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/frames.htm?drug/drg_main.htm**.

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. $Alpha_2$ 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. $Alpha_2$ 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 saqinavir) 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. Extrapyramidal 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.	$Alpha_2$ 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.	$Alpha_2$ 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; $alpha_2$ 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; $alpha_2$ 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

Drug Category	Representative Medications	Comments
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.
$Alpha_2$ 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 serotoninergic 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.

References:

1. Gaughan DM, Hughes MD, Seage GR 3rd, et al. The prevalence of pain in pediatric human immunodeficiency virus/acquired immunodeficiency syndrome as reported by participants in the Pediatric Late Outcomes Study (PACTG 219). *Pediatrics*, 2002. 109(6):1144-52.
2. Pilowsky DJ, Knowlton AR, Latkin CA, et al. Children of injection drug users: impact of parental HIV status, AIDS, and depression. *J Urban Health*, 2001. 78(2):327-39.
3. Hirschfeld S, Moss H, Dragisic K, et al. Pain in pediatric human immunodeficiency virus infection: incidence and characteristics in a single-institution pilot study. *Pediatrics*, 1996. 98(3 Pt 1):449-52.
4. Schechter NL. The undertreatment of pain in children: an overview. *Pediatr Clin North Am*, 1989. 36(4):781-94.
5. McGrath PA. Behavioral Measures of Pain. Measurement of Pain in Infants and Children. In: Progress in Pain Research and Management, 1998. 10:83-102.
6. Hester NO, Foster RL, Jordan-Marsh M, Ely E, et al. Putting pain measurement into clinical practice. Measurement of Pain in Infants and Children. In: Progress in Pain Research and Management, Finley and Mcgrath, ed. *IASP Press, Seattle*, 1998. 10:179-98.
7. Gortmaker S, Lenderking W, Clark C, et al. Development and Use of a Pediatric Quality of Life Questionnaire in AIDS Clinical Trials: reliability and validity of the General Health Assessment for Children. In: Measuring Health-related Quality of Life in Children and Adolescents: Implications for Research and Practice. Mahwah, NJ: Lawrence Erlbaum Associates. 1998:219-35.
8. Missmer SA, Spiegelman D, Gorbach SL, Miller TL. Predictors of change in the functional status of children with human immunodeficiency virus infection. *Pediatrics*, 2000. 106(2):E24.
9. Ingelman-Sundberg M, Oscarson M, McLellan RA. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. *Trends Pharmacol Sci*, 1999. 20(8):342-9.
10. Rogers JF, Nafziger AN, Bertino JS Jr. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450-metabolized drugs. *Am J Med*, 2002. 113(9):746-50.
11. Barks JD, Liu XH, Sun R, Silverstein FS. gp120, a human immunodeficiency virus-1 coat protein, augments excitotoxic hippocampal injury in perinatal rats. *Neuroscience*, 1997. 76(2):397-409.
12. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. *Drugs*, 1996. 51(5):713-37.
13. Yee JD, Berde CB. Dextroamphetamine or methylphenidate as adjuvants to opioid analgesia for adolescents with cancer. *J Pain Symptom Manage*, 1994. 9(2):122-5.
14. Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Support Care Cancer*, 2001. 9(2):73-83.
15. McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clin Infect Dis*, 2003. 37(4):476-82.
16. Trujillo KA, Akil H. Inhibition of opiate tolerance by non-competitive N-methyl-D-aspartate receptor antagonists. *Brain Res*, 1994. 633(1-2):178-88.
17. Carballo-Dieguez A, Sahs J, Goetz R, et al. The effect of methadone on immunological parameters among HIV-positive and HIV-negative drug users. *Am J Drug Alcohol Abuse*, 1994. 20(3):317-29.
18. Li Y, Wang X, Tian S, et al. Methadone enhances human immunodeficiency virus infection of human immune cells. *J Infect Dis*, 2002. 185(1):118-22.
19. American Academy of Pediatrics Committee on Drugs: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. *Pediatrics*, 1992. 89(6 Pt 1):1110-5.
20. Slonim AD, Ognibene FP. Amnestic agents in pediatric bronchoscopy. *Chest*, 1999. 116(6):1802-8.
21. Araujo AP, Nascimento OJ, Garcia OS. Distal sensory polyneuropathy in a cohort of HIV-infected children over five years of age. *Pediatrics*, 2000. 106(3):E35.
22. Mintz M, Tardieu M, Hoyt L, et al. Levodopa therapy improves motor function in HIV-infected children with extrapyramidal syndromes. *Neurology*, 1996. 47(6):1583-5.
23. Olsson G, Berde C. Neuropathic Pain in Children and Adolescents. In: Pain in Infants, Children and Adolescents. Neil L. Schecter, Charles B. Berde, Myron Yaster eds. Baltimore; Williams and Wilkins. 1993:473-89.
24. Tanelian D, Cousins MJ. Celiac plexus block following high-dose opiates for chronic noncancer pain in a four-year-old child. *J Pain Symptom Manage*, 1989. 4(2):82-5.

