**Objectives**

3. Review the effects of highly active antiretroviral therapy on growth in HIV-infected children.
4. Discuss changes in bone formation and pubertal development in HIV-infected children.
5. Review how to perform and interpret basic anthropometric measurements in children.

**Key Points**

1. Growth is an important indicator of a child’s health.
2. HIV infection can lead to growth problems.
3. Bone problems and abnormal pubertal development are more commonly seen in HIV-infected children than in noninfected children.
4. Health care providers who care for children with HIV should evaluate each child’s growth at every visit.
5. When growth problems are found, the health care provider should attempt to identify and treat the underlying cause of the problem.

World Health Organization (WHO) Core Competencies included the following:
- Provide growth monitoring—weight, middle-upper arm circumference, height
- Recognize human immunodeficiency virus (HIV)-related conditions (growth failure)
- Determine eligibility for antiretroviral therapy (WHO growth-related clinical staging)

**Overview**

Growth is an important indicator of a child’s health. Accurate measurements of weight, length/height, and head circumference are essential parts of the health evaluation of growing children. Children who are unhealthy tend to grow and gain weight more slowly than healthy children their age. Human immunodeficiency virus (HIV)-infected children are at particular risk for problems related to growth. HIV and opportunistic infections often negatively influence the growth of young children. A lack of nutritious food necessary for normal growth complicates the lives of many HIV-infected children.

Health care providers who treat children should be able to assess whether a child’s growth is appropriate for the age of the child. By evaluating growth and development at every medical visit, we can learn much about the child’s health. This chapter discusses how HIV affects growth and provides practical tools for growth monitoring.

**Newborns: Birth Weight Comparisons**

Small size at birth is not clearly associated with HIV infection in full-term newborns. Many factors determine a full-term newborn’s birth weight, including maternal nutrition, placental function, and fetal genetics. Studies examining the role of maternal HIV infection in fetal growth have failed to show a consistent relationship. According to the European Collaborative Study and a study from Durban, South Africa, birth weight of infected and uninfected children born to HIV-positive mothers are not significantly different. In contrast, a study based on a U.S. inner-city population concluded that children born to HIV-infected mothers are at increased risk of low birth weight as well as prematurity. Further studies are needed to clarify the reasons for the inconsistencies seen between these populations. At this time, the evidence does not clearly imply a relationship between HIV infection and infant birth weight.

Although full-term newborns who are HIV infected or HIV exposed are not typically smaller than term unexposed infants, prematurity is more common among HIV-exposed infants. A study done prior to the
implementation of prenatal prophylaxis and the routine use of highly active antiretroviral therapy (HAART) showed that the rate of prematurity associated with HIV infection was as high as 19%, more than 30% higher than that in the uninfected population. HAART’s role in preventing prematurity is controversial. Some studies have suggested that HAART may increase the risk of prematurity. However, a recent meta-analysis of 14 separate studies concluded that treatment with antiretroviral regimens during pregnancy is not associated with an overall increased risk of premature delivery.

**Head Growth and HIV**

Head circumference (also called frontal occipital circumference [FOC]) is correlated with brain volume in small children. The brain is one of the primary targets of HIV infection. HIV infection in young children sometimes results in reduced brain growth. Smaller FOC at birth has been associated with developmental delays and reduced academic achievement. Studies have not shown a statistically significant difference in FOC at birth between HIV-infected and uninfected children. The Women and Infants Transmission Study (WITS) did, however, show a trend toward smaller FOC in HIV-infected infants. This study also showed that untreated infants infected with HIV have a decline in brain growth, as evidenced by an increased rate of microcephaly (FOC <5th percentile for age) as they aged. Because microcephaly has been correlated with adverse developmental outcomes, FOC measurements should be used as a tool for the identification of infants at risk for these unfavorable outcomes. FOC measurements are most useful during the first 2 years of life, when head circumference changes most rapidly.

**Variable Onset of Growth Failure**

Many factors affect children’s growth, including general nutrition, overall health, and caretaker nurturing. A child is said to be failing to thrive when he or she loses weight or fails to gain weight at a normal rate for a child of that age. Failure to thrive is a diagnosis that has multiple etiologies, one of which is HIV infection.

The onset of growth failure in children with HIV varies. Growth deceleration can occur as early as the first few months of life, though some children have normal growth for many years. On average, children with untreated HIV infection grow more slowly than uninfected children, a difference that becomes more significant with age. Asymptomatic infected children have growth patterns that are similar to those of mildly or moderately symptomatic children. However, children with severe illness tend to have significantly poorer growth, and high viral loads have been clearly associated with decreased growth.

