - History (acute illness) - Symptom checklist - Targeted physical exam - Adherence assessment/support - Psychosocial assessment - Supportive services as needed - Cotrimoxazole - If PPD+ ensure INH - Multivitamins		
6	Monthly visits for pts on ARVs - Adherence assessment/support - Symptom checklist - Targeted physical examination - Psychosocial assessment - Supportive services as needed - Cotrimoxazole - If PPD+, ensure INH - Multivitamins - Repeat CD4 count	6-month visit - History (acute illness) - Symptom checklist - Targeted physical exam - Psychosocial assessment - Supportive services - If PPD+, ensure INH - Cotrimoxazole (as per site) - Multivitamins - Repeat CD4 count	6-month visit - History (acute illness) - Symptom checklist - Targeted physical exam - Psychosocial assessment - Supportive services - If PPD+, ensure INH - Multivitamins - Repeat CD4 count
then	MONTHLY VISITS (supportive services more frequently if needed)	VISITS EVERY 3 MONTHS (supportive services more frequently if needed)	VISITS EVERY 6 MONTHS (supportive services more frequently if needed)

Appendix 5-3: Adult Antiretroviral Initiation Flowchart



Adult patient with medical indications for first-line ARV therapy and without contraindications, who has successfully completed patient education and adherence support activities and is ready to initiate ARVs?

No → Return to previous page

Yes ↓

ARV initiation visit (week 0):

1. Review dosing instructions with patient
2. Dispense one-week supply of zidovudine/lamivudine (one tab twice a day) + nevirapine (one tab once a day) or lamivudine (one tab bid) + stavudine (one tab bid) + nevirapine (one tab once a day)
3. Arrange follow-up visit in one week
4. Assure that patient understands what to do in case of questions or problems

↓

ARV Initiation Week One visit:

1. Adherence assessment (structured questions)
2. Symptom checklist
3. Targeted physical exam if needed (e.g. if symptoms noted)

↓

Has the patient missed any doses of ARVs?

No

Yes

Determine cause of nonadherence. Does patient need further education? Does patient need referral for supportive services? If so, make appropriate referrals.

Adherence counseling, supportive services as needed.

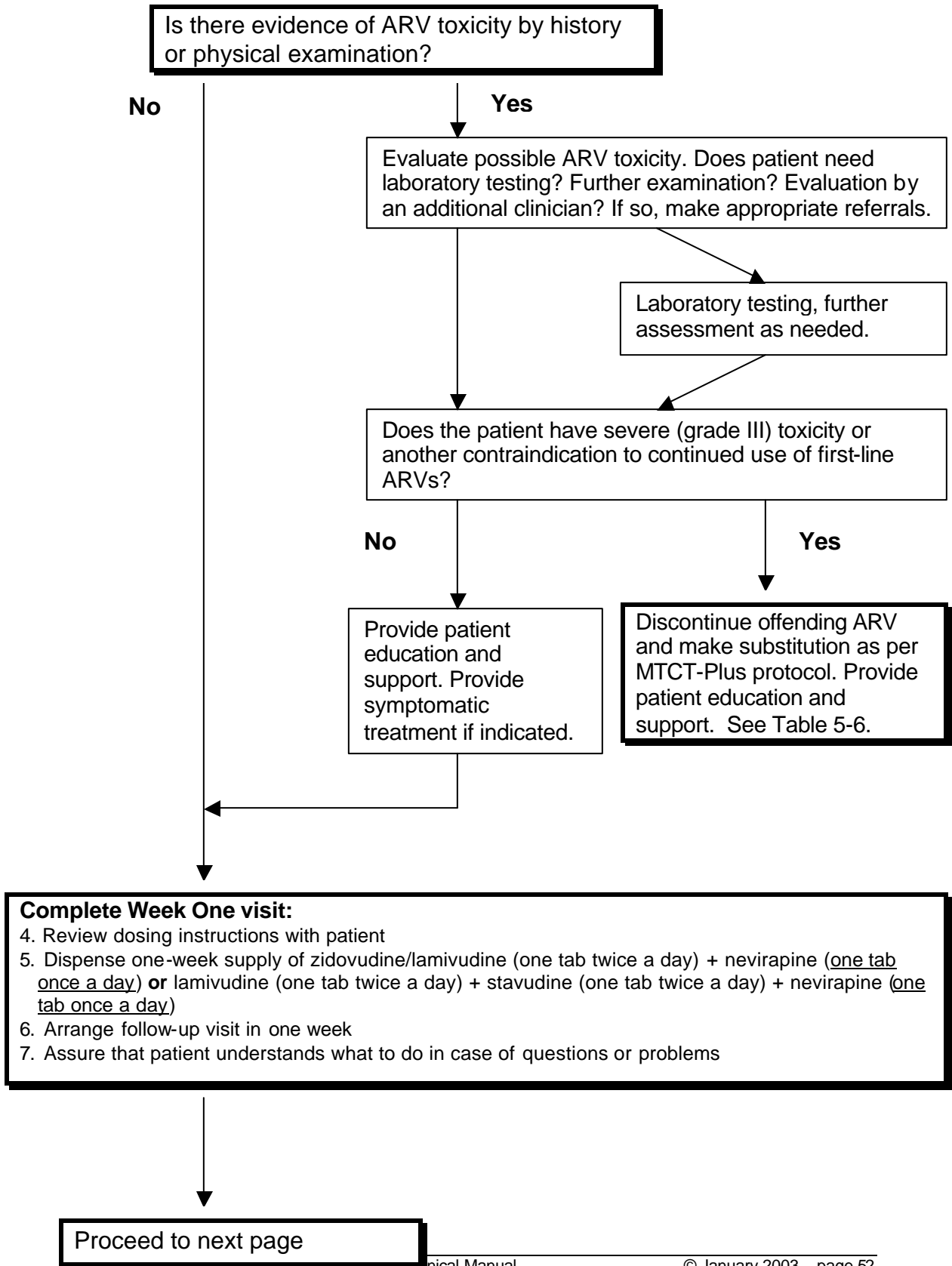
Does continued nonadherence seem likely?

No

Yes

Discontinue ARVs. Refer for appropriate supportive services. Periodically reassess ARV eligibility.

Proceed to next page



Complete Week One visit:

4. Review dosing instructions with patient
5. Dispense one-week supply of zidovudine/lamivudine (one tab twice a day) + nevirapine (one tab once a day) or lamivudine (one tab twice a day) + stavudine (one tab twice a day) + nevirapine (one tab once a day)
6. Arrange follow-up visit in one week
7. Assure that patient understands what to do in case of questions or problems

Proceed to next page

ARV Initiation Week Two visit:

1. Adherence assessment (structured questions)
2. Symptom checklist
3. Targeted physical examination if needed (e.g. if symptoms noted)

Evaluate and manage nonadherence and/or drug toxicity as outlined in “Week One,” above. If no problems with adherence or toxicity and no contraindications to continued ARV therapy:

4. **Escalate dose of nevirapine to one 200-mg tab twice a day.**
5. Review new dosing instructions with patient.
6. Dispense one-week supply of zidovudine/lamivudine (one tab twice a day) + nevirapine (one tab twice a day) **or** lamivudine (one tab twice a day) + stavudine (one tab twice a day) + nevirapine (one tab twice a day)
7. Arrange follow-up visit in one week
8. Assure that the patient understands what to do in case of questions or problems

ARV Initiation Week Three visit:

1. Adherence assessment (structured questions)
2. Symptom checklist
3. Targeted physical examination if needed (e.g. if symptoms noted)

Evaluate and manage nonadherence and/or drug toxicity as outlined in “Week One,” above. If no problems with adherence or toxicity and no contraindications to continued ARV therapy:

4. Review dosing instructions with patient.
5. Dispense one-week supply of zidovudine/lamivudine (one tab twice a day) + nevirapine (one tab twice a day) **or** lamivudine (one tab twice a day) + stavudine (one tab twice a day) + nevirapine (one tab twice a day)
6. Arrange follow-up in one week.
7. Assure that the patient understands what to do in case of questions or problems

ARV Initiation Week Four visit:

1. Adherence assessment (structured questions)
2. Symptom checklist
3. Targeted physical examination

Evaluate and manage nonadherence and/or drug toxicity as outlined in “Week One,” above. If no problems with adherence or toxicity and no contraindications to continued ARV therapy:

4. Review dosing instructions with patient.
5. Dispense two-week supply of zidovudine/lamivudine + nevirapine **or** lamivudine + stavudine + nevirapine
6. Arrange follow-up in one week.
7. Assure that the patient understands what to do in case of questions or problems

Appendix 5-4: Drug-food interactions

ARV	Dietary advice
Zidovudine (ZDV)	No food restrictions
Lamivudine (3TC)	No food restrictions
Didanosine (ddl)	Take on an empty stomach at least ½ hour before or 2 hours after food.
Stavudine (d4T)	No food restrictions
Abacavir (ABC)	No food restrictions
Nevirapine (NVP)	No food restrictions
Efavirenz (EFV)	Do not take with high-fat meals
Nelfinavir (NLF)	Take with food (meal or snack)

Appendix 5-5: Symptom checklist for routine adult follow-up visits

Since the last visit, has the patient experienced any of the following signs or symptoms?

<input checked="" type="checkbox"/> Cough	<input checked="" type="checkbox"/> Nausea and/or vomiting	<input checked="" type="checkbox"/> Rash
<input checked="" type="checkbox"/> Depression	<input checked="" type="checkbox"/> Night sweats	<input checked="" type="checkbox"/> Difficulty breathing
<input checked="" type="checkbox"/> Diarrhea	<input checked="" type="checkbox"/> Numbness or tingling in legs and/or feet	<input checked="" type="checkbox"/> Thrush
<input checked="" type="checkbox"/> Fatigue	<input checked="" type="checkbox"/> Pain – abdominal	<input checked="" type="checkbox"/> New visual problems
<input checked="" type="checkbox"/> Fever	<input checked="" type="checkbox"/> Pain – muscles	<input checked="" type="checkbox"/> Weakness
<input checked="" type="checkbox"/> Headache	<input checked="" type="checkbox"/> Pain – legs/feet	<input checked="" type="checkbox"/> Weight gain
<input checked="" type="checkbox"/> Memory problems	<input checked="" type="checkbox"/> Poor appetite	<input checked="" type="checkbox"/> Weight loss
<input checked="" type="checkbox"/> Other new problems?		

Clinical care of Infants and Children:

The care of children exposed to and infected with HIV requires special expertise. In addition, the counseling and supportive services described in other chapters are essential components of care and are needed to ensure that patients are able to utilize available clinical services. This chapter will focus on clinical issues including the recommended schedule and types of assessment, guidelines for the prophylaxis of opportunistic infections and the provision of ARV therapy in children. As noted, these are not intended to replace the judgment and expertise of treating clinicians.

