

## Managing Complications of HIV Infection in HIV-Infected Children on Antiretroviral Therapy

Children with HIV infection are now surviving into adolescence and young adulthood. The dramatic advances in treatment have also added to the complexity in management of what is now a chronic, though still life-limiting, illness. The optimum management of children with HIV infection will require attention to areas beyond antiretroviral therapy. The initial sections of this supplement on management of complications include guidance on nutrition and pain management, both important in promoting optimal growth and health in children with HIV.

- [Pediatric HIV Pain Management](#)

- [Nutritional Care in Pediatric HIV/AIDS](#)

### PEDIATRIC HIV PAIN MANAGEMENT

#### Background

Pain in children with HIV-1/AIDS is a multifactorial, biologically complex problem associated with diminished quality of life and increased mortality [1]. Pain elimination, amelioration, and (when appropriate) palliative administration of analgesics and sedatives are essential aspects of the care of every HIV-infected child.

#### Sources of Pain

Pain may be the result of neural inflammation, systemic manifestations of AIDS such as cardiomyopathy and myositis, toxicities and adverse drug reactions, invasive secondary infections, discomfort related to invasive procedures, or morbidity associated with non-AIDS – related conditions, including dental disease and tension or migraine headache. The specific etiologies of some painful conditions, such as recurrent abdominal pain or neuropathic pain, are often difficult to ascertain and challenging to manage.

Stressors, which may amplify pain, include living with a chronic disease; poor nutritional status; weight loss and failure to thrive; the potential or actual loss of a parent, caregiver, or sibling; and clinical depression in a parent or the child [2], as well as the normal anxieties and traumas of childhood.

#### Prevalence and Implications of Pain

Almost 60% of HIV-infected pediatric outpatients followed at the National Cancer Institute of NIH reported pain that affected their daily lives [3]. Interestingly, only 55% of caregivers described their children as having pain, a finding not unlike that describing inadequate pediatric pain recognition and treatment by health care providers [4].

Approximately 20% of 985 HIV-infected children in Pediatric AIDS Clinical Trials Group study 219 (PACTG 219) reported having pain [1].

Younger children and girls have reported pain more frequently than older children and boys, with gastrointestinal and limb complaints predominating [3]. The gender difference was confirmed by PACTG 219 data, which calculated the odds of a report of pain for females as 66% greater than for males.

Although the implications of poorly or incompletely controlled pain are not yet fully known, PACTG 219 data analysis found a significant association between report of pain and mortality: patients with pain were more than 5 times more likely to die than those who did not report pain. Pain was also associated with lower CD4 cell percentages and more severe immunosuppression.

#### Pain Assessment

Optimal pain management is based upon a thorough understanding of the child's current medical, neurologic, developmental, psychosocial, and pharmacologic status. Change from baseline or from previous pain-free status is particularly important to characterize.

Quantification of pain is accomplished using standard pediatric visual analogue pain scales and rating systems [5] modified to account for age, developmental status, severity of illness, and cultural factors [6]. Complex cases may require application of several measures, including observational and behavioral assessment, self-report, and functional performance. Functional performance can be measured using the General Health Assessment for Children (GHAC) [7] or the Functional Status II (R) [FSII(R)], which was developed specifically to assess functional status in children with chronic disease and has been shown to correlate with other markers of disease severity in an outpatient population of children with HIV-1 infection [8].

## Principles of Pain Management

Successful management of pain in HIV-infected children begins with aggressive efforts to diagnose and treat, as best as possible, underlying medical conditions, such as opportunistic infections, pancreatitis, and HIV viremia (though the contribution of lowered viral load to improving response to analgesics and supportive care remains unclear). Decisions concerning the goals and specific strategies for pain management are best made with the informed participation of the child (as possible), his or her family and caretakers, and health care providers with a thorough understanding of the patient's overall condition and preferences. Consultation with a pediatric pain specialist should be considered early in the course of treatment.

## Pain Management Strategies

Pain management in HIV-infected children should combine nonpharmacologic and pharmacologic therapies. Nonpharmacologic interventions, listed in [Table 1](#), should be considered for all pediatric patients. Pharmacologic interventions are listed in [Table 2](#). [Table 3](#) lists representative drugs in each medication category. Reassessment after intervention is essential to assure that pain is adequately controlled.

## Initiation of Pharmacologic Support: Important Considerations

Analgesic therapy should be initiated after patient assessment and concurrent with aggressive efforts to

diagnose and treat the underlying pathological conditions causing pain. Standard doses for most analgesics can be found in pediatric reference texts, such as the Harriet Lane Handbook, and in institutional prescribing guidelines. However, dosing of pain medications must be individualized, appreciating that the effective analgesic dose for children with some painful conditions may not have been identified through randomized controlled studies. This is especially true for the tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and anticonvulsant medications with analgesic effect. Anecdotal clinical experience with adjunctive analgesics suggests that the analgesic dose may be lower than the dose identified for the medication's primary indication. For this reason, treatment of pain with these medications may be initiated at low doses, perhaps first at bedtime, then increased as tolerated and necessary, thereby potentially minimizing untoward effects and improving compliance.