NUTRITIONAL CARE IN PEDIATRIC HIV/AIDS

Introduction

Worldwide, malnutrition is the most common cause of immunodeficiency and a leading contributor to childhood mortality. When malnutrition accompanies the immunodeficiency of HIV disease, immune function is further impaired. Micronutrient deficiency compromises host immunity, and the impaired nutrient absorption caused by HIV compromises nutritional status, creating a vicious cycle. Survival in patients with HIV disease, as well as in other chronic diseases such as cystic fibrosis and cancer, is directly related to nutritional status.

In children, growth is related to nutritional status, and appropriate growth rates for age and gender are a sign of good health. In HIV-infected children, immune status and viral load may be important in predicting growth outcomes *[1]*. Studies in the era of highly active antiretroviral therapy (HAART) have shown that regimens with protease inhibitors may improve growth outcomes *[2-9]*, although not all studies demonstrate an increase in weight and height *[10, 11]*. The largest cohort study showed modest improvement in growth *[12]*, while Nachman et al. showed a decline in height and weight z-scores despite control of viral replication with a ritonavir-containing regimen. However, it is difficult to compare findings in these studies because of differences in disease stage at time of enrollment. In addition, a study of 477 children enrolled in PACTG 152 concluded that height growth velocity was predictive of survival independent of age, viral load, and CD4 count *[13]*. The variability of growth outcomes in these studies emphasizes the need for continued research on the long-term effects of HAART on growth.

Clinicians in the United States report that they are spending less time on growth failure issues and more time on weight management and nutrition-related side effects of combination antiretroviral therapy, such as lipodystrophy, insulin resistance, and body habitus changes. These metabolic side effects in children with HIV have been described by several researchers, and are discussed at greater length in the "**Adverse Drug Effects**" supplement to these guidelines *[14-17]*.

It appears that the nutritional status and growth outcomes for children with HIV are still unpredictable. Despite clinician reports of less growth failure, the year 2000 CDC pediatric surveillance statistics show that wasting syndrome is reported in 18% of cases, a slight increase from the 1996 wasting syndrome statistic of 17%. This small increase in the prevalence of wasting syndrome between pre- and post-HAART therapy underscores the need for continued growth monitoring. Additionally, unpublished results of a study examining growth abnormalities in children with HIV show that of 200 children ages 2 to 20 years, 29% are overweight or at risk for overweight (BMI greater than 85%) and 10% are underweight (BMI less than 15%). Furthermore, 12% of these children fall below the fifth percentile on the CDC growth curve for height. These data indicate that there is a fairly high prevalence of children with HIV who are overweight, but there remain children who are underweight and stunted *[18]*. In summary, there are still children with HIV in the United States who experience growth failure and wasting syndrome, but there are also new and emerging nutrition problems, including overweight and obesity, as well as metabolic side effects of HAART.