Healthcare providers must be familiar with issues that distinguish the care of infants and children from that of adults:

- HIV diagnosis in infants is complicated by the presence of passively transmitted maternal antibody. Virologic tests (rather than antibody tests) are needed to identify HIV infection during the first months of life. As outlined below, MTCT-Plus will provide support for a limited number of virologic studies to identify those infants who are infected and most at risk for disease progression. Healthcare providers will need to remain vigilant about signs and symptoms of disease, as progression can occur rapidly during the first months of life.
- Unlike adults, for whom fixed doses are prescribed for most medications, dosing requirements for children vary with size and age. Puberty is another time of changing metabolic requirements, as dosing requirements move from pediatric to adult recommendations. Providers will need to calculate new doses at each visit, taking into account changes in weight and height. Tables for commonly used medications will be provided to facilitate calculation of appropriate dosing.
- While strict adherence to ARV treatment is a challenge in all settings, ensuring that children receive chronic daily therapy can be especially complex. A parent or adult caregiver must be diligent about accurate and regular dosing. Other responsibilities inside and outside the home may conflict or compete with the need to be available twice daily to ensure medication administration. Many medications are poorly palatable and not well tolerated by young children and a child's ability to take medications may vary with developmental stage. Treatment for older children is often complicated by issues of disclosure, especially when adult family members are unwilling to tell the child why s/he needs to take medications. Healthcare providers must remain sensitive to these complicated issues and work closely with families to identify

and address barriers to adherence in order to insure treatment success.

MTCT-Plus sites will utilize their usual procedures for providing acute care and inpatient hospitalization, and for linking patients to local resources.

- *Management of acute illness:* Patterns of acute illness will vary from place to place, and sites will continue to follow local and national guidelines for diagnosis and management. Referral procedures should be explicit – when are patients referred to the local hospital? How is medical information transferred? How is follow-up arranged? For patients receiving preventive or antiretroviral drugs, it will be important to distinguish between an intercurrent illness and an adverse effect of medication; careful and systematic follow-up and documentation will be required. Effective communication between MTCT-Plus care providers and those responsible for inpatient care will be essential.
- *Linkages to local resources:* Resources for patient care and family support will differ from site to site, influencing diagnostic, management, and referral protocols. One example is that of mental health services which, if available, will be an important resource for MTCT-Plus patients. A periodic inventory of local care services is strongly recommended.

Infants and young children (0–18 months)

While the birth of a baby is normally a joyful time, the discovery that the infant is infected with HIV may lead to fear and anxiety. Families will greatly benefit from psychosocial support during this period. Counseling regarding infant feeding options is complex, site-specific, and extremely important. Mortality from HIV is high during the first years of life, and close medical follow-up of infants and young children is essential.

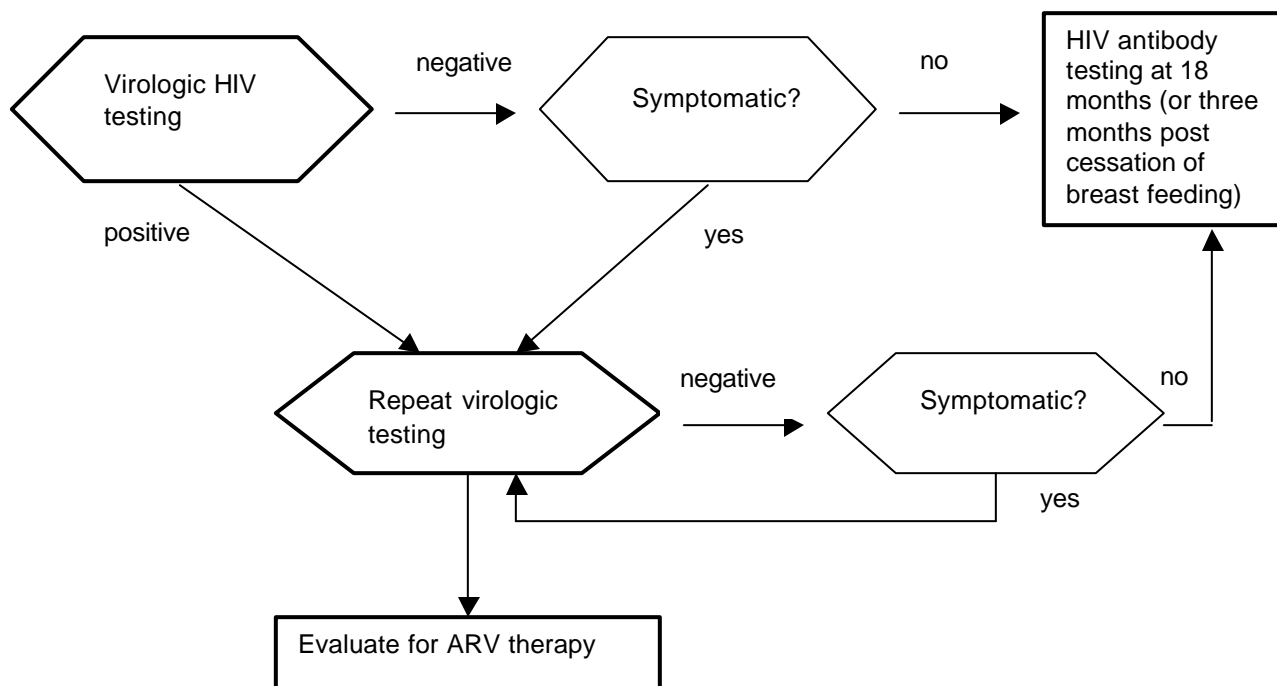
Diagnosis:

HIV testing* should be performed between 6 and 12 weeks of age. HI DNA PCR is the preferred test for infant diagnosis, but HIV RNA PCR can be used as well. It is anticipated that I.D. p24 antigen testing will be available for early infant diagnosis during the coming months and may be substituted for PCR testing at some sites. MTCT-Plus will work with sites to determine the most suitable method for testing, and to enhance testing capacity if needed.

* HIV DNA PCR or I.D. p24 antigen or HIV RNA PCR. MTCT-Plus will work with sites to determine the most suitable method for testing and to enhance testing capacity if needed.

- If the virologic test is negative and the infant is clinically well, the next HIV test should be an HIV antibody test at 18 months (or, if the infant is breast feeding, 3 months after s/he is weaned).
- If the virologic test is negative but the infant has symptoms consistent with HIV infection (Appendices 6-1, 6-2) testing should be repeated. Alternative etiologies for symptoms should also be sought.
- If the virologic test is positive, it should be confirmed with repeat testing and care should follow the protocols outlined below.
 - If the repeat virologic test is negative and the infant is clinically well, the next HIV test should be an HIV antibody test at 18 months (or 3 months after weaning)
 - If the repeat test is negative but the infant has symptoms consistent with HIV infection (Appendix 6-1, 6-2), virologic testing can be repeated.
 - If the repeat virologic test is positive, the infant is HIV-infected. S/he should be evaluated for ARV therapy and followed according to the schedule of visits for HIV-infected children (Appendix 6-3).

Infant HIV testing algorithm:



Infants enrolled between 12 weeks and 18 months should undergo virologic HIV testing at enrollment and follow the algorithm as outlined above. In general, ARV therapy should not be started in children less than 18 months of age without two positive virologic tests. However, if a child is severely ill and virologic testing is pending, ARV therapy can be considered while awaiting confirmatory testing.

If a child who is no longer breast feeding is enrolled after nine months of age, a screening antibody can be performed in place of virologic testing. If negative, the results should be confirmed by a second antibody test. If positive, virologic testing should be performed according to the algorithm above to clarify infection status. Children enrolled after 18 months of age (and no longer breast feeding) should undergo HIV *antibody* testing.

Initial assessment of infants < 18 months

An initial multidisciplinary assessment will be the first step after enrollment in MTCT-Plus and may take place over the course of several visits. We anticipate that the majority of infants will be newborns, and that the baseline assessment will be initiated during the first months of life, but older infants and children are also eligible for MTCT-Plus.

The baseline assessment should include the collection of routine information pertinent to the care of an infant as well as information needed to assess the risk of HIV infection and disease progression. Maternal history should include maternal health status during pregnancy, prenatal care, medications, and delivery circumstances. Specific treatments given to the mother and child for perinatal prevention should be noted.

Determination of infant HIV status requires virologic testing during the first year of life. Disease progression can be rapid, however, and often manifests during the first months of life before infection status can be confirmed. Therefore, the initial evaluation should elicit past and current signs and symptoms consistent with HIV disease. Poor growth is often the first manifestation of HIV infection. Weight, height and head circumference should be measured and plotted on growth curves such as those in chapter 4. Nutritional assessment, including method of feeding and any problems encountered, will be important. Multivitamins are available for all children enrolled in MTCT-Plus.

The initial evaluation should include a review of acute symptoms as well as an assessment of infant development. Slow development and/or loss of previously acquired milestones may be early signs of HIV infection. A thorough physical examination during the initial assessment will both identify HIV-related findings and provide a baseline for future visits.

MTCT-Plus supports the coordination of HIV-specific and routine pediatric care. This model enhances follow-up by decreasing the burden of additional visits to other pediatric providers for routine care, and by increasing maternal familiarity with the program during pediatric visits. Immunizations can be administered at the initial visit as well as follow-up visits, according to national guidelines

Care of an infant always requires an understanding of the family and social context. Since much of the social information will be addressed within the context of his/her mother's medical care, coordinating this data will decrease duplication. Ongoing communication between adult and pediatric providers will be especially useful (see chapter 1).

Follow-up for infants < 18 months

Comprehensive well child care will be provided to all enrolled infants, including monitoring of growth and development, assuring adequate nutrition, and providing immunizations, multivitamins and PCP prophylaxis. An assessment of HIV-related signs and symptoms will be conducted at each visit and treatment for acute illness will be provided. Initial visits will focus on establishing the infant's HIV infection status. After initial HIV testing, content and intensity of follow-up visits will be dictated by whether the results are positive or negative.

- Infants whose initial virologic test is negative will continue to receive comprehensive care until a negative HIV antibody test is obtained at 18 months of age (or three months after the termination of breast feeding if later than 18 months). An initial negative test does not exclude HIV infection, especially in the context of breast feeding, and clinicians should remain vigilant for signs and symptoms consistent with HIV disease (inadequate weight gain, weight loss, CDC stage B/C or WHO stage 3 symptoms [Appendices 6-1, 6-2]) and the need for additional virologic testing. **Indeterminate infants should be seen monthly during the first six months of life and every three months thereafter** (Appendix 6-3). Some children may need less frequent visits after an initial negative viral study if routine care is available in an alternative setting and if PCP prophylaxis can be assured. At 18 months of age (or three months after breast feeding if beyond 18 months) an HIV antibody test should be obtained for all children who are not already identified as HIV-infected. If the HIV antibody test is negative, the child will be referred to local providers of pediatric care and discharged from the MTCT-Plus program.
- If initial HIV tests are positive, management of symptoms and determination of ARV eligibility will be of paramount importance. Once HIV has been diagnosed, lymphocyte subset testing (CD4 number and

percent) will be done and the child will be categorized according to the CDC and WHO classification systems (Appendix 6-1); clinical and immune status will determine ARV eligibility. **HIV-infected infants should be seen monthly during the first six months of life and every three months through 18 months of age unless started on treatment which will independently determine follow-up schedule** (Appendix 6-3). All visits (independent of treatment status) should include an assessment of nutrition, growth and development, review of intercurrent illnesses and HIV-related signs and symptoms, immunization update, targeted physical examination, and determination of HIV clinical category. PCP prophylaxis, multivitamin supplements, and immunizations, will also be provided. For children who have not yet required ARVs, CD4 testing will be performed every six months to monitor immune status and ARV eligibility.

Children >18 months of age

While the majority of children enrolled in MTCT-Plus are likely to be infants and young babies, older children will also be eligible for services. Older children of enrolled women as well as other children within the household will be offered HIV testing and, if positive, enrollment in the program. Therefore, it is assumed that all children > 18 months of age entering the program will have already been determined to be HIV infected.