Opioids, sedatives, anticonvulsants, and various anesthetic agents undergo hepatic metabolism by conjugation or oxidation, primarily through the CYP450 system using isoenzymes CYP3A4 and CYP2D6. Caution must be used when these agents are used in conjunction with HIV protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), particularly when adding analgesics and sedatives with a narrow therapeutic index in situations where microsomal isoenzyme activity is inhibited. The simultaneous use of these medications may result in increased plasma drug concentrations, toxicity, or overdose for the pain medications; additionally, hepatic isoenzyme changes induced by the pain medications can also alter PI or NNRTI pharmacokinetics. Because detailed information concerning CYP450 isoform metabolism is lacking for many analgesics and sedatives, conservative dosing is recommended, titrated according to individual patient response. The CYP450 system has considerable polymorphism [9], and pharmacokinetic responses to analgesics are influenced by variations in gene frequency and expression between ethnic groups, as well as between individuals within a population [10]. For additional information regarding potential drug interactions between pain medications and antiretroviral medications, see:

<http://hivinsite.ucsf.edu/arvdb?page=ar-00-02>  
and <http://www.hiv-druginteractions.org/>

Meperidine (Demerol) should be used only with considerable caution, or not at all. This opioid undergoes hepatic metabolism to normeperidine via the CYP450 enzyme CYP2D6, allowing for possible alteration of PI pharmacokinetics and accumulation of either meperidine or normeperidine.

Normeperidine is a potent CNS stimulant with associated toxicities of seizures, paradoxical hyperalgesia, agitation, insomnia, and myoclonus. Meperidine is vagolytic, increasing heart rate, and therefore has the potential to accelerate pre-existing tachycardias into unstable rhythms.

Clonidine, an  $\alpha_2$  adrenergic agonist, is analgesic in and of itself, but also has great utility in blocking escalating narcotic tolerance and facilitating weaning from chronic opioid dependence, such as might be encountered after prolonged intensive care. Oral dosing is possible, but missed doses may result in breakthrough pain and rebound hypertension. Transdermal administration has the benefit of excellent steady-state blood levels and ease of use. Clonidine should not be prescribed for children with significant clinical depression, hypotension, bradycardia, or unresolved sepsis syndrome. The transdermal patch must be removed immediately in hypotensive, septic patients.

The N-methyl-D-aspartate (NMDA) receptor on neurons is excitatory. Excessive activation of the NMDA receptor occurs in the presence of gp120, a protein in the outer envelope of HIV particles [11], and contributes to chronic pain, escalating narcotic and sedative requirements, severe insomnia, and discomfort during narcotic weaning. Dextromethorphan and ketamine block the NMDA receptor, but have substantial untoward effects that limit their use. Specifically, high doses of dextromethorphan cause ataxia and dizziness. Ketamine induces a hallucinogenic state, which may be recalled, but more importantly has been anecdotally associated with severe cardiac rhythm disturbances in children with advanced HIV-1/AIDS (see also the discussion below, under “[Analgesia and Sedation for Painful Procedures](#)”).

The neurotransmitter gamma-aminobutyric acid (GABA) is a CNS depressant. GABA agonists include diazepam, lorazepam, midazolam, and baclofen. Indications for administration include insomnia or the need for sedation, induction of amnesia, and reduction of spasticity. The GABA agonists’ sedating and respiratory depressant effects are increased with co-administration of opioids.

## Special Considerations

### Opioids

For the majority of children in moderate to severe pain, opioids provide excellent analgesia with a wide margin of safety, although individual response will vary according to the type of pain being addressed, prior opioid exposure, genetic polymorphism, and drug interactions.

Dose schedules and routes of administration must be individualized and breakthrough pain addressed. If breakthrough pain occurs, one or more additional doses of narcotics (“rescue” dose) may be required. A rescue dose of narcotics may be calculated as approximately 5 to 10% of the daily opioid requirement [12]. If multiple “rescue” doses are required to control pain, then consideration should be given to increasing the total daily narcotic dose by 5 to 10%, titrated to patient response.

Concurrent administration of opioid drugs with GABA agonists,  $\alpha_2$  adrenergic agonists, anticonvulsants with analgesic effect, or tricyclic or SSRI therapy may improve analgesia beyond that achieved with narcotics alone.

Excessive sedation may occur at opioid doses sufficient for analgesia. Small morning doses of dextroamphetamine or methylphenidate improve daytime alertness [13]. Itching and constipation may be limited by using very small amounts of naloxone (Narcan) or by selecting an alternative opioid, such as methadone. Nausea and vomiting may resolve by changing narcotics.

Incomplete cross-tolerance may complicate efforts to switch opioid-tolerant patients from other narcotics to methadone. Patients previously maintained on high-dose morphine, Dilaudid, or fentanyl should NOT be started on full equi-analgesic doses of methadone because of increased risk of respiratory depression. Starting methadone at 20% of the opioid-naive equipotent dose has been recommended [14]. PIs (most notably lopinavir) and the NNRTIs nevirapine and efavirenz induce the metabolism of methadone and may lead to withdrawal symptoms [15]. Dosing of methadone may need to be increased with concurrent use of these medications. Conversely, when PIs or NNRTIs are discontinued, methadone toxicity may develop.

NMDA receptor antagonism by methadone makes it the long-term opioid of choice for patients with neuropathic pain refractory to management with non-narcotics. NMDA receptor blockade may also limit narcotic tolerance and the need for continuous dose escalation [16]. These positive effects must be weighed against preliminary observations in adults suggesting that methadone administration may be associated with lower CD4 cell percentage and CD4/CD8 cell ratios [17], as well as *in vitro* data suggesting an increase in HIV replication in human blood monocyte-derived macrophages exposed to methadone [18].

Health care providers may hesitate to prescribe narcotics for HIV-infected pediatric outpatients, especially patients cared for by parents with a past or current history of narcotic abuse. This is a difficult, multidisciplinary challenge for all involved, but one that must be met to assure patient comfort and safety.