Assessment

Growth should be monitored regularly and anthropometry equipment should be calibrated routinely. Height, weight, head circumference, and BMI (2 to 20 years) should be plotted accurately on the 2000 CDC growth curves (**http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm**). 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. Body composition studies can indicate changes in lean and fat tissue. Assessment also includes evaluation of clinical symptoms such as pain, gastrointestinal losses, or acute illness. Physical activity, food availability, and food and fluid intake should also be assessed *[19]*. Other assessment factors include biochemical parameters such as albumin, pre-albumin or transferrin, Hgb, Hct, cholesterol, triglycerides, SGOT (AST), SGPT (ALT), BUN, creatinine if on total parenteral nutrition (TPN), and viral load.

Compromised nutritional status and antioxidant deficiency begin early in the course of HIV-1

infection and may contribute to disease progression *[20]*. Diet should be assessed and clinical signs and symptoms of vitamin or micronutrient deficiencies should be sought in the child with delayed growth or malnutrition. Deficiencies of vitamins B12, E, A, and beta-carotene have been associated with an accelerated disease progression of HIV infection to AIDS in adults *[21]*. It is important that a deficiency of any of these nutrients be corrected. Iron, carnitine, and vitamin A deficiencies also impact immune function and should be evaluated in the HIV-infected child who is not achieving expected growth milestones or has other signs or symptoms of possible deficiency. Other micronutrient and vitamin deficiencies, such as in zinc, selenium, or vitamin D, are less common in children with HIV infection living in the United States. Although the etiology is unclear, children with HIV have compromised bone mineral accrual and evidence of calcium deficiency, and therefore may be at increased risk for osteoporosis and related complications *[22, 23]*. It is important to assess each child's diet and emphasize adequate dietary calcium and vitamin D intake for age.

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: 1) persistent weight loss > 10% of baseline OR 2) downward crossing of two percentile lines on the CDC weight-for-age chart in a child $\geq$1 year of age OR 3) < 5th percentile on weight-for-height chart on two consecutive measurements $\geq$30 days apart; PLUS 4) chronic diarrhea (i.e., at least two stools per day for 30 days) OR 5) documented intermittent or consistent fever for $\geq$30 days. These signs and symptoms should not be due to any concurrent illness other than HIV infection. Nutrition intervention should begin before a child has met the criteria for wasting syndrome.

No abnormalities in linear growth, such as decreased height or height velocity, are included in the CDC Pediatric HIV Classification system, although results of recent research indicate that poor linear growth is indicative of advanced disease. This research also found that the rate of growth is inversely related to the level of HIV replication *[24]*.

Prevention, Weight Management, and Hyperlipidemia

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, sex, and height. Specific macronutrient and micronutrient requirements engendered by HIV infection itself are not known. Calorie and protein intake should promote normal growth velocity and lean body mass.

The focus of nutritional care in pediatric HIV infection has been to prevent or treat growth failure. To date, weight management guidelines for children with HIV have not been published. However, children who are classified as at risk for overweight (> 85% on BMI curve) or who are overweight (> 95% on BMI curve) should be referred to a nutritionist and begin a pediatric weight management protocol to slow the rate of gain.

Treatment guidelines for hyperlipidemia are also limited due to lack of research in children with HIV. 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. Dietary change is difficult due to complex cultural, psychosocial, and environmental aspects of food access and eating. Nevertheless, patients and families should be encouraged to eat foods with cardio-protective benefits and to participate in safe and enjoyable physical activity.