Initial assessment of children > 18 months

A multidisciplinary assessment will be the first step after enrollment in MTCT-Plus, and may take place over the course of several visits. While a comprehensive medical and social history is desirable, it is recognized that not all information will be available for each child. Children may not be living with biologic parents and current families may be unaware of the child's past history. However, as part of the initial evaluation, all available information should be collected and recorded. Birth history should include birth weight, gestational age if known and any complications of delivery. In addition, maternal health status during pregnancy, prenatal care, medications and specific treatments given to the mother and child for perinatal prevention should be reviewed.

The initial evaluation should seek to determine the level of illness the child has experienced. A thorough medical history with attention to previous AIDS-defining illnesses, recurrent infections or illnesses, and hospitalizations will enable the provider to categorize the severity of disease. If available, previous growth data as well as immunization records should be reviewed and recorded.

An assessment of the child's current developmental status and, where appropriate, school performance, should be conducted during the course of the initial evaluation. Neurologic manifestations of HIV as well as psychosocial circumstances can influence the acquisition of normal developmental milestones. A psychiatric history may also be pertinent for older children, especially those in their teens.

A comprehensive physical examination, with specific attention to stigmata of HIV should be completed as part of the initial evaluation. Height, weight and head circumference (in children younger than two years) should be measured and plotted against age-appropriate growth curves (see Appendix 4.2). Nutritional status should be assessed, including food availability and child's dietary habits. CD4 testing (number and percent) will be used to assess the need for PCP prophylaxis, to determine ARV eligibility, and to facilitate categorization of the severity of disease.

Care of a child always requires an understanding of the family and social context. Since much of the social information will be addressed within the context of his/her mother's care, a family-centered approach to collection and organization of this data will be necessary to decrease duplication and enhance coordination. Ongoing communication between adult and pediatric providers will be especially useful (see chapter 1).

By the end of the initial evaluation a thorough profile for the child and family should be completed. Each child should be categorized according to the CDC or WHO classification system (Appendices 6-1, 6-2) based on past medical history, physical examination and lymphocyte subset counts gathered during the initial evaluation. The child's status will determine eligibility for ARV therapy as well as frequency of follow-up visits (Appendix 6-3).

Follow-up for children >18 months

Disease progression in children can occur quite rapidly. Children should therefore be followed at frequent intervals to monitor for disease progression, intercurrent illness and immune deterioration.

- Children > 6 months of age who are not receiving ARV therapy should be seen every three months.
- Children with advanced disease will be eligible for ARV treatment and will generally be seen monthly after an eight week period of weekly visits upon initiation of therapy.
- For the subset of HIV-infected children > 2 years of age with asymptomatic disease and normal immune function, an appointment can be scheduled every six months at a minimum.

Follow-up visits include an assessment of intercurrent illnesses, new signs and symptoms and a targeted physical examination. Height and weight should be measured and plotted against age-appropriate growth curves. Nutritional status should be assessed, including food availability and dietary habits. The evaluation should include an assessment of developmental achievement and/or school advancement. Lymphocyte subset studies should be obtained every six months. Counseling should be provided at each visit. The need for additional supportive services should be routinely assessed. As families become engaged with the health care team, they may be more willing to access additional services.

An assessment of eligibility for ARV therapy should be done at the completion of each follow-up visit for children not on treatment. Does the child have new clinical or laboratory criteria which would qualify them for treatment? If not, the child can be rescheduled for follow-up. If so, the child and family can be scheduled for a return visit to discuss interest in ARV treatment and readiness to begin therapy.

Special issues for older children:

Several issues particular to the needs of older children should be addressed either as part of the initial evaluation or during follow-up appointments. Many providers will find that the complexity of these issues often requires an established relationship with the child and caretaker before open discussion can be initiated.

- **Disclosure**

Many families are reluctant to talk about HIV or to let their child know that they have HIV disease (that the child is HIV-infected and that the parent is HIV-infected). Some families prefer to give the disease another name (anemia, etc.) while others may deny that there is anything wrong with the child at all. Many adults fear that the child will become depressed and lose the will to live upon learning their diagnosis. Many worry that the child will share the information with other children or adults and the child and family will face discrimination within the community. And still others, particularly mothers, feel both responsible and guilty for their child's condition.

While the experience varies for each child and family, experience with HIV infection as well as other chronic and fatal illnesses suggests that telling children their diagnosis is an important part of their care. Most children understand that they are ill and many already know their diagnosis. However, they are able to maintain the secrecy established by their adult caretakers. Teens who eventually learn their status often complain that they were not told at a younger age.

Disclosure to a child should be viewed as an ongoing process that may take several years. Parents can be encouraged to talk with their children about their illness and their medical care starting early in life, using developmentally appropriate language. Many children will ask questions about going to the doctor, taking medications and having blood tests. Parents should be encouraged to discuss these questions and to provide simple, but honest answers. [“You have a problem in your blood and the medicine will help keep you healthy.” “The doctor checks your blood to make sure that the medication is working.”] Pediatric providers should also respond directly to questions from young children.

As children age, questions are likely to become more sophisticated, and families should consider beginning a discussion about HIV disease. The family will ultimately make the decision about when to tell the child their diagnosis, but program staff can encourage the family to begin the dialogue. Furthermore, many parents will require guidance about what to say and how to say it. It is often useful for a member of the program to participate in the discussion with the child and, at times, to be the person to disclose the information.

The process of disclosure does not end after the child has learned the diagnosis. The family should be prepared to continue to address the issue repeatedly in the future. Most children need to hear the information multiple times, in multiple ways. It is important for the family to maintain an open attitude, which enables the child to raise questions and concerns. Many families may not be prepared to assist the child in this way. In this case, the health care team may provide a safe place for the child to further explore issues related to HIV. Further information about psychosocial assessment and support can be found in chapter 3.

- **Adolescence, sexuality, and secondary prevention**

The majority of children enrolled in MTCT-Plus will be infants and young children. However, older children and young teens may be identified within families and households and, thus, enrolled in the program. In addition, over the course of the program, with successful care and treatment, many children will age into adolescence.

As children enter adolescence, they will naturally begin to develop an interest in sexual relationships. The challenge for healthcare providers, in partnership with families, will be to enable these young people to develop healthy sexual lives while providing them with the tools to prevent HIV transmission to their partners and children.

Young people may be reluctant to discuss the topics of sexuality and puberty when their parent or caregiver is in attendance. Healthcare providers should begin to develop independent relationships with teenage patients. Teens are often anxious to have their questions answered and their concerns addressed, and respond to a nonjudgmental, open approach. In addition, the availability of peer advisors and support groups can be especially valuable.

For young people who are sexually active, routine assessments should include questions about genitourinary symptoms. A menstrual history should be taken for young women, including last menstrual period and the possibility of pregnancy. All teens should receive information about safe sex and prevention of secondary transmission. Again, peer education may be the most effective way to successfully communicate prevention messages. Family planning and contraceptives should also be made available either on site or through appropriate referrals. Healthcare providers will need to carefully consider issues of confidentiality for the teen and how to balance the needs and interests of the caretaker/parent with those of their child.

The vast majority of children enrolled in MTCT-Plus will have been born to an HIV-infected mother. However, it is not unlikely that some children, particularly young teens, will have had sexual contact with an HIV-infected adult. While route of transmission will not change the management and treatment of HIV disease, children with sexually transmitted infection, especially those who were molested, will have special psychological and social needs. Furthermore, information about the route of infection may not be disclosed until a relationship has been established between the care team and the family. The healthcare providers should remain sensitive to the complex issues within families and offer access to supportive services for the child, as well as the family, when indicated.

Prophylaxis

***Pneumocystis carinii* prophylaxis**

Pneumocystis carinii pneumonia can occur during the first months of life and is often fatal in young infants. Not infrequently, the diagnosis of PCP is made before the infection status of the HIV-exposed infant is determined. In resource-rich settings, prophylaxis of all HIV-exposed infants with cotrimoxazole has led to a dramatic reduction in PCP in infants. MTCT-Plus will provide cotrimoxazole for all infants starting at 4 weeks of age. Therapy should be continued through the first year of life for all infants.

- For infants who are not immediately determined to be HIV-infected, cotrimoxazole should be continued until at least 12 months of age or until HIV infection is definitively excluded.
- For HIV-infected infants and children continuation of PCP prophylaxis beyond one year of life is based upon the child's age and immunologic status. Children should be given cotrimoxazole if they meet the following criteria:
 - ✓ All children < 12 months
 - ✓ Ages 1–5 years: CD4% <15 or CD4+ <500
 - ✓ Ages 6–11 years: CD4% <15 or CD4+ <200
 - ✓ All children previously diagnosed with PCP. If ARV therapy produces immune reconstitution, discontinuation of prophylaxis can be considered if normal immune function is sustained.

Cotrimoxazole (trimethoprim sulfamethoxazole), 150mg/m²/day can be administered in two divided doses on three consecutive days each week. Alternatives include giving the drug in two divided doses on three alternating days each week or as a single dose once daily.

Dapsone can be dispensed to children (>1 month of age) intolerant to cotrimoxazole. The appropriate dose is 2mg/kg/day with a maximum of 100mg/day.

Tuberculosis prophylaxis

In most circumstances, local protocols will govern screening for and treatment of latent TB infection (LTBI), and site medical directors will make the final decisions in this regard. We recommend annual tuberculin skin testing (TST) using PPD (5 units) in HIV-infected children to identify those eligible for isoniazid (INH) treatment of latent tuberculosis infection, LBTI. Children who have received BCG vaccination may have a false positive TST result. However, in light of the high prevalence of tuberculosis, it is recommended that all children with a positive TST receive treatment.

- TST should be placed annually starting at 24 months of age for all HIV-infected children. If positive (\geq 5mm):
 - Exclude active TB as per local and national guidelines and then
 - Provide INH (10–15mg/kg, maximum 300mg) daily for nine months (with pyridoxine as per local guidelines).
- INH should also be given to all children under the age of three years who are in contact with an adult diagnosed with active tuberculosis.
- Additionally, INH prophylaxis should be considered for any child with known contact with an active case of TB.
- INH should not be given to patients who have previously received INH prophylaxis, were previously treated for TB, have contraindications to INH or who are suspected of having active tuberculosis.

Vaccination

Comprehensive care for infants and children includes the provision of immunizations. HIV-infected children may have limited responses to immunizations especially if there is significant immune compromise. However, most vaccines are routinely given to children with HIV and few complications have been reported. Children enrolled in MTCT-Plus should be immunized according to local/country guidelines. Immunizations can be provided during follow-up visits for infants and young children. Documentation of immunizations should be sought for older children, and missing or undocumented vaccines should be administered.

Antiretroviral therapy

Basic principles of antiretroviral use

The use of highly active ARV therapy has dramatically reduced HIV-associated mortality and morbidity among children and adolescents in resource-rich settings. Despite their immense benefit to patients with advanced disease, however, the medications are not without risk, including drug toxicity and viral resistance. Furthermore, new information about long term side effects of chronic HAART treatment continues to emerge. Years of experience with HAART have taught providers the central role of informed patient participation, the need for meticulous medication adherence, the complexity of drug interactions, and the importance of regular monitoring.

- *Patient readiness:* ARV readiness is especially complex for children, where successful treatment requires the collaboration of the child and their caregiver. An adult must administer or supervise administration. The child has to agree to take the medications and the adult must agree to be available twice daily to insure that the medications are taken. In some cases, this requires little preparation. In others, a significant amount of patient support is needed before ARV therapy can be prescribed.