### ***Weaning From Long-Term Opioid and Benzodiazepine Support***

Weaning from high-dose narcotics and sedatives, such as intravenous fentanyl, methadone, morphine, or lorazepam, is often necessary in patients following discharge from the intensive care unit. Alpha<sub>2</sub> adrenergic agonist modulation of sympathetic responses with oral or transdermal clonidine, if not otherwise contraindicated, significantly facilitates narcotic withdrawal while maintaining patient comfort. Transition to methadone from continuous fentanyl infusion or transition to fentanyl patch, morphine, or MS Contin are additional options. Transition from midazolam to lorazepam, which can be given orally or IV, is recommended if midazolam weaning is poorly tolerated or impractical.

All patients should be weaned with a goal of minimizing physiological stress. A 5 to 10% wean of the daily methadone dose might be tolerated as frequently as every other to every third day, alternating with a 5 to 10% lorazepam wean. After the patient is off narcotics and comfortable for at least 3 to 5 days, clonidine can be weaned, then withdrawn under medical supervision.

Frequent assessment for symptoms of withdrawal is needed during this process, and the weaning rate should be slowed for patients unable to tolerate the

initial plan. To date, there is no widely accepted, validated withdrawal scoring system for children beyond infancy. Reassessment by physical examination and interview of caretakers should therefore be repeated in an effort to improve sensitivity and response to individual patients.

### ***Paradoxical Hyperalgesia, Insomnia, and Escalating Narcotic and Sedative Requirements***

Escalating drug requirements, paradoxical hyperalgesia, and CNS excitation are seen in HIV-infected children undergoing prolonged intensive and invasive care and in patients with extreme neuropathic or severe escalating chronic pain. Treatment begins with recognition of the patient at risk for development of these problems. Alpha<sub>2</sub> adrenergic agonist and NMDA receptor antagonist medications should be initiated as soon as physiologically possible. Clonidine, small doses of dextromethorphan, methadone substitution for other narcotics, and lorazepam substitution for midazolam are the most often-used strategies. Elective rotation of narcotics has also been recommended for chronically maintained cancer pain patients, but published pediatric experience for children with HIV/AIDS is lacking. Regional anesthesia may be considered for intractable localized pain.

### ***Analgesia and Sedation for Painful Procedures***

Prevention of pain and stress during potentially painful procedures must be a priority for every patient at every encounter with health care providers. Non-pharmacological interventions ([Table 1](#)) combined with topical and local anesthesia should be routine for venipunctures, injections, etc. Discomfort from lumbar puncture and more invasive procedures may require intravenous sedation.

The American Academy of Pediatrics standards for conscious sedation [19] should be followed, as well as the Joint Commission for Accreditation of Health Care Organizations (JCAHO)-mandated protocols of the specific institution. Fentanyl combined with midazolam is an often-used combination for pediatric conscious sedation by non-anesthesia personnel. Increased midazolam levels have been seen with concurrent use of some PIs (ritonavir and saquinavir) and NNRTIs (delavirdine and efavirenz) due to inhibition of CYP3A4. While not studied, all

agents metabolized by the CYP450 enzyme CYP3A4 may have this consequence; if used, close monitoring is recommended. Close monitoring is also recommended with fentanyl use in patients on PI or NNRTI therapy, as profound respiratory and cardiac depression may occur if conventional loading doses are used. Sedation should be initiated at substantially lower than conventional doses, titrated to patient response, and appropriately monitored until the patient is fully awake and baseline vital signs have returned.

Some patients will have little apparent response to the conventional doses of fentanyl and midazolam specified in conscious sedation guidelines. Consultation with the anesthesia service is warranted for these children, even if the hospital's guidelines allow ketamine administration in children inadequately sedated with fentanyl or midazolam.

Ketamine use in pediatric HIV/AIDS is controversial. In children with advanced disease, use of ketamine carries the risk of sensitization to endogenous or exogenously administered catecholamines, cardiac rhythm disturbances, electrolyte abnormalities, and even cardiac arrest. In addition, acute respiratory bronchospasm occurred in HIV-infected children undergoing bronchoscopy with this agent [20]. Propofol administration by qualified anesthesia personnel may be the safest alternative, but each patient must be individually assessed.

### ***Peripheral Neuropathy***

Peripheral neuropathy has been documented in HIV-infected children [21] but, in general, appears to be less painful and extensive than the distal sensory neuropathy documented in HIV-infected adults. Lidoderm patch application to the painful area, in combination with one or more of the other medications listed in [Table 2](#), and discontinuation of medications precipitating the peripheral neuropathy constitute standard treatment. Neurological consultation is recommended.

### ***Movement Disorders***

Movement disorders in HIV-infected children can result in considerable pain and immobility. Extrapyrimal dysfunction may improve with levodopa [22]. Consultation with neurological, physical medicine rehabilitation, and anesthesia specialists is recommended.

### ***Neuropathic and Abdominal Pain***

Neuropathic pain is defined as pain persisting or intensifying independent of ongoing tissue injury or inflammation [23]. Multiple therapeutic interventions, as listed in [Table 2](#), may be needed to control neuropathic pain. Because resistance to pure mu opioids is frequently present, combinations of non-narcotic medications are prescribed, targeting specific and overlapping pain-perpetuating pathways in the peripheral and central nervous system. Consultation with a pain specialist should be initiated as soon as the diagnosis of neuropathic pain is considered to facilitate timely therapeutic efforts and minimize pain escalation.

Pancreatitis, erosive and difficult-to-treat infections of the gastrointestinal tract, gall bladder and biliary tract disease, malabsorption syndromes, tumors, and adverse side effects of many drugs are among the sources of persistent abdominal pain in children with HIV/AIDS. A diagnosis of neuropathic abdominal pain is made only after all other sources of discomfort are excluded by thorough investigation; even then, practitioners should be extremely cautious attributing the pain to neuropathic causes.