**Growth as a Predictor of Prognosis**

Children infected with HIV have been classified in three clinical groups with regard to the timing of their disease progression. Infants who develop symptoms of AIDS or who die within the first year of life are rapid progressors. Children who suffer from an AIDS-defining illness or who die within 1-5 years of infection are intermediate progressors. Those children who do not develop symptoms and who survive past 5 years of age are slow progressors. Growth failure in children has been clearly associated with accelerated progression from asymptomatic HIV infection to AIDS. Rapid progressors have the highest incidence of growth failure.

Perinatally acquired HIV infection is sometimes associated with early and progressive reductions in weight and length. Studies in Thailand, Rwanda, and the United States suggest that growth failure can signal rapid disease progression. Babies who failed to gain 2 kg by 4 months of age were more likely to progress to AIDS rapidly. Also, height growth velocity (rate of growth) can predict survival independently of age, viral load, and CD4+ cell count. In resource-limited environments, where obtaining laboratory data is sometimes not possible, growth monitoring may be the best available tool for assessing risk of disease progression.

**Effects of HAART on Growth**

Early studies demonstrated that mono or dual antiretroviral therapies containing zidovudine, didanosine, or zalcitabine temporarily increased weight and linear growth rate. Because HAART is less likely to lead to resistance and treatment failure, more sustainable clinical growth responses are seen among children on HAART. Patients on HAART who achieve and maintain virologic suppression generally have corresponding long-term improvements in growth. After patients begin HAART, beneficial effects are first seen as increases in weight followed by increases in height (usually by 96 weeks on therapy).
Bone Growth: Osteopenia, Osteoporosis, and Osteonecrosis

Bone mass increases during childhood and adolescence. Peak bone mass is normally achieved during the third decade of life. When people have low bone density for their age, they are said to have osteopenia. Those whose bone density is less than 2.5 standard deviations below the mean have the severe form of bone wasting called osteoporosis. Children who fail to form bone normally are at increased risk for this complication because they accumulate bone density more slowly than noninfected children and because certain HAART regimens may further decrease bone density.

The mechanisms by which bone mass decreases among HIV-positive children are complicated. HIV can infect certain bone cells directly. The virus also elevates levels of several cytokines (interleukin 1, interleukin 6, and tumor necrosis factor α) that contribute to increased activity of osteoclasts (cells that break down bone). Vitamin D deficiency also contributes to abnormal bone metabolism and has been reported more frequently in patients with HIV. Although increased rates of bone fractures are not commonly seen among HIV-infected children, these children are at high risk of fractures later in life because of their early development of osteopenia and osteoporosis.

The appearance of bones on plain X rays can provide qualitative evidence for the existence of osteopenia or osteoporosis. Where available, one can quantify low bone density by using DEXA (dual-energy X-ray absorptiometry) or quantitative computed tomography scans.

Weight-bearing exercises (e.g., jogging, dancing, and weight lifting) can help children with HIV maximize their bone development. Providing a diet that is rich in vitamin D, especially in areas where children have limited exposure to sunlight, will also help to ensure the best possible bone growth. Studies evaluating the use of medicines and hormone replacement therapies to help rebuild bone in HIV-infected patients with osteopenia and osteoporosis are currently being carried out in several settings.

Children and adults with HIV infection are also at increased risk of osteonecrosis of the hip. In children, this condition is called Legg-Calve-Perthes disease (LCPD). A study of perinatally HIV-infected children demonstrated a prevalence of LCPD that was more than eight times that of the general population. LCPD is diagnosed on the basis of typical X-ray findings in a symptomatic patient. Treatments for LCPD include the use of nonsteroidal anti-inflammatory and pain control medications, temporarily avoiding weight bearing, and exercises to maintain the range of motion. Severe cases may require surgery or immobilization of the joint.

Puberty

Delay of sexual maturation is common among children with chronic diseases. Children with HIV infection have delays both in the age of onset of puberty and in their progression through the pubertal stages (Table 1 and Table 2). The median delay in pubertal onset is 2 years for girls and 1 year for boys. Entry into the late pubertal

<table>
<thead>
<tr>
<th>Table 1. Female pubertal (Tanner) staging</th>
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<tbody>
<tr>
<td>Stage</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>V</td>
</tr>
</tbody>
</table>
Growth in HIV-Infected Children

Growth in HIV-infected children is delayed by about 2.5 years in girls and 1.5 years in boys. Children with increased immune system dysfunction tend to have the most substantial delays in pubertal development. Therefore, tracking pubertal development may help to clarify underlying disease progression in settings where laboratory markers are not readily available.

**How Do We Measure Growth?**

Growth monitoring in children requires obtaining accurate measurements of weight and length/height. Head circumference should also be monitored in children who are younger than 2 years.