A parent or primary caregiver does not always directly supervise the child. Some attend school, participate in work activities, or spend time with other family members or baby sitters. These normal circumstances of child rearing present particular issues for HAART therapy. Medication must be administered on a regular schedule each day without missed doses. Unless the family is prepared to disclose HIV status to other adults involved in the care of the child, medication administration cannot be assured. The health care team should explore these issues sensitively and thoroughly before prescribing treatment.

There is no substitute for informed patient participation in this type of decision making, and patient education and adherence programs should be part of any HIV/AIDS care initiative. Patient education and adherence programs must also center on the specific developmental needs of the child as well as those of the adults responsible for his/her care.

- *Minimizing viral resistance:* Providers can play an important role in delaying the occurrence of HIV resistance through good prescribing practices and assisting patients in achieving adherence (see chapter 2). These include:
 - Never prescribe ARVs in the absence of adherence counseling and support.
 - Work with families to minimize barriers to medication adherence.
 - Pay meticulous attention to other medications and treatments and their potential to interact with ARV therapies.
 - Never prescribe monotherapy or dual therapy for treatment of chronic HIV infection (these may be used for pMTCT or for post-exposure prophylaxis).
 - Never add a single drug to a failing regimen.
 - If ARV medications are to be discontinued, stop all treatments as instructed.
- *Drug-drug interactions:* ARV agents, particularly protease inhibitors, have multiple interactions with other medications and should not be prescribed without a careful review of each patient's regimen, including herbal and traditional agents.
- *Drug-food interactions:* While the first-line agents used in MTCT-Plus do not have stringent dietary rules, patients taking some second-line medications will need to follow specific guidelines with regard to the timing of medicines and food. This can be extremely complex in the case of an infant who requires frequent feeds with breast milk or formula.
- *Drug Formulations:* Many of the most powerful ARV agents are not available in formulations suitable for young children. Others taste bad and make strict adherence extremely difficult. Health care teams will need to work closely with the child to insure that prescribed formulations are adequately palatable. They should also note that ease of administration and acceptability of treatment may vary as the child ages. Infants who tolerate one formulation may reject it when they are older. It will also be important to offer ways to enhance palatability by mixing medications with food or drinks.

o *Special considerations in patients with tuberculosis who are taking ARVs:*

At most MTCT-Plus sites, the local TB program will treat active tuberculosis as per local and national protocols. Communication between providers of anti-TB therapy and providers of HIV care is critical, both to avoid drug-drug interactions that may threaten successful therapy, and to heighten awareness of the potential for immune reconstitution syndromes.

- As noted in chapter 5, protease inhibitors and nevirapine interact with rifampin, and co-administration of these drugs is contraindicated. One alternative is to change the ARV regimen to a triple-nucleoside or efavirenz-containing combination. These regimens are further complicated during infancy, when neither efavirenz nor abacavir is routinely prescribed. Another choice is to use non-rifamycin-based TB therapy, or dose-adjusted rifabutin. In circumstances where an ARV-regimen compatible with antituberculous therapy cannot be provided, ARVs should not be initiated or should be temporarily discontinued until anti-TB therapy has been completed.
- With vigorous immune reconstitution due to ARV therapy, some HIV-infected patients may develop complications in the first few months after initiation of ARVs. This phenomenon has been described primarily in adults, but it has been observed in children as well, and all patients should be followed carefully after the initiation of ARVs. Patients with TB who are receiving ARVs may experience a transient paradoxical worsening of TB symptoms in this context. These reactions are difficult to differentiate from those that might be associated with TB symptoms or TB treatment failure. Providers should be familiar with this “immune reconstitution syndrome,” and patients should be counseled to report early symptoms.

When to initiate ARVs

Education and adherence counseling are essential components of ARV therapy. ARV medications should never be prescribed until the family has made an informed decision to insure proper administration. Intermittent or inconsistent use of ARVs carries more risk than benefit.

For the purposes of determining eligibility for antiretroviral therapy, children should be categorized according to either the CDC or WHO classification systems (appendices 6-1, 6-2). There is significant overlap between the two. The CDC allows for a greater degree of specificity in diagnosis, while WHO criteria allow for easy classification in the clinical setting. WHO category I correlates with CDC category N. WHO category II correlates with CDC category B. WHO category III correlates with CDC

category C. The exception concerns bacterial infections. If a child has recurrent severe bacterial infections within two years, s/he meets criteria for CDC category C but WHO II (unless s/he is diagnosed with recurrent septicemia or meningitis/WHO III).

MTCT-Plus will provide ARV for children who meet the following criteria:

Infants (1–12 months with two positive virologic HIV tests):

- Failure-to-thrive (no weight gain or weight loss or z score < -2) OR
- AIDS-defining illness (CDC category C/ WHO III) OR
- Asymptomatic with CD4% <20 (CDC category 2/3)

Children (1–5 years):

- Failure-to-thrive (no weight gain or weight loss or z score < -2) OR
- AIDS-defining illness (CDC category C/ WHO III) OR
- Asymptomatic patients with CD4% <15 (CDC category 3)

Children (> 6 years):

- Failure-to-thrive (no weight gain or weight loss or z score < -2) OR
- AIDS-defining illness (CDC category C) OR
- Asymptomatic and CD4% <15* (CDC category 3)

**In an asymptomatic child \geq 6 years of age, the clinician may consider waiting until the CD4% reaches 10, or until there is evidence of rapid immune deterioration. In the absence of data, some argue that the difficulties of maintaining adherence in an asymptomatic child and the potential toxicities of antiretroviral use outweigh the benefits of earlier treatment. If treatment is postponed in this setting, we recommend more frequent monitoring of CD4 counts/% (every three to four months).*

It is possible that a child will have severe clinical manifestations of HIV infection without developing an AIDS-defining diagnosis or laboratory evidence of advanced immune suppression. Such a child would not meet the criteria above, although s/he might benefit from antiretroviral therapy. Once other non-HIV-related causes of the symptoms have been excluded, treatment of these children can be discussed on a case-by-case basis with the MTCT-Plus Secretariat.

Initial ARV regimens:

The ARV regimens selected by MTCT-Plus are all highly active and offer a balance between efficacy, toxicity, palatability, logical sequencing of treatments to maintain future options, and cost concerns. The program suggests the first-line alternatives listed below, all of which are consistent with WHO guidelines. We have prioritized the use of zidovudine,

lamivudine and nevirapine, a highly active regimen that is potent, palatable and has a well established, tolerable side effect profile. In special circumstances and based on discussions between site director and Secretariat staff, alternate regimens may be selected for use by a site. Specific information about each drug can be found in chapter 10.

Recommended initial regimen: Zidovudine + lamivudine + nevirapine

Zidovudine (ZDV, Retrovir) + lamivudine (3TC, Epivir) + nevirapine (NVP, Viramune)

Alternate regimens:

Zidovudine + lamivudine + nelfinavir

Zidovudine (ZDV, Retrovir) + lamivudine (3TC, Epivir) + nelfinavir (NLF, Viracept)

Stavudine + lamivudine + nevirapine

stavudine (d4T, Zerit) + lamivudine (3TC, Epivir) + nevirapine (NVP, Viramune)

Stavudine + lamivudine + nelfinavir

stavudine (d4T, Zerit) + lamivudine (3TC, Epivir) + nelfinavir (NLF, Viracept)

Zidovudine + lamivudine + abacavir

Zidovudine (ZDV, Retrovir) + lamivudine (3TC, Epivir) + abacavir (ABC, Ziagen)

Before prescribing antiretroviral therapy, the provider should ask the following questions:

- **Does the patient have a medical indication for antiretroviral therapy?** These are outlined above.
- **Is there a medical contraindication to the planned first-line regimen?** The next step is to exclude medical contraindications to the specific first-line regimen selected by the site medical director (table 6-1). Minimal laboratory investigation includes assessment of renal function, liver function and a complete blood count.
- **Is there a non-medical contraindication to antiretroviral use?** Not every patient with a medical indication for antiretroviral therapy is ready to begin treatment. One purpose of multidisciplinary, psychosocial, and adherence assessments is to exclude “non-medical” contraindications to ARV use, and to confirm that a child and his/her family are prepared to take the medications consistently and correctly. While many patients will be ready to begin treatment, identifying modifiable barriers to adherence will enable providers to intervene for others prior to ARV initiation.
- **Has adherence been formally addressed?** A great deal of preparation is required prior to initiating treatment in children. It is crucial to teach parents and/or caregivers how to prepare and administer ARVs. A “taste test” should be done at the clinic prior

to dispensing medications. Many older children will refuse or spit out bad-tasting the drugs, and it is better to discover this in clinic than in the home. Clinical staff should demonstrate administration of the ARVs, and may need to assist families to develop clever ways to disguise their taste. In general, antiretroviral therapy is not an emergency and can be postponed until the family is prepared.

Table 6-1: Medical Contraindications to Initiation of first-line ARV therapy

Contraindication	Definition	Comments	Recommendation
Severe anemia	Hb \leq 7.0 g/dL	Zidovudine use requires close laboratory monitoring.	OK to start first-line regimen, but Hb measurement should be repeated within two weeks of initiation (or if symptoms arise). If repeat labs show Hb has fallen, make a single-drug substitution to alternate first-line regimen: Lamivudine/stavudine/nevirapine
Severe thrombocytopenia	Platelets \leq 49,000 mm ³	Zidovudine use requires close laboratory monitoring.	OK to start first-line regimen, but platelet measurement should be repeated within two weeks of initiation (or if symptoms arise). If repeat labs show platelets have fallen, make a single-drug substitution to alternate first-line regimen: Lamivudine/stavudine/nevirapine
Severe neutropenia	ANC < 250 mm ³	Zidovudine use requires close laboratory monitoring.	OK to start first-line regimen, but ANC measurement should be repeated within two weeks of initiation (or if symptoms arise). If repeat labs show ANC has fallen, make a single-drug substitution to alternate first-line regimen: Lamivudine/stavudine/nevirapine
Renal insufficiency	Children < 2 yrs: Cr > 1.2 Children \geq 2 yrs: Cr > 1.7	Contraindication to use of antiretrovirals	Patient not currently eligible for ARVs. Conduct diagnostic evaluation as per local guidelines and reassess for ARV eligibility if renal function improves.
Hepatic insufficiency	> 10x upper limits of normal	Contraindication to use of antiretrovirals	Patient not currently eligible for ARVs. Conduct diagnostic evaluation as per local guidelines and reassess for ARV eligibility if hepatic function improves.
History of prior ARV use (other than pMTCT)	Use of any ARV for more than four weeks	Potential for ARV resistance	Expert management required. Consult local expert or Secretariat for case-by-case advice.
History of prior ARV intolerance	If intolerant of ZDV, use 3TC+ D4T + NVP. If intolerant of nevirapine, consider EFV in children 2 years and older. Other substitutions may require expert advice.		
Current use of anti-TB medications	Use of rifampin	Drug-drug interactions with nevirapine	Expert management required. Consult local expert or Secretariat for case-by-

How to monitor patients on ARVs:

Careful monitoring is an essential component of effective ARV use, permitting early detection of adverse effects, ongoing reinforcement of patient adherence, and periodic assessment of treatment efficacy. The type and frequency of monitoring will be somewhat dependent on local resources. The following are monitoring recommendations for children receiving ARV therapy in the MTCT-Plus program; these represent *minimal* monitoring requirements and should be modified for individual patients at their clinicians' discretion.