The treatment of neuropathic abdominal pain can be quite difficult. Palliative celiac plexus block may be considered if pain is refractory to the therapies listed in [Table 2](#) [24].

### ***Conclusion***

Despite advances in the treatment and control of HIV-1 infection in children, for some patients with advanced disease, pain may complicate medical management and diminish quality of life. Because pain in this population is often complex, optimal management will best be achieved through the coordinated collaboration of multiple specialists, including anesthesiologists, pain specialists, social workers, nursing staff, and others with distinct areas of expertise in the areas outlined in this supplement. The guidelines and recommendations presented here offer a framework for pain management by a multidisciplinary team.

**Table 1. Nonpharmacologic Pain Management Interventions**

- Relaxation techniques and behavior modifications
- Environmental management, including play opportunities, music, scheduled (rather than random) medical and nursing interventions, and structured opportunities for sleep and rest
- Gentle handling and supportive positioning
- Nutritional support, adequate hydration, and electrolyte replacement
- Optimized tissue perfusion and oxygenation
- Transcutaneous electrical stimulation (TENS), gentle massage, whirlpool baths, physical therapy
- Electrical or needle stimulation of acupuncture meridians, when available and provided by HIV-knowledgeable practitioners

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**Table 2. Treatment of Specific Pain Syndromes and Presentations**

Indication	Goals of Treatment	Pharmacologic Approach
Localized or regional pain due to tissue damage, inflammation, invasive infection, tumor	Decrease inflammation and limit tissue damage. Interrupt pain transmission. Analgesia.	Topical analgesics; local anesthetics; capsaicin; topical steroids; NSAIDs; opioids; regional anesthesia
Myopathic process	Resolve underlying process. Decrease inflammation.	Stop offending medications; maximize antiretroviral therapy; NSAIDs; consider systemic steroids
Systemic inflammatory process	Decrease inflammation and stress.	NSAIDs; consider corticosteroids
Difficult-to-manage withdrawal from opioids or GABA agonists	Minimize stress responses. Allow time for weaning at physiologically tolerable rate.	Alpha <sub>2</sub> adrenergic agonist; opioid with NMDA blocking effect; long acting GABA agonist
Encephalopathic process with extreme irritability, insomnia	Improve sleep. Decrease CNS inflammation.	GABA agonists; antiretroviral therapy; NMDA receptor complex blockade; consider anticonvulsant with analgesic effect
Escalating syndrome of narcotic and anesthetic resistance	Blunt escalation. Preserve opioid responsiveness.	Alpha <sub>2</sub> adrenergic agonist; opioids with NMDA blocking effect; NMDA receptor blockade
Peripheral neuropathy	Limit inflammation and progression.	Lidoderm patch; tricyclic or SSRI therapy; anticonvulsants with analgesic effect; alpha <sub>2</sub> adrenergic agonist; stop offending medications
Movement disorder with rigidity, spasticity; difficult or painful positioning for activities of daily living	Improve comfort and mobility.	GABA agonists; L-dopa; regional anesthesia
Neuropathic pain syndromes	Modulation of CNS excitatory and sympathetic responses. Decrease stress. Analgesia. Mobilization.	Tricyclic or SSRI; alpha <sub>2</sub> adrenergic agonist; NSAIDs; anticonvulsants with analgesic effect; NMDA receptor antagonist; opioids with NMDA receptor blocking effect; systemic lidocaine/mexiletine; regional anesthesia
Respiratory distress or congestive heart failure with low cardiac output	Appropriate level of sedation +/- analgesia to tolerate medical interventions, support comfort.	Oxygen; morphine and other narcotics; GABA agonists

NSAIDs: non-steroidal anti-inflammatory drugs. CNS: central nervous system. SSRI: selective serotonin reuptake inhibitor.

NMDA: N-methyl-D-aspartate. GABA: gamma-aminobutyric acid.

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**Table 3. Representative Medications by Class**

<b>Drug Category</b>	<b>Representative Medications</b>	<b>Comments</b>
GABA agonists	Baclofen, midazolam, lorazepam, diazepam	Baclofen is often used for muscle spasms. It stimulates the GABA-B receptors, inhibiting the release of the excitatory amino acids glutamate and aspartate. It has a beneficial action on reflex muscle contractions and provides marked relief from painful spasm, automatism, and clonus.
Mu opioid agonists	Fentanyl, morphine	Respiratory monitoring required. Transdermal fentanyl should not be used for episodic pain, as it has a slow onset and long duration.
NMDA receptor antagonists	Dextromethorphan, ketamine	Ketamine may increase heart rate, blood pressure, cardiac output, and intracranial and intraocular pressure. Ketamine may also cause hallucinations. Dextromethorphan may cause ataxia, dizziness.
Mixed agonists	Methadone (mu opioid and NMDA effects); tramadol (Ultram) (mu opioid and norepinephrine, serotonin effects)	Methadone is available in liquid form for young children. Marked variability in clearance requires close monitoring to avoid excessive sedation. Pediatric dosage, safety, and duration of administration have yet to be determined for tramadol.
Alpha <sub>2</sub> adrenergic agonist	Clonidine	Modulates sympathetic responses. Opioid-sparing effect. Transdermal dosing available. Remove if patient is hypotensive, septic, or depressed.
Tricyclic antidepressants	Amitriptyline, nortriptyline	Blocks NMDA receptors. Releases endogenous opioids. Clearance is variable. Some patients may benefit from additional morning dose. Plasma concentrations may be helpful to guide higher doses.
SSRIs	Paroxetine (Paxil), sertraline (Zoloft), fluoxetine (Prozac)	Mechanism of antinociceptive effect unknown, but may involve both central opioid and the serotonergic pathways.
Anticonvulsants with analgesic effect	Gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax)	Gabapentin modulates the action of calcium channels, increases GABA synthesis, and reduces glutamate. Used in the treatment of neuropathic pain. Excreted unchanged in the urine. Monitor topiramate for drug interactions with antiretroviral agents.
NSAIDs	Ibuprofen, celecoxib (Celebrex), diclofenac (Voltaren), acetaminophen (Tylenol), ketorolac (Toradol)	Causes inhibition of cyclooxygenase-2 (COX-2). Few class differences. Ketorolac is the primary parenteral NSAID available in the U.S., but may cause hepatic dysfunction and GI bleeding.