General pediatric recommendations from the American Academy of Pediatrics and the American Heart Association are that children between the ages of 2 and 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 less than 10% of calories be from saturated fat and that cholesterol intake be less than 300 mg per 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 *[25]*. Children with hypertriglyceridemia should try to decrease consumption of concentrated sweets in addition to eating a low fat diet. Lipid lowering agents used in adults for the treatment of hyperlipidemia have not been used extensively in pediatric HIV infection. The limited treatment options, as well as

recommendations for management of hyperglycemia and insulin resistance, fat maldistribution, and body habitus changes, are addressed further in the "**Adverse Drug Events**" supplement to these guidelines.

Treatment of Nutritional Deficiency and Growth Failure

Maximizing nutritional support and avoiding malnutrition in children with HIV infection is accomplished by treating underlying gastrointestinal or infectious diseases that interfere with nutrient intake and absorption or increase nutrient loss, as well as providing sufficient nutrition for catch-up growth. Some children with poor linear growth will require an endocrine evaluation for the possible use of growth hormone, thyroid hormone replacement, or other therapies that address endocrine changes associated with HIV disease and the aging perinatally HIV-infected child.

Oral Supplementation and Dietary Management

The goals outlined above can best be realized when nutritional services are provided in a proactive fashion, including the use of enteral supplements. These supplements should be initiated early to prevent sequelae of malnutrition while overall intake is increased through greater frequency of feedings, use of concentrated formulas and calorically dense foods, and provision of specific nutrients (vitamins and minerals). Specific examples of oral enteral supplements for children ages 1 to 10 years include: PediaSure, Kindercal, Nutren Jr (isotonic, intact supplements), and Peptamen Jr (a semi-elemental product for children with malabsorption). Older children and adolescents usually tolerate supplements formulated for adults. Children with HIV infection may develop lactose intolerance earlier than predicted by genetic predisposition. 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 and esophageal lesions can result in decreased caloric intake and can be managed by offering soft, warm, or cool foods; avoiding salty, acidic, or spicy foods; and applying topical anesthetic agents, such as Benadryl or lidocaine swishes, before meals, in addition to appropriate antimicrobial therapy.

Tube Feeding

Nasogastric or gastrostomy feedings are indicated if oral dietary management fails to promote weight gain. While children with higher CD4 cell counts have a better response to caloric supplementation, there are no data showing that intensive enteral nutrition support alone results in significant long-term nutritional improvement and growth *[26]*. Tube feedings increase fat mass, but may not significantly increase lean body mass *[27]*. Nasogastric tube feedings are painful, increase the possibility of sinusitis, and limit oral intake. Nevertheless, they can serve as an initial means to evaluate the potential efficacy of long-term gastrostomy tube feedings. Gastrostomy tube buttons can be safely placed endoscopically, provide access for enteral support, and do not restrict normal activities. Although invasive, tube feedings via gastrostomy tube buttons can result in improved quality of life in children with nutritional disturbances. Furthermore, many clinics are now recommending the use of gastrostomy buttons for medication administration when adherence to oral medication is a problem.

Parenteral Feeding

Total parenteral nutrition 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, TPN should be reserved for children with severe nutritional disturbances. Children with HIV infection, despite immunocompromise, may benefit from TPN and not experience an increase in catheter-associated infection *[28, 29]*. Even after TPN has been initiated, efforts should be made to continue enteral nutrition in some capacity to maximize the functional integrity of the gastrointestinal tract, provide oral gratification, and gain the psychosocial benefits of a defined meal. Long-term TPN is frequently continued throughout the course of illness for palliative care goals, in addition to addressing acute short-term nutritional support.

Appetite Stimulants and Growth Hormone

There have been few pediatric studies of the use of appetite stimulants. Some experts in the care of HIV-infected children have noted that there is an increase in appetite and weight gain in some children treated with non-specific (e.g., corticosteroids, cyproheptadine) or specific (e.g., megestrol acetate [Megace], dronabinol) appetite stimulants. Megace provides weight gain primarily by increasing fat mass *[30]*, but there have been no studies to date examining the effect of Megace on lean body mass in children. One study in children demonstrated significant weight gain at a dose of approximately 8 mg/kg/day, but body composition was not assessed and linear growth was not observed over significant time. Weight gain was not sustained or weight loss recurred when the medication was terminated *[31]*. Dronabinol has psychological side effects that may limit its use in children.