Clinical monitoring for children receiving ARV therapy:

As patients initiate ARV therapy, weekly visits are recommended for the first 8 weeks. These "initiation" visits should focus on adherence assessment and support, and on assessing adverse events or ARV toxicity via structured symptom checklist. Common early symptoms of toxicity depend on the treatment regimen used and may include rash, nausea, diarrhea, headache, fatigue, irritability, diminished appetite. Several of these symptoms—headache and fatigue, for example—often resolve over time. Others can be treated symptomatically (diarrhea, nausea). In infants these symptoms may be subtle and difficult to distinguish from signs of acute illness. Some findings may require changes in drug dosing or drug regimen.

Some children may develop symptoms early after initiation of ARV (e.g. cough, fever, lymphadenopathy) that may indicate an underlying infectious process that has become evident due to a vigorous immunologic reconstitution. A number of cases of such immune reconstitution syndromes have been seen in children, primarily older children and teens. Appropriate management of these symptoms and conditions should be instituted as per site usual procedures.

After the initial 8-week initiation period, children can be seen monthly for clinical monitoring. At each visit adherence should be reviewed with the parent/caregiver as well as the older child. The visit should also include interval medical history, symptom checklist, targeted physical examination, growth monitoring and nutritional assessment. Patients should be referred for psychosocial assessment and supportive services as indicated.

Dosing:

Dosing for children is calculated based on weight or surface area. As children grow, their medication doses need to be adjusted accordingly. This is particularly important in the case of a child with failure-to-thrive who responds to ARV treatment with a robust increase in weight. In such

cases, dosing is likely to increase frequently and often dramatically. ARV doses should be recalculated at each patient visit based on the child's current weight and height. This is complex and often a challenge for families who need to be counseled about dosing changes and assured that these changes are based on growth rather than an indication that the treatment is not working.

Infants and young children often metabolize medications more rapidly. For some medications, the daily dose is greater for children than for adults. Once a child completes puberty, standard adult dosing can be used. It is generally recommended that children continue to receive pediatric dosing throughout the course of pubertal development.

Laboratory monitoring for children receiving ARV therapy:

CD4 count and percent should be monitored every six months for children on treatment. MTCT-Plus supports a model of clinical monitoring for children receiving antiretroviral therapy. Laboratory tests should only be obtained if indicated by symptoms and signs; this decision is at the discretion of the treating clinician. If laboratory studies are obtained, the clinician will need to distinguish between toxicities caused by the medications, intercurrent illnesses and advancing HIV disease. Further work-up should be dictated by local guidelines for care and treatment. However, if the abnormalities listed in table 6-1 are identified, it may be necessary to stop or change ARV treatment, as discussed in the following section.

When to change ARVs:

The first ARV regimen should be both potent and durable. If adherence is adequate, clinical and immunologic benefits should be long lasting. Changing ARV medication should be done with caution. Resistance and cross-resistance are important considerations, and ARV sequencing can have important therapeutic impact. In addition, premature changes in ARV risk exhausting the ARV options available to that patient in the future. However, it is anticipated that some children will need to change therapy either due to toxicity or to therapeutic failure. In the case of **toxicity**, a single drug substitution may be indicated (see Tables 6-2, 6-3, 6-4). In the case of **therapeutic failure**, the entire regimen should be changed (see Table 6-5).

Changing ARVs due to toxicity:

ARV-associated adverse events may be detected by symptoms or by laboratory investigation. Some symptoms are mild and/or transient, while others require supportive therapy (such as antiemetics or antimotility agents) or more frequent clinical monitoring. Severe side effects may require interruption of HAART. Nevirapine, for example, may be

associated with a rash of varying severity. Nelfinavir may cause diarrhea, which does not respond to dietary changes or antimotility agents. Similarly, laboratory abnormalities due to ARVs may be mild or severe. While individual medications may be associated with specific side effects or toxicities, it is not always possible to identify the responsible medication. When a serious adverse event appears to be caused by a specific ARV, a single-drug substitution can be made. In some cases, however, the entire regimen will need to be changed. Tables 6-2 and 6-3 detail criteria for changing ARVs due to toxicity and Table 6-4 indicates which drugs to substitute.

The most common toxicity in adults and children receiving nevirapine is rash, which may develop in up to 20 percent of those taking the drug. Skin manifestations are generally mild to moderate, but two to five percent may need to discontinue therapy because of this side effect. Skin manifestations generally occur within the first 2–6 weeks of treatment. Rash can be minimized by introducing drug at a reduced dose for 14 days and then increasing to full dose, and this “dose escalation” is the standard of care in MTCT-Plus. Nevirapine treatment should be continued for grade 1 and 2 toxicities, but discontinued for grade 3 or greater.⁸

Nevirapine treatment can also result in hepatotoxicity. Fatal hepatic failure has been reported in some adult patients treated with nevirapine. Liver function will be monitored at the discretion of the treating clinician. If liver dysfunction is detected, an evaluation of the etiology should be undertaken. Nevirapine should be permanently discontinued if Grade 3 or greater toxicities develop. In adult patients, efavirenz has been successfully substituted when nevirapine has been associated with liver dysfunction. However, as no data are available in children, this drug substitution should be done with great caution and in consultation with the Secretariat.

Abacavir treatment is generally well tolerated. Nausea, vomiting, malaise, and fatigue are the most commonly reported side effects. A hypersensitivity reaction, characterized by generalized erythematous rash, fever, flu-like symptoms and multi-organ involvement has been described in three to five percent of individuals treated with abacavir. Symptoms are generally reversible with discontinuation of therapy and supportive care, but **ongoing treatment or reintroduction of abacavir can be fatal**. If a hypersensitivity reaction is suspected, abacavir should be discontinued immediately and NEVER restarted.

⁸ Grade 1 = erythema, pruritis. Grade 2 = diffuse maculopapular rash or dry desquamation. Grade 3 = vesiculation or moist desquamation or ulceration. Grade 4 = any one: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis, or exfoliative dermatitis.

Medication changes based on laboratory values should be carefully considered, guided by the clinician's experience and judgment, and view in the clinical context of the patient's care. No changes should be made on the basis of a single test. Intercurrent illness may create transiently abnormal laboratory values. Repeat testing should be completed and evaluated for trends over time.

Table 6-2: Laboratory indications to change ARVs due to toxicity/adverse event

Parameter	Grade 3 toxicity
Hematology	
Hemoglobin	≤ 7.0 g/dL
Absolute neutrophil count	< 250 mm ³
Platelets	< 49,000 mm ³
Chemistries	
Bilirubin	> 3.0–7.5 x upper limits of normal
Creatinine	> 1.2–1.5 (<2 yr), 1.7–2.0 (>2yr)
Liver function tests	
AST (SGOT)	> 10 upper limits of normal
ALT (SGPT)	> 10 upper limits of normal
Pancreatic enzymes	
Amylase, lipase	> 2–3x upper limits of normal

Table 6-3: Clinical indications to change ARVs due to toxicity

Symptom	
Nausea	Severe discomfort or minimal intake for ≥ 3 days
Vomiting	Severe vomiting of all foods/fluids in 24 hours or orthostatic hypotension or IV therapy required
Diarrhea	Bloody diarrhea or orthostatic hypotension or IV therapy required
Fever	Unexplained fever of ≥ 39.6 C (103 F)
Headache	Severe or requires narcotic therapy
Allergic reaction	Generalized urticaria, angioedema or anaphylaxis
Peripheral neuropathy	Severe discomfort, objective weakness, loss of 2–3 previously present reflexes or absence of 2–3 previously present sensory dermatomes
Fatigue	Normal activity reduced > 50 %

Table 6-4: Recommended ARV changes for children for early toxicity

Primary regimen	Single-drug substitution for toxicity
ZDV + 3TC + NVP	<i>If ZDV toxicity: ABC+3TC+NVP</i>
	<i>If NVP toxicity: ZDV+3TC+NLF for children < 12 months ZDV+3TC+ABC for children ≥ 12 months</i>
D4T + 3TC + NVP	<i>If D4T toxicity: ZDV+3TC+NVP</i>
	<i>If NVP toxicity: D4T+3TC+NLF for children < 12 months D4T+3TC+ABC for children ≥ 12 months</i>
ZDV + 3TC + NLF	<i>If ZDV toxicity: ABC+3TC+NVP</i>
	<i>If NLF toxicity: ZDV+3TC+NVP for children < 12 months ZDV+3TC+ABC for children ≥ 12 months</i>
ZDV + 3TC + ABC	<i>If ZDV toxicity: D4T + 3TC + ABC</i>
	<i>If ABC toxicity: ZDV + 3TC + NVP for children < 24 months ZDV + 3TC + EFV for children ≥ 24 months</i>
D4T + 3TC + NLF	<i>If D4T toxicity: ABC+3TC+NLF</i>
	<i>If NLF toxicity: D4T+3TC+NVP for children < 12 months D4T+3TC+ABC for children > 12 months</i>

Changing ARVs due to therapeutic failure:

Successful ARV therapy leads to clinical and immunologic improvements with associated suppression of HIV replication. It is reasonable to expect a symptomatic patient to show significant clinical improvement within three months of initiating ARVs. Within six months, CD4 counts generally rise by a minimum of 50 cells/mm³, although, the magnitude of the rise in CD4+ cell count is dependent on the baseline value. In general, however, one can expect a significantly greater increase in CD4 number/percent for children with adequate viral suppression.

The most common reason for treatment failure is inadequate adherence. Before any regimen is changed, adherence should be carefully assessed. If adherence cannot be assured, the decision to change therapy may need to be postponed until the child and family are ready to address the barriers to treatment. However, if poor adherence is related to drug formulation or palatability, a regimen change may result in improved adherence. Efforts should be made to insure that the child will be able to tolerate the new regimen before it is dispensed. This may require “taste testing” and practice sessions to familiarize the child with the new treatments and to assure the staff that the family can administer the medications. It is absolutely essential to discuss these issues openly with the child, if appropriate, and with the family in a nonjudgmental and supportive setting (chapters 1 & 2).

Infants who become HIV-infected despite nevirapine prophylaxis may be at risk for the development of resistance mutations to nevirapine. When these occur, the mutations appear to fade over time. However, the introduction of nevirapine may exert sufficient selective pressure for the mutations to reemerge. If so, the efficacy of this treatment is likely to be limited. The clinical significance of these mutations has not been studied and the impact upon the choice of nevirapine as part of the treatment regimen remains unclear at this time. This question is likely to be especially pertinent to infants beginning treatment with a nevirapine-based regimen and warrants careful follow-up.

The entire ARV regimen should be changed if therapeutic failure is determined based on the following:

- No improvement in or worsening of clinical status after 3 months on ARVs (no improvement in growth or weight loss, new AIDS-defining illness*)
- CD4 failure to improve (by ~ 50 cells/mm³ or 3 percent) or worsening at 6 months. If a patient has made marked clinical improvement, the initial ARV regimen should be continued despite a rise of < 50 CD4 cells/mm³.
- A subsequent return in CD4% to or below pre-therapy baseline. In children > 8 years, fall of 30 percent or more in CD4 count or percent from peak value after six months of ARVs.

*Excluding immune reconstitution syndrome

Secondary ARV regimens:

As noted, ARV agents should not be changed casually. The choice is based on expected resistance patterns that occur with specific agents and take into account the need for replacement of a specific regimen with another with minimal potential for cross resistance. The following sequencing suggestions are based on settings where providers and patients lack ready access to viral load or viral resistance testing.