**Measuring Weight**

When weighing young children, consider these basic guidelines to ensure accuracy:

- Use the same scale at each visit.
- Record the weight to the nearest 0.1 kg.
- When weighing infants, weigh them in the supine position with no clothing (except perhaps a dry diaper).
- If available, infant scales should be used for children weighing less than 20 kg. Another option is tared weighing, where the caregiver is weighed, the scale is tared (or “zeroed”), and then the undressed child is held by the caregiver, capturing the weight of the child only.
- If the child is older and will stand still, it is best to weigh the child standing alone on the scale.

**Measuring Length and Height**

Children younger than 2 years should be measured while they are lying on a flat surface. This measurement is called the child’s length. Older children who can stand should be measured in a standing position, which measures the child’s height. When measuring length and height, consider these basic guidelines to ensure accuracy:

- Measure the length of children aged 0-2 years when they are lying down with a length board, with back flat, knees straight, and ankles in neutral position. Record the measurement to the nearest 0.5 cm.
- If the child is aged 2 or more years, measure standing height (heels against wall, without shoes) by using a height board mounted at a right angle.
- Because standing height is about 0.7 cm less than recumbent length and growth charts for children older than 2 years assume that the child will be measured in the standing position, you must subtract 0.7 cm from the measurement of children aged 2 years or older who are measured lying down before plotting them on the standardized World Health Organization (WHO) growth charts.

**Measuring Head Circumference**

When measuring head circumference, consider these basic guidelines to ensure accuracy:

- Head circumference should be routinely checked for the first 24 months of life by using a nonstretchable tape (usually plastic coated or metallic) and recorded to the nearest 0.5 cm.
- The tape should encircle the bony prominence.

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**Table 2. Male pubertal (Tanner) staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Normal Age Range (yrs)</th>
<th>Testis Growth</th>
<th>Penis Growth</th>
<th>Pubic Hair Growth</th>
<th>Other Significant Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0–15</td>
<td>Preadolescent testes (&lt;2.5 cm)</td>
<td>Preadolescent</td>
<td>None</td>
<td>Preadolescent</td>
</tr>
<tr>
<td>II</td>
<td>10–15</td>
<td>Enlargement of the testes (&gt;2.5–3 cm); scrotal sac darkening</td>
<td>Minimal or no enlargement</td>
<td>Downy pubic hair develops at base of the penis</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>10.5–16.5</td>
<td>Further enlargement (&gt;3.0–3.5 cm)</td>
<td>Significant enlargement, especially in diameter</td>
<td>Hair increased in amount; curling</td>
<td>None</td>
</tr>
<tr>
<td>IV</td>
<td>12–17</td>
<td>Further enlargement (&gt;3.5–4.0 cm)</td>
<td>Further enlargement, especially in diameter</td>
<td>Adult in type, but more limited distribution</td>
<td>Development of axillary hair and some facial hair; most boys reach peak growth velocity during this stage</td>
</tr>
<tr>
<td>V</td>
<td>13–18</td>
<td>Adult sized (&gt;4.0 cm)</td>
<td>Adult sized</td>
<td>Adult distribution (medial aspect of thighs and linea alba)</td>
<td>Body hair continues to grow; muscles continue to increase in size</td>
</tr>
</tbody>
</table>
of both the forehead and the occiput and should reflect the head’s greatest diameter to avoid an underestimation.

- Ideally, the head circumference should be measured twice in moving children to ensure that the widest diameter has been measured.

**Plotting Measurements on Growth Charts**

Once weight and height (or length) are measured, they should be plotted and interpreted using a standard growth chart. The WHO has developed growth charts that reflect the range of growth potential for children worldwide who receive proper nutrition and health care. These growth charts depict age on the horizontal axis and weight, height, or head circumference on the vertical axis. They offer a simple, systematic way to document a child’s nutritional status at a point in time and allow the tracking of a child’s growth rate over time.

Using these charts or other locally validated charts, one should plot the weight, height, and head circumference of HIV-infected children at regular intervals. Weight should be checked each visit and height checked every 3 months throughout childhood. Head circumference should be plotted at least every 3 months until 24 months of age and more frequently during the first 6 months of life. Once weight and height are plotted on the growth chart according to the age of the patient, they offer a visual representation of the child’s growth compared with that of healthy children of the same age.

Weight and height also make it possible to define other essential growth parameters—weight-for-height ratio and body mass index (BMI). The weight-for-height ratio is a growth indicator that relates weight to length (for children <2 years) or height (for children ≥2 years). BMI, often used for older children and adolescents, indicates a person’s weight in proportion to height, calculated as kilograms per square meter of body surface area. Like other measurements, weight-for-height ratios and BMI are best interpreted while taking into consideration the age of the child, and standard charts and reference tables have been developed to assist the clinician. The most relevant WHO growth charts are included within this chapter. Additional charts are available through the WHO child growth standards Web site: http://www.who.int/childgrowth/en.