In HIV-infected adults, recombinant human growth hormone therapy results in increased body weight and lean body mass. 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. Increases in lean body mass, as observed in adults, should be expected to occur in the pediatric population. Growth hormone accelerates bone age commensurate with height, whereas other anabolic agents accelerate bone age out of proportion to linear growth. This aspect makes growth hormone particularly well-suited for use in children. Because of the expense of this therapeutic intervention, it should be initially evaluated in a controlled clinical trial *[32, 33]*.

Summary

Nutritional intervention should be integrated into the care plan of all HIV-exposed and -infected children. Because nutritional issues affect the entire family, therapy must be directed at the family unit to have an impact. Efficacy of medical treatment and quality of life are improved by finding a nutritional strategy that maintains appropriate growth and physical activity. These guidelines are intended to provide a basis for intervention, but implementation requires a multidisciplinary team composed of nurses, nutritionists, pharmacists, physicians, and social workers.

References:

1. Hilgartner MW, Donfield SM, Lynn HS, et al. The effect of plasma human immunodeficiency virus RNA and $CD4^+$ T lymphocytes on growth and measurements of hemophilic boys and adolescents. *Pediatrics*, 2001. 107(4):E56.
2. Miller TL, Mawn BE, Orav EJ, et al. The effect of protease inhibitor therapy on growth and body composition in human immunodeficiency virus type 1-infected children. *Pediatrics*, 2001. 107(5):E77.
3. Dreimane D, Nielsen K, Deveikis A, et al. Effect of protease inhibitors combined with standard antiretroviral therapy on linear growth and weight gain in human immunodeficiency virus type 1-infected children. *Pediatr Infect Dis J*, 2001. 20(3):315-6.
4. Verweel G, van Rossum AM, Hartwig NG, et al. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a sustained effect on growth. *Pediatrics*, 2002. 109(2):E25.
5. Melvin AJ, Mohan KM, Arcuino LA, et al. Clinical, virologic and immunologic responses of children with advanced human immunodeficiency virus type 1 disease treated with protease inhibitors. *Pediatr Infect Dis J*, 1997. 16(10):968-74.
6. Canani RB, Spagnuolo MI, Cirillo P, Guarino A. Ritonavir combination therapy restores intestinal function in children with advanced HIV disease. *J Acquir Immune Defic Syndr*, 1999. 21(4):307-12.
7. Nadal D, Steiner F, Cheseaux JJ, Rudin C. Ritonavir promotes increased growth in HIV-infected children. Paediatric AIDS Group of Switzerland. *AIDS*, 1998. 12(17):2356-7.
8. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics*, 1998. 102(1 Pt 1):101-9.
9. Wintergerst U, Hoffmann F, Solder B, et al. Comparison of two antiretroviral triple combinations including the protease inhibitor indinavir in children infected with human immunodeficiency virus. *Pediatr Infect Dis J*, 1998. 17(6):495-9.
10. Sung L, Lawrence CA, Dayneka NL, et al. Efficacy and tolerability of ritonavir in children with HIV infection: follow-up at 1 year (abstract). *Pediatr Res*, 1998. 43(2):158A. Abstract 918.
11. Thuret I, Michel G, Chambost H, et al. Combination antiretroviral therapy including ritonavir in children infected with human immunodeficiency. *AIDS*, 1999. 13(1):81-7.
12. Buchacz K, Cervia JS, Lindsey JC, et al. Impact of protease inhibitor-containing combination antiretroviral therapies on height and weight growth in HIV-infected children. *Pediatrics*, 2001. 108(4):72.