GABA: gamma-aminobutyric acid. NMDA: N-methyl-D-aspartate. SSRI: selective serotonin reuptake inhibitor. NSAIDs: non-steroidal anti-inflammatory drugs.



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## NUTRITIONAL CARE IN PEDIATRIC HIV/AIDS

### Key Points:

- Malnutrition, infection, and immune system function have reciprocal negative interactions, which can lead to significant morbidity and mortality.
- Nutritional concerns in HIV-infected children include both growth failure and being at-risk for being overweight or overweight.
- Nutrition monitoring, assessment, and intervention are integral to the care of HIV-infected children.
- Further data on vitamin and mineral deficiencies in HIV-infected children are needed.
- Current evidence suggests that children and youth with HIV infection require the Dietary Reference Intake for vitamins and minerals from a balanced diet. For HIV-infected children and adolescents who cannot consume adequate vitamins and minerals in a well-balanced diet, a standard daily multivitamin and mineral supplement, at concentrations approximating recommended Dietary Reference Intakes, might be considered.
- Over-supplementation of vitamins and minerals (“megavitamin therapy”) and non-standardized nutritional supplements should be avoided.

### Background

Worldwide, malnutrition is the most common cause of immunodeficiency, and is a leading contributor to childhood mortality. Nutrition and immune function are inextricably linked. Macro- and micro-nutrient deficiency compromise host immunity, and at the same time impaired nutrient absorption and increased excretion of nutrients caused by HIV infection and HIV-associated opportunistic infections further compromise nutritional status, creating a vicious cycle [1-5].

Malnutrition can be multifactorial in etiology; a convenient manner in which to classify its causes are to group conditions into those associated with decreased intake, increased output, or increased

metabolic demand (Figure 1). Causes of a decreased or inadequate intake include anorexia or nausea due to medications or infections such as esophagitis or oral ulcers; poor nutritional habits; depression; and inability to afford food. Causes of increased output include vomiting or diarrhea, which may lead to loss of nutrients and electrolytes. Finally, the increased metabolic demand from fever or HIV viral replication may accentuate malnutrition.

Historically, poor growth has been a common outcome for children perinatally infected with HIV, as manifested by poor weight gain and linear growth, weight loss, wasting syndrome and height stunting [6]. Cumulatively, among the 9,441 children with AIDS reported to CDC through 2005, 19% had wasting syndrome [7]. Poor length growth in HIV-infected children was predictive of mortality independent of age, viral load, and CD4 count in the PACTG 152 study [8]. Insufficient weight gain also was identified as an independent risk factor for death in children receiving zidovudine in PACTG 043.

Since the advent of HAART, growth outcomes have improved [9-20]. Paradoxically, the recognized epidemic of obesity in healthy children and youth in the United States, as well as metabolic adverse effects of antiretroviral therapy, has complicated our ability to understand the effect of HIV infection on weight status and growth [21-23]. The prevalence of being overweight among children and youth with perinatally acquired and behaviorally acquired HIV infection and whether they differ significantly, is not known. However, the Reaching for Excellence in Adolescent Care and Health Cohort study (REACH) of HIV-infected and uninfected youth (13–23 years of age) showed that of 264 youth with HIV acquired through sexual activity or intravenous drug use, 49.4% were overweight or obese. For HIV-infected youth with CD4 counts >500 cells/mL, the prevalence rate for being overweight was similar to that in uninfected youth. The prevalence of being overweight or obese decreased in the lower CD4 T-cell strata, although only obesity rates among females showed a significant decrease [24]. Thus, although some perinatally HIV-infected children still experience wasting syndrome and growth problems, almost

half of youth with behaviorally acquired HIV infection are at-risk for being overweight or are overweight.

Micronutrient deficiencies of zinc, vitamin B12, vitamin E, vitamin A, and beta-carotene have been associated with an accelerated disease progression of HIV infection to AIDS in adults and children, but an exact cause and effect relationship is difficult to ascertain [2, 25-27]. The REACH study data suggest that compared to HIV-negative matched controls, HIV-infected adolescents and youth may have greater vitamin requirements due to increased oxidative stress [28], yet consume inadequate quantities of vitamins and minerals [24, 29]. The Nutrition for Healthy Living cohort, a longitudinal study of 881 HIV-infected adults from 1995–2005, evaluated serum micronutrient levels of adults on HAART and concluded that zinc deficiency remains common and higher zinc levels may be associated with improved virologic control [30]. Findings from this study also indicate both wasting and metabolic syndrome remain important problems among adults with HIV infection [31].