Once measurements have been plotted, the resulting growth curve makes it easy to determine whether the child is experiencing growth failure. Figure 1 shows two examples of the type of growth failure commonly observed among children with HIV infection.

**Figure 1.** This orphan had severe growth failure and malnutrition when he first presented to the Baylor clinic at age nine years, with a weight too low to fit on the WHO weight-for-age chart and no previous medical records. After treatment for TB and the initiation of HAART, the child’s nutritional status and weight for age improved dramatically. He is now almost ten years old, and his weight should continue to normalize as HAART and immune system recovery continue. Note the slower improvement in height in the height-for-age chart. Though his weight is recovering quickly, his height will lag behind, and he is likely to remained stunted, with a lower than average adult height.
Using Growth Plots To Classify Poor Growth and Nutritional Deficiency

In the short term, patients who are not growing well become thin, or “wasted.” Over time, if poor growth continues, the children will also fail to gain height at the normal rate. The failure to gain height results in short stature for age, or “stunting.” Children with HIV who have stunting have a poorer prognosis than that of children with more normal long-term growth. Health care providers should therefore aim to identify poor growth early before stunting occurs.

A variety of different criteria exist to aid in the timely diagnosis of clinically significant poor growth. Three criteria that are commonly used to indicate a growth abnormality are

- Weight loss of 10% or more of body weight
- Deceleration in weight gain resulting in a downward crossing of two or more of the percentile lines for age (e.g., 97th, 85th, 50th, 15th, 3rd)
- Weight-for-height ratio or BMI of less than –1 standard deviation below the mean with failure to follow a normal upward curve

Measuring the middle-upper arm circumference (MUAC) provides another useful tool to identify a child with wasting syndrome. As a child loses subcutaneous fat and muscle, the MUAC becomes low for age.

In addition to looking at a child’s growth chart, one should always examine the child for other physical signs of malnutrition. Some children with severe protein energy malnutrition develop edema. The presence of edema makes the weight and MUAC appear falsely elevated. The nutrition chapter discusses other clinical signs of malnutrition in more detail.

What To Do If a Child Has Poor Growth

Children who fail to meet growth parameters should be targeted for treatment of potentially reversible causes of poor growth, including untreated HIV infection. Most countries currently use WHO clinical staging as a basis for determining eligibility for initiating HAART. Nutritional status plays an important role within these HAART eligibility criteria (Table 3).

### Table 3. WHO presumptive and definitive criteria for recognizing HIV-related growth problems

<table>
<thead>
<tr>
<th>Clinical Stage and Diagnosis</th>
<th>Presumptive Diagnosis</th>
<th>Definitive Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3: unexplained moderate malnutrition</td>
<td>Weight loss: low weight for age, up to –2 standard SDs, not explained by poor or inadequate feeding and/or other infections, and not adequately responding to standard management.</td>
<td>Documented loss of body weight of –2 SDs, failure to gain weight on standard management and no other cause identified during investigation</td>
</tr>
<tr>
<td>Stage 4: unexplained severe wasting, stunting, or severe malnutrition not adequately responding to standard therapy</td>
<td>Persistent weight loss not explained by poor or inadequate feeding or other infections and not adequately responding in 2 weeks to standard therapy. Characterized by visible severe wasting of muscles, with or without edema of both feet, and/or weight for height of –3 SDs.</td>
<td>Documented weight loss of &gt;–3 SDs with or without edema. SDs, standard deviations</td>
</tr>
</tbody>
</table>

Other HIV-related conditions can profoundly affect nutritional status and should be considered in any child with poor growth. Opportunistic infections should also be considered in the presence of poor growth because they increase the body’s metabolism. Diarrheal illnesses can lead to poor absorption of nutrients. Painful oral or esophageal infections that interfere with eating are also common problems in HIV-infected patients. To ensure adequate intake, give children with poor growth counseling regarding adequate intake of high-energy and nutrient-rich foods. The nutrition chapter gives more information on nutrition in the context of HIV.
CDC Growth Charts: United States

Weight-for-stature percentiles: Boys

Revised and corrected November 21, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Body mass index-for-age percentiles: Boys, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Stature-for-age percentiles: Boys, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Growth in HIV-Infected Children

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Weight-for-age percentiles: Boys, 2 to 20 years

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Stature-for-age percentiles: Girls, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-length percentiles:
Boys, birth to 36 months

Revised and corrected June 8, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
Growth in HIV-Infected Children

CDC Growth Charts: United States

Head circumference-for-age percentiles: Boys, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-age percentiles: Boys, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Length-for-age percentiles: Boys, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-age percentiles: Girls, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Length-for-age percentiles: Girls, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
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References