13. Chantry CJ, Byrd RS, Englund JA, et al. Growth, survival and viral load in symptomatic childhood human immunodeficiency virus infection. *Pediatr Infect Dis J*, 2003. 22(12):1033-9.
14. Amaya RA, Kozinetz CA, McMeans A, et al. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*, 2002. 21(5):405-10.
15. Lainka E, Oezbek S, Falck M, et al. Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. *Pediatrics*, 2002. 110(5):e56.
16. Arpadi SM, Cuff PA, Horlick M, et al. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ -lymphocyte count and CD4+ -lymphocyte percentage at baseline and use of protease inhibitors and stavudine. *J Acquir Immune Defic Syndr*, 2001. 27(1):30-4.
17. Brambilla P, Bricalli D, Sala N, et al. Highly active antiretroviral-treated HIV-infected children show fat distribution changes even in absence of lipodystrophy. *AIDS*, 2001. 15(18):2415-22.
18. Personal communication Pamela Rothpletz-Puglia. Preliminary results from a study entitled: The prevalence of growth abnormalities in children and youth with HIV infection: a need assessment. 2002.
19. Heller, Papathakis, Rothpletz-Puglia, HIV/AIDS Medical Nutrition Therapy Protocol for The Pediatric Population. Medical Nutrition Therapy Across the Continuum of Care. *The American Dietetic Association*, 1998.
20. Bogden JD, Kemp FW, Han S, et al. Status of selected nutrients and progression of human immunodeficiency virus type 1 infection. *Am J Clin Nutr*, 2000. 72(3):809-15.
21. Tang AM, Smit E. Selected vitamins in HIV infection: a review. *AIDS Patient Care STDS*, 1998. 12(4):263-73.
22. Arpadi SM, Horlick M, Thornton J, et al. Bone mineral content is lower in prepubertal HIV-infected children. *J Acquir Immune Defic Syndr*, 2002. 29(5):450-4.
23. O'Brien KO, Razavi M, Henderson RA, et al. Bone mineral content in girls perinatally infected with HIV. *Am J Clin Nutr*, 2001. 73(4):821-6.
24. Arpadi SM, Cuff PA, Kotler DP, et al. Growth velocity, fat-free mass and energy intake are inversely related to viral load in HIV-infected children. *J Nutr*, 2000. 130(10):2498-502.
25. Saltos E. Adapting the food guide pyramid for children: defining the target audience, USDA Cooperative State Research, Education and Extension. *Service Family Economics and Nutrition Review*, 1999. 12:3-17.
26. Miller TL, Awnetwant EL, Evans S, et al. Gastrostomy tube supplementation for HIV-infected children. *Pediatrics*, 1995. 96(4 Pt 1):696-702.
27. Henderson RA, Saavedra JM, Perman JA, et al. Effect of enteral tube feeding on growth of children with symptomatic human immunodeficiency virus infection. *J Pediatr Gastroenterol Nutr*, 1994. 18(4):429-34.
28. Futterman D, Connor EM, Boland M, Oleske J. Experience with central venous catheters in pediatric AIDS. Presented at the 5th International Conference on AIDS; Montreal, Canada. 1989.
29. Skiest DJ, Grant P, Keiser P. Nontunneled central venous catheters in patients with AIDS are associated with a low infection rate. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1998. 17(3):220-6.
30. Von Roenn JH, Armstrong D, Kotler DP, et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med*, 1994. 121(6):393-9.
31. Clarick RH, Hanekom WA, Yogev R, Chadwick EG. Megestrol acetate treatment of growth failure in children infected with human immunodeficiency virus. *Pediatrics*, 1997. 99(3):354-7.
32. Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. Serostim Study Group. *Ann Intern Med*, 1996. 125(11):873-82.
33. Krentz AJ, Koster FT, Crist DM, et al. Anthropometric, metabolic, and immunological effects of recombinant human growth hormone in AIDS and AIDS-related complex. *J Acquir Immune Defic Syndr*, 1993. 6(3):245-51.