One of the few controlled trials of micronutrient supplementation in HIV-infected individuals in the United States involved a small number of adults randomized to receive a placebo or a combined multivitamin-antioxidant preparation during a 12-month period [32]. Subjects receiving the multivitamin-antioxidant supplement experienced a 24% greater mean increase in absolute CD4 count, although there were no significant changes in plasma HIV RNA concentrations, other metabolic parameters, or distal symmetric polyneuropathy [32]. In contrast, controlled vitamin and mineral supplementation trials in the developing world have shown confusing and sometimes conflicting results, possibly because of differences in the degree of initial micronutrient deficiency in the population being studied, differences in the supplements administered, and interactions among the micronutrients themselves [3]. For example, maternal vitamin and mineral supplementation has led to better birth outcomes in terms of increased birth weight, improved infant growth, and decreased infant diarrhea and malaria rates; however, in some, but not all, studies it has also increased mother-to-child transmission rates and child mortality [33-39]. Two randomized, controlled trials of multivitamin and mineral supplementation to HIV-infected children in developing countries reported beneficial effects in decreasing mortality and increasing

growth, but the validity of these results for nutritionally replete children in industrialized countries is uncertain [40, 41].

In summary, further research on requirements, intake, and clinically appropriate methods of measurement for both macro- and micronutrients are sorely required [3-5, 27, 42-47]. At present, there is insufficient evidence to recommend or refute individual micronutrient supplementation for HIV-infected individuals in the United States [42, 43, 45, 46], and conflicting information from international settings [3-5]. HIV-infected children and adolescents in the United States may still experience growth failure and wasting syndrome, but new and emerging nutrition problems need to be addressed, such as obesity, metabolic syndrome, osteopenia, dyslipidemia, and lipodystrophy [48-53]. These metabolic problems, which can be accentuated by antiretroviral therapy, are described in the [Adverse Drug Effects](#) supplement to these guidelines.

## Monitoring and Assessment

The diverse nutrition and growth-related issues in children with HIV infection underscore the need for careful nutritional assessment and targeted intervention. Anthropometric, dietary, and medical data are reliable indicators for nutritional risk [54-56]. In children, appropriate growth rates for age and gender are a sign of good health. When a nutritional risk has been identified, a nutritional assessment may help determine the factors that may be affecting growth and nutritional status.

The components of routine nutritional monitoring and assessment ([Table 1](#)) should include:

- Serial measurement and recording of height, weight, and (until 3 years of age) head circumference
- Assessment of diet and physical activity, including use of dietary supplement and herbal therapies
- Review of medical data including food allergies.
- Psychosocial assessment

Additional evaluations are indicated in certain circumstances ([Table 2](#)):

- Body composition studies
- Laboratory testing

Growth should be monitored regularly (every 3 months) and anthropometrics equipment (scales, height stadiometer) should be calibrated routinely. Height, weight, head circumference, and BMI (2–20 years of age) should be plotted accurately on the 2000 CDC growth curves (<http://www.cdc.gov/growthcharts>). Growth faltering on the CDC growth curves warrants further investigation and consideration of referral to a nutritionist experienced in the care of pediatric HIV patients. Unexplained growth failure may warrant a referral to an endocrinologist since neuroendocrine abnormalities can affect growth. Body composition studies can indicate changes in lean and fat tissue.

AIDS wasting, which involves weight loss and/or slowed weight gain velocity, is the only specifically defined growth abnormality included in the AIDS case definition for HIV-infected children. Wasting syndrome is defined by the CDC as: persistent weight loss >10% of baseline OR downward crossing of 2 percentile lines on the CDC weight-for-age chart in a child  $\geq 1$  year of age; OR the combination of <5th percentile on weight-for-height chart on 2 consecutive measurements  $\geq 30$  days apart, PLUS either chronic diarrhea (i.e.,  $\geq 2$  stools per day for 30 days) OR documented intermittent or consistent fever for  $\geq 30$  days. None of these signs and symptoms should be due to a definable concurrent illness other than HIV infection when making the diagnosis of wasting syndrome.

Abnormalities in linear growth, such as decreased height or height velocity, are not included in the CDC Pediatric HIV Classification system, although many studies indicate that poor linear growth is indicative of advanced disease, and that the rate of growth is inversely related to the level of HIV replication [57]. Linear growth should be monitored regularly until a child reaches his or her adult height.

Assessment also includes evaluation of clinical symptoms such as pain, gastrointestinal losses, and acute or chronic illness. Physical activity, food availability, and food and fluid intake should also be assessed [54, 56]. A careful dietary intake assessment should be obtained if clinical signs and symptoms of vitamin or micronutrient deficiencies are present.

## Treatment of Nutritional Deficiency and Growth Failure

Numerous studies have shown that HAART, including regimens containing PIs, improve both linear and ponderal growth, with few exceptions [9-20, 58]. Adequate antiretroviral control is likely the most critical determinant of growth in the majority of HIV-infected children and adolescents in the United States.

Treatment of additional causes of inadequate or decreased intake (including, but not limited to, medication- or acute illness-induced anorexia and nausea, conditions such as esophagitis or oral ulcers, depression, and inability to afford food, should be undertaken as clinically indicated, especially for those children with growth failure despite adequate retroviral control.

Rarely, a child with poor linear growth will require an endocrine evaluation for the possible use of growth hormone, testosterone, thyroid hormone replacement, or other therapies that address endocrine changes associated with HIV disease and the aging perinatally HIV-infected child; however, such hormone deficiencies represent the exception rather than the rule [59, 60].

## Oral Macronutrient Supplementation and Dietary Management

The use of enteral supplements may help achieve the desired maintenance and catch-up caloric intake in children with HIV infection [56]. Specific examples of oral enteral supplements for children ages 1–10 years include: PediaSure, Kindercal, Nutren Jr (isotonic, intact supplements), and Peptamen Jr (a semi-elemental product for children with malabsorption). In some situations, children with significant food allergies and eczema may benefit from nutritional support with an amino acid-based formula such as Neocate, EO28, or Elecare. Older children and adolescents usually tolerate supplements formulated for adults such as Sustacal, Nutren, Ensure, etc. Children with HIV infection may develop lactose intolerance earlier than predicted by genetic predisposition and lactose-free diets are preferred for these children. For children with significant chronic diarrhea without an identifiable cause, lactose-free diets, lactase supplements, soluble fiber, medium chain triglycerides, or protein hydrolysate formulas may be better absorbed.