Table 6-5: Secondary ARV regimens

If the failing regimen is...	Then switch to...
ZDV + 3TC + NVP	ddl + D4T + NLF
D4T + 3TC + NVP	ZDV + ddl + NLF
ZDV + 3TC + NLF	D4T + ddl + NVP (for children < 24 months)
	D4T + ddl + EFV (for children ≥ 24 months)

D4T + 3TC + NLF	ZDV + ddl + NVP (for children < 24 months)
	ZDV + ddl + EFV (for children ≥ 24 months)
ZDV + 3TC + ABC	D4T+ ddl + NLF(for children < 24 months)
	D4T + ddl + EFV (for children ≥ 24 months)
D4T + 3TC + ABC	ZDV + ddl + NVP (for children ≤ 24 months)
	ZDV + ddl + EFV (for children ≥ 24 months)

The choice of secondary regimens continues to balance potency, toxicity, formulation, and cost. As new data become available, it is likely that recommendations for second-line regimens will change. We also anticipate that efavirenz liquid will become available for young children, increasing the options for therapeutic regimens.

Adherence support

Adherence support is an essential component of ARV use, and expert guidelines emphasize that ARVs should not be prescribed without it. Suggestions for adherence assessment and support are detailed above and in chapter 2.

Appendix 6-1: CDC Staging for Infants & Children

CDC immunologic categories based on age-specific CD4+ counts and percent of total lymphocytes

	<12 mos	1-5 yrs	6-12 yrs
Immunologic category	uL (%)	uL (%)	uL (%)
1: No evidence of suppression	≥ 1,500 (≥ 25)	≥1,000 (≥ 25)	≥ 500 (≥ 25)
2: Evidence of moderate suppression	750-1,499 (15-24)	500-999 (15-24)	200-499 (15-24)
3: Severe suppression	< 750 (<15)	< 500 (<15)	< 200 (<15)

CDC clinical categories for children with HIV infection

CATEGORY N: NOT SYMPTOMATIC

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

CATEGORY A: MILDLY SYMPTOMATIC

Children with two or more of the conditions listed below but none of the conditions listed in Categories B and C.

- Lymphadenopathy (≥ 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

CATEGORY B: MODERATELY SYMPTOMATIC

Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to:

- Anemia (<8 gm/dL), neutropenia (<1,000/mm³), or thrombocytopenia (<100,000/mm³) persisting ≥ 30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children >6 months of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month of age
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month of age

- Varicella, disseminated (complicated chickenpox)

CATEGORY C: SEVERELY SYMPTOMATIC

Conditions included in clinical Category C for children infected with human immunodeficiency virus (HIV)

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Pneumocystis carinii pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child \geq 1 year of age OR c) <5th percentile on weight-for-height chart on two consecutive measurements, \geq 30

days apart PLUS a) chronic diarrhea (i.e., at least two loose stools per day for >30 days) OR b) documented fever (for \geq 30 days, intermittent or constant)

Appendix 6-2: WHO Staging for Infants and Children

<p><i>Clinical Stage I</i></p> <p>Asymptomatic Generalized lymphadenopathy</p>	
	<p><i>Clinical Stage II</i></p> <p>Unexplained chronic diarrhea Severe persistent or recurrent candidiasis outside the neonatal period Weight loss or failure to thrive Persistent fever Recurrent severe bacterial infections</p>
	<p><i>Clinical Stage III</i></p> <p>AIDS-defining opportunistic infection Severe failure to thrive Progressive encephalopathy Malignancy Recurrent septicaemia or meningitis</p>

APPENDIX 6-3a: Follow-up visits for infants of indeterminate HIV status (0–18 mo)

1 month	Medical history (acute illness) Dietary history/nutritional assessment (MVI) Symptom checklist Developmental milestones/ behavioral checklist Targeted physical exam Cotrimoxazole prophylaxis Ensure appropriate vaccines Counseling, including infant feeding	
2 month	Medical history (acute illness) Dietary history/nutritional assessment (MVI?) Symptom checklist Developmental milestones/ behavioral checklist Targeted physical exam Cotrimoxazole prophylaxis Ensure appropriate vaccines Counseling, including infant feeding HIV testing * (6-12 weeks)	
3 month	Medical history (acute illness) Dietary history/nutritional assessment (MVI?) Symptom checklist Developmental milestones/ behavioral checklist Targeted physical exam Cotrimoxazole prophylaxis Ensure appropriate vaccines Counseling, including infant feeding HIV testing * (6-12 weeks)	If HIV test* positive, repeat test and assess for ARV treatment If HIV testing negative, but symptomatic, repeat HIV testing *
4 month	If HIV antigen testing negative Medical history (acute illness) Dietary history/nutritional assessment (MVI?) Symptom checklist Developmental milestones/ behavioral checklist Targeted physical exam Cotrimoxazole prophylaxis Ensure appropriate vaccines Counseling, including infant feeding	If HIV testing* positive, repeat test and assess for ARV treatment If HIV testing negative, but symptomatic, repeat HIV testing *
5 month	Medical history (acute illness) Dietary history/nutritional assessment (MVI?) Symptom checklist Developmental milestones/ behavioral checklist Targeted physical exam Cotrimoxazole prophylaxis Ensure appropriate vaccines Counseling, including infant feeding	If HIV testing* positive, repeat test and assess for ARV treatment If HIV testing negative, but symptomatic, repeat HIV testing *
6 month 9 month 12 month 15 month	Medical history (acute illness) Dietary history/nutritional assessment (MVI?) Symptom checklist Developmental milestones/ behavioral checklist Targeted physical exam Cotrimoxazole prophylaxis Ensure appropriate vaccines TST testing (9-12 months) Counseling, including infant feeding	If symptomatic, HIV testing* If HIV testing* positive, repeat test and assess for ARV treatment
18 month	As above, plus HIV antibody testing or repeat HIV antibody 3 months post cessation of breast feeding	

* HIV DNA PCR or I.D. p24 Antigen or HIV RNA PCR. MTCT+ will work with sites to determine most suitable method for testing and/or enhance testing capacity.

Appendix 6-3b: Follow-up visits for HIV-infected infants and children not on ARVs

0–24 months	> 24 months, asymptomatic	> 24 months, symptomatic
Monthly visits x 6 months	Visits every 6 months	Visits every 3 months
Then visits every 3 months		
<ul style="list-style-type: none"> ✓ Medical history (acute illness) ✓ Dietary history/nutritional assessment (MVI) ✓ Symptom checklist ✓ Developmental milestones/ behavioral checklist ✓ Targeted physical exam ✓ Cotrimoxazole prophylaxis ✓ Ensure appropriate vaccines ✓ Counseling, including infant feeding ✓ CD4 testing every six months ✓ Repeat clinical and immunologic staging, assess for ARV need 	<ul style="list-style-type: none"> ✓ Medical history (acute illness) ✓ Dietary history/nutritional assessment (MVI) ✓ Symptom checklist ✓ Developmental milestones/ behavioral checklist ✓ Targeted physical exam ✓ Cotrimoxazole prophylaxis ✓ Ensure appropriate vaccines ✓ Counseling ✓ Annual TST if PPD negative ✓ CD4 testing every six months ✓ Repeat clinical/ immunologic staging, assess for ARV need 	<ul style="list-style-type: none"> ✓ Medical history (acute illness) ✓ Dietary history/nutritional assessment (MVI) ✓ Symptom checklist ✓ Developmental milestones/ behavioral checklist ✓ Targeted physical exam ✓ Cotrimoxazole prophylaxis ✓ Ensure appropriate vaccines ✓ Counseling ✓ Annual TST if PPD negative ✓ CD4 testing every six months ✓ Repeat clinical/ immunologic staging, assess for ARV need
	For adolescent patients, include a sexual history, an expanded symptom checklist (including GU), provision of contraception/ family planning if indicated, RPR if indicated	

Appendix 6-3c: Follow-up visits for infants and children on ARVs

		For adolescents, add
HAART initiation visit	Adherence counseling Dose calculator, instructions ARV prescription (1 week's supply) Return visit in 1 week	
Weekly visits x 8 weeks	Adherence assessment/support Psychosocial assessment Supportive services as needed Intercurrent history (symptom checklist) Tolerance (symptom checklist) Toxicity (targeted physical exam if indicated by symptom checklist) ARV prescription (1 week's supply) Return visit in 1 week (or 1 month if 8 th visit)	
Monthly visits	Medical history (acute illness) Dietary history, MVI if indicated Psychosocial assessment Symptom checklist Targeted physical examination Developmental assessment Ensure appropriate vaccines Counseling, supportive services Cotrimoxazole prescription* ARV prescription (1 month supply) Repeat CD4 every 6 months Annual TST if PPD negative	Sexual history Expanded symptom checklist Contraception/family planning if indicated RPR if indicated

** Cotrimoxazole can be discontinued if CD4 remains above prophylaxis recommendations for two consecutive measurements.

Patient Education:

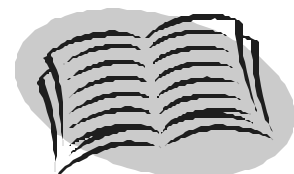
What is patient education?

Patient education is the information, recommendations and personalized advice that is given to patients. Some of the many goals of patient education for patients living with HIV/AIDS are:

- Managing their illness
 - Understanding HIV and its major complications
 - Knowing how to access and use the health care system
 - Understanding the benefits of care for asymptomatic patients
 - Understanding the goals of MTCT-Plus and the commitment required for successful therapy
 - Knowing what to do in case of new symptoms or acute illness
 - Knowing what to do in case of an emergency
 - Adhering to the care plan (see chapter 2)
- Maintaining good health and avoiding preventable complications (secondary prevention)
 - Knowing the importance of preventive care, such as OI prophylaxis
 - Understanding enteric infections and infectious diseases (water, raw foods, animal waste, personal hygiene)
 - Following general nutritional and specific dietary recommendations
 - Maintaining sexual health
- Prevention education
 - Precautions in the handling of blood and body fluids
 - Understanding sexual transmission and safer sex
 - Understanding vertical transmission (pMTCT and family planning options)

Why is patient education important?

HIV/AIDS is a frightening, complicated and confusing illness. Many patients will have already seen family and friends die of AIDS and will be experiencing some combination of fear, denial and hope about being in treatment. Many patients have misconceptions about HIV disease as well as about treatment, and education is likely to dispel many myths and misunderstandings. Education is also one of the key tools to help HIV-infected individuals gain control over their lives by helping them understand their illness and what they can do to stay healthy. A patient who understands



his/her illness is more likely to stay in treatment and to be adherent to complicated treatments. Appropriate education can also help reduce the transmission of HIV to others.

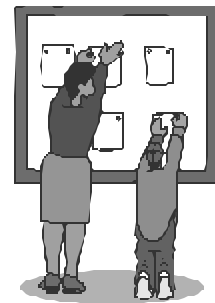
How should patient education be done and who should do it?

Effective patient education occurs at many levels and will involve most, if not all, members of the health care team. The range of topics to be covered and the many different approaches to patient education are often best coordinated by a nurse or social worker who takes overall responsibility for this area.

Patients need to have a basic understanding of HIV and its complications. Some of this information can be conveyed through written pamphlets, posters or videos available in the waiting room. There is a lot to understand and patients often appreciate written materials to take home. Simple written information sheets on HIV, on medications, or on what to do in case of an emergency can all be helpful.

The primary care provider can be a powerful educator, but may have limited time. Certainly, providers should carefully educate patients about any new medications. Patients should always be told why a medication is being prescribed, how it should be taken, and what side effects to watch for.

The role of the primary provider can be complemented by a nurse educator, a peer educator, or by “Living with HIV” support groups run by another member of the care team. Frequent home visits can be instrumental, as patients may feel more comfortable asking some questions in their home environment. Basic information about HIV and its treatment can be reinforced and more detailed and personalized information about diet, hygiene and prevention can be discussed at more length. The more specific and personalized the advice given about a healthy lifestyle, the more likely the advice is to be effective.