### **Oral Micronutrient Supplementation**

HIV-infected children and adolescents, who cannot consume adequate vitamins and minerals in a well-balanced diet might benefit from the regular intake of a multivitamin with minerals containing nutrients at levels near the USA/Canada Dietary Reference Intakes (DRI) [46]. However, over-supplementation (“megavitamin therapy”) or the use of nonstandardized nutritional or herbal supplements should be avoided. Several micronutrients (particularly vitamins A and D, iron, and possibly vitamins E and C, beta-carotene, zinc, and selenium) appear to have a “U-shaped” curve of risk vs. dose, causing harm in both deficiency and excess [3, 5, 27, 45, 61, 62].

### **Tube Feeding**

Nasogastric or gastrostomy feedings may be very helpful if oral dietary management fails to promote weight gain [63-65]. Gastrostomy tube buttons can be safely placed endoscopically, provide access for enteral support, and do not restrict normal activities. The use of gastrostomy tube buttons can result in improved quality of life in children with nutritional disturbances, and ease medication administration when adherence to oral medication is problematic because of palatability. The gastrostomy button can be removed and the stoma allowed to heal when the child is older and can adhere to tablet-containing regimens.

### **Parenteral Feeding**

Total parenteral nutrition (TPN) should be restricted to those children who are unable to tolerate sufficient enteral nutrition to maintain appropriate growth parameters, because of its expense and the risks of indwelling catheters [66]. Even after TPN has been initiated, efforts should be made to continue enteral nutrition to maximize the functional integrity of the gastrointestinal tract, provide oral gratification, and gain the psychosocial benefits of a defined meal.

### **Appetite Stimulants**

There have been few pediatric studies of the use of appetite stimulants (e.g., non-specific agents such as corticosteroids or cyproheptadine, or specific ones

such as megestrol acetate [Megace] or dronabinol). Megestrol provides weight gain primarily by increasing fat mass rather than lean body mass, and weight gain was not sustained when the medication was terminated [67, 68]. In addition, both published and unpublished reports of serious adrenal suppression resulting from megestrol use have lessened enthusiasm for this agent among many experts [69]. Dronabinol has had some salient effects in adults and older adolescents but psychological side effects such as drowsiness, confusion, hallucinations, and the potential for dependency that may limit its use in children.

### **Growth Hormone**

In HIV-infected adults, recombinant human growth hormone therapy results in increased body weight and lean body mass [70, 71]. Growth hormone therapy is a potentially beneficial therapeutic intervention in HIV-infected children or adolescents who have decreased linear growth or diminished lean body mass, but data are conflicting as to whether sustained improvement occurs with its use [59, 60, 72].

### **Prevention, Weight Management, and Hyperlipidemia**

A child’s diet should meet the U.S. Dietary Reference Intakes (DRI) recommendations for age including adequate dietary calcium and vitamin D intake for age [DRIs available at the Institute of Medicine Food and Nutrition Board web page, <http://www.iom.edu/CMS/3788/4574.aspx>]. General nutrition guidelines for asymptomatic children with HIV include the provision of a varied, nutrient-dense diet, adequate in fiber, to maintain healthy weight for age, gender, and height. Specific macronutrient and micronutrient requirements associated with HIV infection itself are not known. Caloric and protein intake should promote normal growth velocity and lean body mass [44, 56, 73, 74].

Specific weight management guidelines for children with HIV have not been published; it is likely that those published for HIV-uninfected children will serve HIV-infected children as well [74]. Children who are classified as being at-risk of being overweight (>85% on BMI curve) or overweight (>95% on BMI curve) may benefit from being evaluated by a nutritionist and beginning a pediatric weight management protocol.

Dietary treatment guidelines for hyperlipidemia are also limited due to lack of research in children with HIV infection. However, dietary recommendations made for the general pediatric population can be applied to children with HIV to prevent long-term complications such as diabetes or cardiovascular disease. General pediatric recommendations from the American Academy of Pediatrics and the American Heart Association are that children between the ages of 2–5 years gradually adopt a diet containing 30% or less of calories from fat while consuming enough calories to support growth and development. It is also recommended that <10% of calories be from saturated fat and that cholesterol intake be <300

mg/day. When decreasing a child’s total fat intake, more emphasis should be placed on providing adequate calories and nutrients for normal physical activity, growth, and development [73, 74]. Children with hypertriglyceridemia should try to decrease consumption of concentrated sweets in addition to eating a low fat diet. The treatment options, as well as recommendations for management of hyperlipidemia, hyperglycemia and insulin resistance, fat maldistribution, and body habitus changes, are addressed further in the [Adverse Drug Events](#) supplement to these guidelines.