How often should patient education be done?

Written and visual information should always be available and offered to patients. If the patient is literate s/he should be given a written sheet about any new medication when it is prescribed. If not, diagrams and pictures will be helpful.

All newly diagnosed patients should have a preliminary assessment by the team member responsible for health education. This session

should determine gaps in the patient's understanding of HIV or misconceptions s/he may have. There should also be a discussion of how to maintain good health and avoid complications.

Many patients may have difficulty retaining information about HIV, and repetition is absolutely critical. Patients may feel uncomfortable asking their questions to medical personnel and may respond better to "Living with HIV" groups run by peer educators. These groups complement other forms of psychosocial and adherence support and should be run frequently so that patients have the opportunity to review the information they have been given and to ask outstanding questions.

Ongoing patient education should be tailored to disease stage and individual needs.

What is community outreach and mobilization?

Complex health interventions that are isolated from their communities and contexts will not succeed. HIV/AIDS care is no exception, involving as it does new care paradigms, complex family dynamics, sexual behavior, behavior change, and stigma. HIV/AIDS care programs will always benefit from informed community involvement and support. Community outreach is a formal attempt to increase public awareness of and support for care programs; community mobilization supports the active input and participation of stakeholders and the creation of a shared vision. Outreach work may also aim to bring tailored health education to specific populations with the aim of changing knowledge or behaviors.

Why is community outreach and mobilization important?

Community outreach and mobilization enables health care workers to:

- Maximize the success of the intervention by establishing a supportive environment that enables program participants to be fully engaged in the program and to achieve maximum adherence.
- Mobilize supportive resources within the community (e.g. providers, and services).
- Enhance the scope of the intervention by educating people other than those directly involved in the program.
- Develop a forum for dispute resolution by maintaining open lines of communication with community stakeholders.
- Identify beliefs, ideas and new trends within the community that may affect individual patient behavior.
- Educate the community about the program and increase enrollment of new patients.
- Reinforce health education messages provided within the clinic setting.
- Reduce the rate of patient drop-out and encourage retention and commitment to services.
- Find out more about the community's perception of the project and suggest ways to improve the program and increase access.

Who should be involved in community outreach and mobilization?

Every member of the MTCT-Plus program can contribute to outreach and mobilization. The support of administrative and clinical leadership is necessary, but involvement of health educators, counselors and the patients themselves will be essential.

The involvement of the local community is likely to vary from setting to setting. In some places, well-established organizations may be prepared to partner with MTCT-Plus. In others the program may need to facilitate the development of community-based activities, and linkages to local community and religious groups as well as larger national associations. Outreach projects program should employ staff who will be perceived as peers by the target population.

How should community outreach and mobilization be done?

- Local NGOs are critical to success and expansion. Links to these important stakeholders are a priority and can be created and/or maintained by attending relevant meetings, ensuring that accurate and timely information is conveyed, and attending to ongoing communication and collegial relationships.
- Traditional healthcare providers play a prominent role in the lives of most patients and should be included in any community outreach strategy.
- Community Advisory Boards provide an indispensable forum and a critical bridge to the community; we strongly recommend the creation of CABs if none exist. While each CAB is different, successful strategies include:
 - Mixed membership. Treatment specialists, program experts, patients, patient advocates and community stakeholders (e.g. NGOs, community leaders, religious leaders, traditional healers, and teachers) should all be involved.
 - Careful participant selection: Participants should be stakeholders but also “ambassadors” to the community and vigilant reviewers of the program;
 - Limited size: Successful CABs are often composed of eight to twelve members.
 - Organization: As with any committee, regularly scheduled meetings, agendas and minutes are invaluable.
- Simple and precise descriptions of the program in the local language(s) in the form of flyers or other written literature should be available and accessible.

- Home visits for patients enable interaction with the family, household, and broader community.
- Patient education and peer support are ways to empower patients themselves to extend the intervention as they discuss what they have learned with members of the community.
- Periodic visits by program staff to local community meetings, while not appropriate in all settings, provide additional linkages. When program staff attends social groups, church, school, or professional meetings and report back to the program team, these “ambassadorial” visits provide clear channels of communication.
- Ongoing communication with stakeholders is optimal. The community should be aware of updates, changes, and progress and given the opportunity to provide feedback as the program incorporates suggestions and modifies procedures.

What are some examples of outreach and mobilization programs?

- *Outreach that targets those involved directly and indirectly in implementing the project.* This might include staff from the organizations hosting the MTCT-Plus project as well as staff from organizations in the area involved in care and services utilized by people with HIV. Target populations may also include social clubs, support groups, traditional healers, local town/village/city leadership, and local churches. The goal of this outreach is to increase community awareness and support for the project.
- *Outreach that targets people with HIV or at risk of HIV who are not yet enrolled in the project.* The availability of treatment may encourage uptake of voluntary testing and counseling services, pMTCT services and requests for care. The more members of the local community understand about the project, the more likely they are to value and support it. Familiarity will also help to counter any inaccurate perceptions about the project.
- *Outreach targeting people with HIV enrolled in the program.* The goal of this type of outreach is to reinforce health education messages provided within the clinic setting. Outreach targeting patients enrolled in the program is vital to support adherence, attendance, and continuity of care. Because an outreach worker can soon become labeled as an “AIDS worker,” and the individual they are visiting therefore assumed to have HIV infection, it is important to ensure that confidentiality issues are carefully considered and that patients give permission for outreach visits in advance.

Care of the Caregiver

Caregiver support is a vital component of HIV/AIDS care programs such as MTCT-Plus. Other chapters have discussed the importance of providing support to household members and lay caretakers of those with HIV/AIDS. This chapter will focus on MTCT-Plus staff.

Psychosocial support:

It is difficult to quantify the stress felt by health care workers during epidemics. Like other members of society, they are surrounded by death and loss. Exhaustion, fear, and “burn out” are constant risks, and the possibility of occupational exposure creates the potential for personal, professional, and ethical conflicts.

In one fictional account of a plague without treatment or cure, Camus describes the impact on clinicians:

“No resource was left to him but to tighten the stranglehold on his feelings and harden his heart protectively. For he knew that this was the only way of carrying on...

... and in this feeling that his heart had slowly closed in on itself, the doctor found a solace, his only solace, for the almost unendurable burden of his days...”⁹

The introduction of care and treatment for families with HIV/AIDS will provide hope for clinicians as well as patients, giving them the tools to fight the disease and empowering them to act. It may also introduce additional stress, as issues of rationing, triage, and access to antiretroviral therapy come to the fore.

Psychosocial support is as important for site staff as it is for patients, and can take many forms. It is hard to overstate the importance of a sense of teamwork, camaraderie, and mutual respect among caregivers. Acknowledgment of the difficulties at hand, incorporation of suggestions made by team members, and periodic feedback regarding progress are simple yet valuable interventions.

The regular team meetings described in chapter 1 can be a valuable forum in which to share thoughts about patients and programs. They are also an opportunity to reinforce individual team member

⁹ Camus, Albert. *La Peste*. Librairie Gallimard, Paris, 1947.

achievements, to provide support and sympathy, and to exchange suggestions and coping strategies.

Continuing education and skills training further empower caregivers, provide opportunities for networking and teambuilding, and can provide a valuable “time out” of the clinical setting.

Site staff may occasionally benefit from more formal psychosocial support, including supportive counseling and psychiatric care such as the treatment of depression. The availability of such care will, of course, vary from site to site; maintaining and disseminating an inventory of local resources for staff is strongly recommended.

Universal precautions:

Each member of the MTCT-Plus site staff, from clinicians to janitors, should be aware of the importance of “universal” or “standard” precautions to prevent transmission of blood-borne pathogens such as HIV. These guidelines, supported by the CDC and WHO, recommend that all individuals in the health care settings should be treated as though they are infectious. Limiting exposures by supporting safe practices – using barriers such as gloves (and gowns, where appropriate) avoiding reuse or recapping of needles, safely disposing of needles and other “sharps” – and educating staff regarding what to do in the case of an exposure are critical pieces of any HIV care program.

Post-exposure prophylaxis:

Each member of the MTCT-Plus team should be familiar with the management of exposures to potentially infectious materials. While procedures may be slightly different from site to site, each site should have formal protocols for HIV exposure that include:

- Reporting exposure
- Management of the exposure site
- Evaluation and testing
- Counseling
- Post-exposure prophylaxis if indicated
- Follow-up and monitoring

Care of HIV-infected site staff:

In settings where HIV is prevalent among young adults, there is every reason to assume that health care workers carry an equal risk of HIV-infection. Thus, it is likely that HIV-infected staff will be employed at each MTCT-Plus site, and it is program policy to support the care and treatment of these individuals. Eligibility criteria and specific treatment protocols will be determined by site directors.

Chapter Ten

Additional Resources

Zidovudine (AZT, ZDV, Retrovir®)

Zidovudine is a nucleoside analogue reverse transcriptase inhibitor; it is one of the oldest and most widely used antiretroviral agents.

Preparations:

Syrup 10 mg/ml, capsules 100 mg, tablets 300 mg

Tablets in combination with lamivudine: Combivir = 300 mg zidovudine + 150 mg lamivudine

Dosing and administration:

Adults: 300 mg twice daily

Children 6 weeks to 12 years: 240 mg/m² twice daily

Children > 12 years: 300 mg twice daily

Child with HIV encephalopathy: 300 mg/m²/ twice daily

Peak serum concentrations within 0.5-1.5 hours

Metabolized by liver, excreted by kidneys

May be taken with or without food

Adverse effects:

More common:

- Hematologic toxicity (including granulocytopenia and anemia)
- Headache (often transient)
- Malaise (often transient)

Less common:

- Myopathy
- Myositis
- Liver toxicity

Unusual (but severe):

- Lactic acidosis and severe hepatomegaly with steatosis

Major drug interactions:

Stavdine (D4T): antagonistic effect – stavdine lowers the intracellular concentration of ZDV

Other marrow suppressing agents

Pregnancy class: C

Prescribing zidovudine:

What to check:

- Is the patient anemic? ZDV should not be given to patients with grade 3 anemia (Hb \leq 6.9 g/dL). Other patients with anemia may require closer monitoring.
- Is the patient neutropenic? ZDV should not be given to patients with grade 3 neutropenia (ANC \leq 749 mm³ in adults, \leq 250 mm³ in children). Other patients with neutropenia may require closer monitoring.
- Is the patient thrombocytopenic? ZDV should not be given to patients with grade 3 thrombocytopenia (platelets $<$ 49,999 mm³). Other patients with thrombocytopenia may require closer monitoring.
- Does the patient have renal insufficiency? ZDV should not be given to adults with creatinine $>$ 3 x normal, to children $<$ 2 years with creatinine $>$ 1.2 mg/dL, or to children \geq 2 years with creatinine $>$ 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.

- Does the patient have hepatic insufficiency? ZDV should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.

Lamivudine (3TC, Epivir®)

Lamivudine is a nucleoside analogue reverse transcriptase inhibitor.

Preparations:

Syrup 10 mg/ml, tablets 150 mg

Tablets in combination with zidovudine: Combivir = 300 mg zidovudine + 150 mg lamivudine

Dosing and administration:

Adults: 150 mg twice daily

Child age 6 weeks to 12 years: 4 mg/kg/dose twice daily

Child 12 years and older or more than 60 kg: 150 mg twice daily

May be taken with or without food

Adverse effects: Generally very well tolerated

More common:

- Headache
- Fatigue
- Gastrointestinal symptoms (nausea, diarrhea, abdominal pain)
- Rash

Less common:

- Neutropenia
- Peripheral neuropathy
- Liver toxicity

Unusual (but severe):

- Lactic acidosis and severe hepatomegaly with steatosis
- Pancreatitis

Major drug interactions: None

Pregnancy class: C

Prescribing lamivudine:

What to check:

- Is the patient anemic? 3TC should not be given to patients with grade 3 anemia (Hb \leq 6.9 g/dL). Other patients with anemia may require closer monitoring.
- Is the patient neutropenic? 3TC should not be given to patients with grade 3 neutropenia (ANC \leq 749 mm³ in adults, \leq 250 mm³ in children). Other patients with neutropenia may require closer monitoring.
- Is the patient thrombocytopenic? 3TC should not be given to patients with grade 3 thrombocytopenia (platelets < 49,999 mm³). Other patients with thrombocytopenia may require closer monitoring.
- Does the patient have renal insufficiency? 3TC should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children \geq 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.
- Does the patient have hepatic insufficiency? 3TC should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.

Nevirapine (NVP, Viramune®)

Stavudine is a non-nucleoside analogue reverse transcriptase inhibitor.

Preparations:

Oral Solution: 10 mg/mL

Tablet: 200 mg

Dosing and administration: **Dose-escalation** decreases the risk of side effects

Adults: 200 mg once daily for 14 days, then 200 mg twice daily

Children 2 months to 8 years: 4 mg/kg once daily for 14 days, then 7 mg/kg twice daily

Children 8 years and older: 4 mg/kg once daily for 14 days, then 4 mg/kg twice daily. (Maximum dose = 200 mg twice daily)

May be taken with or without food

Adverse effects:

More common:

- Rash (usually mild-moderate but can be severe, including Stevens-Johnson syndrome)
- Gastrointestinal side effects, particularly nausea
- Headache

Less common:

- Severe liver toxicity
- Fever
- Granulocytopenia

Major drug interactions:

- Rifampin (do not co-administer)
- Ketoconazole
- Estrogen-based oral contraceptives (alternative methods of birth control should be used)
- Protease inhibitors (dose-adjustment often required)
- Methadone

Pregnancy class: C

Prescribing nevirapine:

What to check:

- Does the patient have renal insufficiency? NVP should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children ≥ 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.
- Does the patient have hepatic insufficiency? NVP should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.
- Is the patient taking oral contraceptives? Alternate birth control should be prescribed.
- Is the patient being treated for TB? NVP and Rifampin should not be co-administered.

Stavudine (D4T, Zerit®)

Stavudine is a nucleoside analogue reverse transcriptase inhibitor.

Preparations:

Oral Solution: 1mg/cc (*must* be refrigerated)

Capsules: 15, 20, 30, 40 mg

Dosing and administration:

Adults \geq 60 kg: 40 mg twice daily

Adults < 60 kg: 30 mg twice daily

Child under 30 kg: 1 mg/kg twice daily

Child from 30 to 60 kg: 30 mg twice daily

Child more than 60 kg: 40 mg twice daily

May be taken with or without food

Adverse effects:

More common:

- Gastrointestinal side effects
- Headache
- Rash

Less common:

- Peripheral neuropathy (particularly when given in combination with didanosine)
- Liver toxicity
- Oral ulcers

Unusual (but severe):

- Lactic acidosis and severe hepatomegaly with steatosis
- Pancreatitis

Major drug interactions:

Should not be given with zidovudine – antagonistic effect

Pregnancy class: C

Prescribing stavudine:

What to check:

- Does the patient have renal insufficiency? D4T should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children \geq 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.
- Does the patient have hepatic insufficiency? D4T should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.
- Is the patient taking ZDV? D4T and ZDV should not be co-administered.
- If the patient is an infant and is taking oral solution, check to make sure refrigeration is available.

Didanosine (DDI, Videx®)

Didanosine is a nucleoside analogue reverse transcriptase inhibitor.

Preparations:

Chewable tablets 25, 50, 100, 150, 200 mg

Dosing and administration:

Adults \geq 60 kg: 400 mg once daily

Adults < 60 kg: 250 mg once daily

Child age 6 weeks to 8 months: 100 mg/m² twice daily

Child 8 months and older: 120 mg/m² twice daily

Must be taken on an empty stomach (one hour before or two hours after a meal).

Adverse effects:

More common:

- Gastrointestinal side effects (nausea, vomiting, abdominal pain, diarrhea)

Less common:

- Peripheral neuropathy (particularly when given in combination with stavudine)
- Liver toxicity

Unusual (but severe):

- Lactic acidosis and severe hepatomegaly with steatosis
- Pancreatitis

Major drug interactions:

Decrease in absorption of tetracycline and fluoroquinolone antibiotics (administer two hours before or two hours after DDI)

Possible decrease in absorption of ketoconazole, itraconazole and dapsone (administer two hours before or two hours after DDI)

Pregnancy class: B

Prescribing didanosine:

What to check:

- Does the patient have renal insufficiency? DDI should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children \geq 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.
- Does the patient have hepatic insufficiency? DDI should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.
- Does the patient have a history of pancreatitis or current heavy alcohol use? Prescribe with caution – may need closer monitoring.

Abacavir (ABC, Ziagen®)

Abacavir is a nucleoside analogue reverse transcriptase inhibitor

Preparations:

Oral Solution: 20 mg/mL

Tablet: 300 mg

Dosing and administration:

Adults: 300 mg twice daily

No efficacy data available for infants < 6 months: use is not recommended

Children 6 months to 16 years: 8mg/kg twice daily

May be taken with or without food

Adverse effects:

More common:

- Gastrointestinal side effects
- Headache
- Rash

Less common:

- Hypersensitivity reaction: Approximately 5% of adults and children develop a hypersensitivity reaction to ABC. It is essential that providers and patients know what to expect and what to do if this syndrome occurs.
 - Symptoms include: fever, GI symptoms (rash, fatigue, nausea, vomiting, diarrhea) and respiratory symptoms (cough, pharyngitis, dyspnea)
 - Laboratory abnormalities include: elevated liver function, creatine phosphokinase, creatinine, lymphopenia
 - These symptoms and signs are nonspecific and there is no single diagnostic test for ABC hypersensitivity. However, **if the syndrome is suspected, ABC should be discontinued immediately and never restarted** as re-exposure can be fatal

Unusual (but severe):

- Liver toxicity
- Pancreatitis

Major drug interactions:

None

Pregnancy class: C

Prescribing abacavir:

What to check:

- Does the patient have renal insufficiency? ABC should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children ≥ 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.

- Does the patient have hepatic insufficiency? ABC should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.

Efavirenz (EFV, Sustiva®)

Efavirenz is a non-nucleoside analogue reverse transcriptase inhibitor.

Preparations:

Capsules: 50mg, 100mg, 200mg, 600mg

Dosing and administration:

Adults: 600 mg once daily

May be taken with or without food, but should not be taken with high-fat meals.
Bed-time dosing is recommended to minimize neuropsychiatric side effects.

Adverse effects:

More common:

- Rash (usually mild-moderate but can be severe)
- Neuropsychiatric symptoms (somnolence, insomnia, confusion, nightmares): usually transient

Less common:

- Liver toxicity
- Hyperlipidemia

Major drug interactions:

- Protease inhibitors (dose-adjustment often required)
- Sedative-hypnotics: benzodiazepines
- Phenobarbital, phenytoin clarithromycin

Pregnancy class: *Teratogenic. Should not be given to women who are or may become pregnant.*

Prescribing efavirenz:

What to check:

- Does the patient have renal insufficiency? EFV should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children ≥ 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.
- Does the patient have hepatic insufficiency? EFV should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.
- Is the patient a woman of child-bearing age? EFV should not be prescribed to women who are or who may become pregnant. If continued access to effective contraception is in question, EFV should be avoided. Women taking EFV should be asked about potential pregnancy at every clinical visit.

Nelfinavir (NLF, Viracept®)

Nelfinavir is a protease inhibitor.

Preparations:

Tablets: 250 mg

Dosing and administration:

Adults: 1250 mg (5 tablets) twice daily

Children 1-12 months: 75 mg/kg twice daily

Children > 12 months: 55-65 mg/kg twice daily

Children > 20 kg: 1250 mg twice daily

NB: always round up the dose for infants and children

Take with a meal or a light snack.

Adverse effects:

More common:

- Diarrhea

Less common:

- Liver toxicity
- Rash
- Nausea
- Abdominal pain

Rare:

- Hyperglycemia, diabetes
- Hyperlipidemia

Major drug interactions:

- Antihistamines
- Non-nucleoside reverse transcriptase inhibitors (NVP, EFV)
- Phenobarbital, phenytoin, clarithromycin
- Estrogen-containing oral contraceptives (reduces efficacy – alternative birth control methods should be used)
- Rifampin (do not use concurrently)

Pregnancy class: B

Prescribing nelfinavir:

What to check:

- Does the patient have renal insufficiency? NLF should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children ≥ 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.
- Does the patient have hepatic insufficiency? NLF should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.
- Is the patient using estrogen-containing oral contraceptives? Prescribe alternate method of birth control.
- Is the patient being treated for TB? NLF should not be co-administered with rifampin.

Lopinavir/Ritonavir (LPV/r, Kaletra®)

Lopinavir and ritonavir are protease inhibitors. In this formulation, ritonavir acts as a pharmacokinetic enhancer of lopinavir, inhibiting lopinavir metabolism and increasing concentration.

Preparations:

Oral Solution: 80 mg/ml lopinavir + 20 mg/ml ritonavir

Capsules: 133.3 mg lopinavir + 33.3 mg ritonavir

Dosing and administration:

Adults: 3 capsules twice daily

Children 7- 15 kg: 12 mg/kg (LPV) twice daily

Child from 15- 40 kg: 10 mg/kg (LPV) twice daily

Child more than 40 kg: 400 mg (LPV) twice daily (3 capsules or 5mL twice daily)

Take with food.

Should be refrigerated, although may be kept at room temperature (< 77F, 25C) for two months

Adverse effects:

More common:

- Diarrhea
- Headache
- Nausea/ vomiting
- Fatigue
- Hyperlipidemia

Less common:

- Liver toxicity
- Rash

Rare:

- Hyperglycemia, diabetes
- Hyperlipidemia
- Pancreatitis

Major drug interactions:

- Non-nucleoside reverse transcriptase inhibitors (NVP, EFV): will require dose-adjustments
- Antihistamines
- Phenobarbital, phenytoin, carbamazepine
- Dexamethasone
- Estrogen-containing oral contraceptives (reduces efficacy – alternative birth control methods should be used)
- Rifampin, rifabutin (do not use concurrently without expert assistance)
- Calcium channel blockers
- Ketoconazole, itraconazole

Pregnancy class: B

Prescribing Lopinavir/ritonavir:

What to check:

- Does the patient have renal insufficiency? LPV/r should not be given to adults with creatinine > 3 x normal, to children < 2 years with creatinine > 1.2 mg/dL, or to children \geq 2 years with creatinine > 1.7 mg/dL. Other patients with renal insufficiency may require closer monitoring.
- Does the patient have hepatic insufficiency? LPV/r should not be given to adults with LFTs > 5x normal or to children with LFTs > 10x normal. Other patients with hepatic insufficiency may require closer monitoring.
- Is the patient using estrogen-containing oral contraceptives? Prescribe alternate method of birth control.
- Is the patient being treated for TB? LPV/r should not be co-administered with rifampin.

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