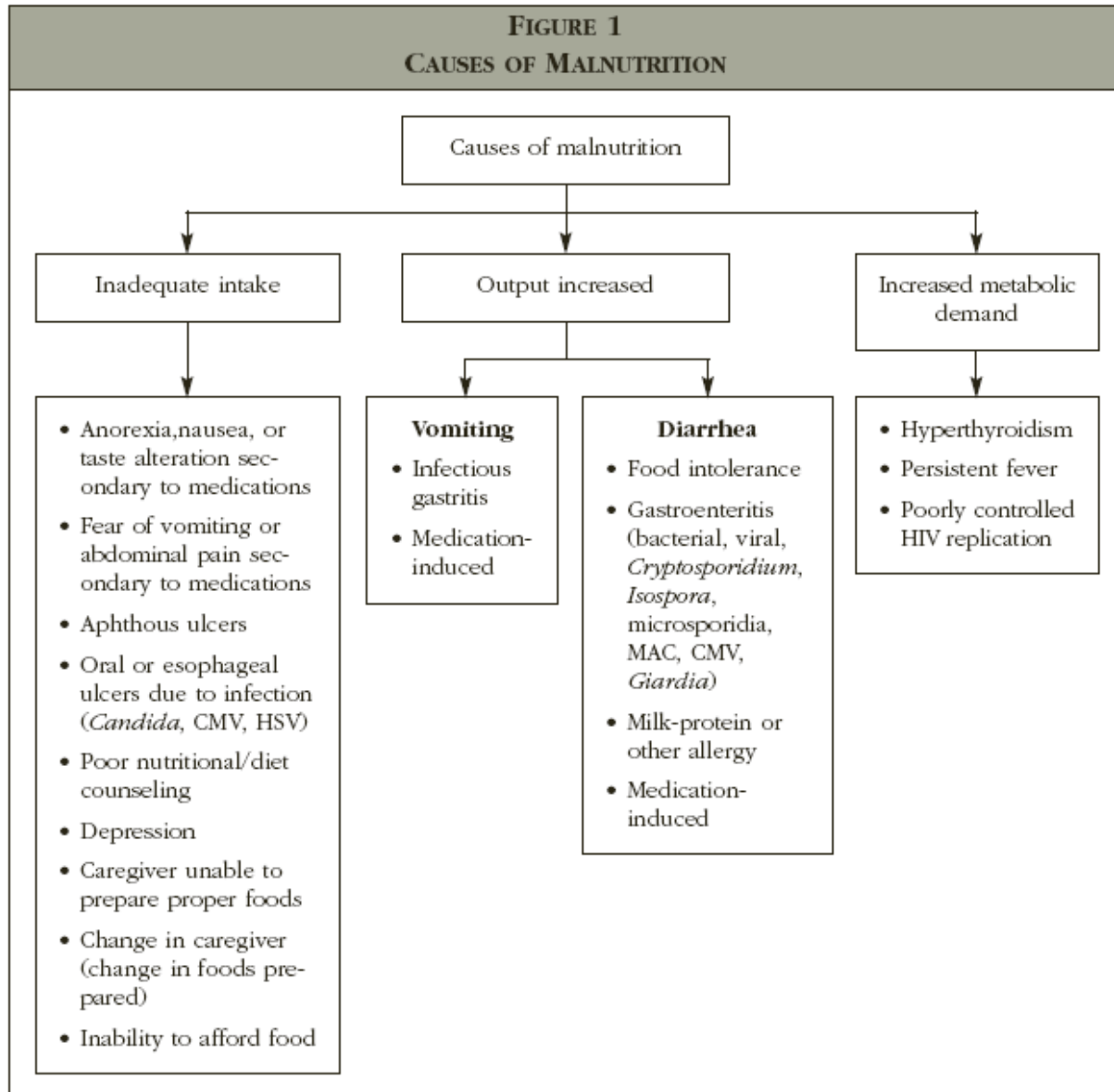
**Table 1: Routine Monitoring**

Components of Nutrition Assessment	Frequency
<ul style="list-style-type: none"> <li>• Simple anthropometrics – Height (Ht), Weight (Wt), and Head circumference (HC).</li> <li>• Diet history including assessment of food availability and use of supplements and herbal therapies</li> <li>• Physical activity assessment</li> <li>• Other information that may influence nutritional status— e.g., presence of new opportunistic infections, food allergies, oral lesions, developmental delay</li> <li>• Psychosocial assessment: behavioral issues, food availability, parental health and ability to prepare food</li> </ul>	<ul style="list-style-type: none"> <li>• Wt and Ht and HC at each visit or every 3 months (HC until 3 years). Record serial measurements on growth curves.</li> <li>• On initial assessment and at each visit or every 3 months</li> <li>• On initial assessment and at each visit or every 3 months</li> <li>• On initial assessment and at each visit or every 3 months</li> <li>• On initial assessment and annually; more often if poor growth noted without other explanation</li> </ul>

**Table 2: Supplemental Monitoring as Clinically Indicated**

Components of Nutrition Assessment	Frequency
<ul style="list-style-type: none"> <li>• Albumin, prealbumin, hemoglobin, hematocrit, transferrin saturation, glucose, triglycerides and cholesterol</li> <li>• Bone mineralization assessment, e.g., DEXA scan and bone age; serum vitamin D (25-OH vitamin D)</li> <li>• Specialized anthropometrics: skinfold measurements, bioelectrical impedance</li> </ul>	<ul style="list-style-type: none"> <li>• See <b>Hyperlipidemia*</b> and <b>Hyperglycemia and Insulin Resistance*</b> for frequency in monitoring lipids and glucose</li> <li>• As indicated; see <b>Osteopenia*</b></li> <li>• For research assessment of subcutaneous fat or protein stores; if available clinically, serial skinfold measurements may help follow muscle mass estimates</li> </ul>

\* See [Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection – Supplement III: Adverse Drug Effects](#). Available at <http://aidsinfo.nih.gov>.



Source: New York State Department of Health AIDS Institute. *Growth, Body Composition, and Metabolism*. In: *Guidelines for the Care of Children and Adolescents with HIV Infection*. November, 2007 revision. Available at <http://hivguidelines.org/GuidelineDocuments/p-nutr.pdf>

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