Growth as a part of the composite endpoint in paediatric antiretroviral clinical trials

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Paediatric HIV is a rapidly emerging disease in many resource-poor countries. Survival into adulthood is possible for HIV-infected children provided that they receive effective antiretroviral therapy (ART). Large trials comparing multiple regimens of ART in children of resource-poor countries have not been completed. Design of those trials will need to incorporate both lessons learned from trials completed in developed countries as well as unique aspects of the developing countries in which they are conducted. Trial design will necessarily include close attention to the endpoint, and in children, special consideration will need to be given to growth as a component of the endpoint—whether or not growth should be a component of the composite endpoint, and if so, how.

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Introduction

Studies of paediatric HIV infection, due to the diverse manifestations of the disease, have required study designs that often included composite endpoints. These composite endpoints have included death, new opportunistic infections and clinical markers of HIV disease progression unique to children. Because some aspects of care, like prophylaxis against opportunistic infections or advanced nutritional support, are not equally available in all countries, the structure of the composite endpoints will require re-evaluation as antiretroviral paediatric trials are conducted outside of the USA.

Therapeutic trial endpoint

The primary endpoint of a trial can vary from an unambiguous and simple-to-measure endpoint like death, to a more complex composite endpoint, that includes, for example, the first event among several such as death, new opportunistic infection, neurological deterioration or poor growth velocity. Although endpoints may incorporate biological markers like HIV viral load or CD4+ lymphocyte count, studies have shown that changes in CD4 count, albeit correlated, are not consistently a good surrogate endpoint for HIV clinical progression.

Because so few HIV-positive children are expected to die during a clinical trial, composite endpoints have often been employed by the Pediatric AIDS Clinical Trials Group (PACTG) to evaluate antiretroviral therapy. The choice of the composite endpoint merits attention: all aspects of the composite endpoint should be potentially observable in each patient and each event should have a similar clinical significance. For example, in paediatric HIV studies, time to occurrence of first opportunistic infection is used rather than time to specific (e.g. oesophageal candidiasis) opportunistic infection.

Paediatric HIV infection studies composite endpoint

The primary composite endpoint for paediatric HIV therapeutic trials is often time to first evidence of clinical progression of HIV disease; where clinical progression includes: (1) death; (2) new Centers for Disease Control Clinical Category C diagnosis; (3) central nervous system (CNS) disease progression; or (4) weight growth failure. The paediatric-specific features for the paediatric composite endpoint are CNS disease progression and growth failure. CNS disease progression is evaluated through baseline and interval assessments of brain growth, and cognitive and motor function. Growth failure in PACTG trials has largely centred on weight velocity.

Growth

Weight growth failure has been defined as three consecutive months with less than the third percentile for age- and gender-specific 6 month weight growth velocity on incremental growth
curves, without a documented alternative explanation (e.g. intentionally restricted dietary intake). Growth velocity is incorporated in the paediatric HIV composite endpoint because pre-pubertal children are expected to grow vertically and gain weight according to established standards. Growth parameters have an additional advantage of being relatively inexpensive to measure with the tools being relatively easy to use and learn to produce consistent measurements. Growth can be measured at each visit and can provide multiple data points that can be analysed to improve the accuracy of the assessment. Single-event endpoints have an inherent lack of precision in that, except for day of death, the process can be ongoing but not detected until either a scheduled evaluation or a clinically apparent threshold is reached. Lastly, the entire study population can be assessed at regular intervals for growth parameters, whereas other endpoints consist of single events that will only occur in a proportion of the study population.

In HIV-negative children, the most common pattern of growth failure is weight loss relative to height for age, followed by declines in height for age and finally slowed head-circumference growth. The most common reason for growth failure in childhood is decreased nutritional intake because of social reasons such as child neglect, malnutrition and food shortages. However, in HIV-infected children, the disease itself adversely affects growth in a manner that is symmetrical, with equal effects on weight and height.

Growth failure is evaluated using a variety of tools including standardized growth charts, incremental growth curves and Z-scores. Use of Z-scores allows an investigator to compare data from children of various ages, reducing sample size requirements for any one particular age. A Z-score of one is equivalent to a standard deviation unit. Thus, a weight-for-age Z-score of −1 signifies that a child weighs 1 standard deviation less than the mean of a population of same age and gender children. Similarly, a child of ‘average’ height (at the 50th percentile for height) will have a Z-score for height of 0. If the same child had an increase in her Z-score of +1.5 over 12 months it would signify that she had gained enough height relative to her peers to be 1.5 standard deviations taller than average.

Individual Z-scores are calculated using equations that use measurements obtained from the child and nationally derived constants. The constants are obtained from a table for the measurement of interest (e.g. weight, height, head circumference, etc.). The tables are derived from national growth databases and are available at http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/zscore/zscore.htm.

Growth as a clinical trial endpoint
Historically, deterioration in weight for age Z-score (WAZ), rather than height for age Z-score scores (HAZ), has been used as part of the composite endpoint. WAZ has been used as a result of a perception that it was more accurate than HAZ because of greater precision in measurement. We have recently evaluated the potential use of height (HAZ) as a part of the composite endpoint in paediatric antiretroviral trials, by comparing the association between growth parameters (HAZ or WAZ) to clinical and laboratory progression. Clinical and laboratory progression was pre-defined as death, new Centers for Disease Control Clinical Category C diagnosis, CNS disease progression, rise in HIV viral load or decline in CD4+ cell count. In each comparison, HAZ was more closely related to other clinical endpoints and biological markers than WAZ. We postulate that although the weight measurement may be more precise than height measurement, the stronger correlation between change in height and HIV disease progression means that HAZ is the more accurate measurement and would be preferable.

Endpoints for international studies
The challenge for international studies is to identify study endpoints that are disease sensitive, cost effective, technically feasible and interpretable in all clinical settings. In a recent retrospective analysis of data from HIV infected children in the USA, low cost laboratory markers (such as total lymphocyte count, haematocrit and serum albumin) were associated with 12 month mortality. These low cost markers may serve as a reasonable alternative to the more expensive CD4 cell count.

Prospective studies to compare and contrast different potential ‘low tech’ clinical and laboratory markers have not been conducted. However, use of all surrogate markers, whether ‘high tech’ (HIV RNA and CD4 cell count) or ‘low tech’, must be validated in resource-poor settings because co-infections, disease manifestations and the dynamics of disease progression vary among regions.

In addition to variability in interpreting laboratory values, clinical events can be different. For example, infections common in developing nations that contribute to mortality in HIV-infected children include tuberculosis and malaria, both of which may occur at relatively high CD4 cell counts. Growth measurements, on the other hand, may be readily adaptable to many settings. Not only is growth sensitive to HIV replication, but in tropical settings where malnutrition and diarrhoeal disease have a major impact on HIV disease progression and death, growth may be a sensitive indicator of general clinical deterioration.

Future steps in growth and paediatric HIV
Several questions need to be addressed regarding the relationship between growth and HIV disease progression. First, are there inherent difficulties unique to developing countries that will prevent reliable growth measurements even in the paediatric HIV research setting? Second, should measurements used to determine growth velocity as an endpoint be separated by >6 months; and if such measurements should be separated by >24 months, should growth velocity be used as an endpoint? Third, which aspect (or aspects) of growth velocity should be used as an endpoint: i.e. weight, height, weight for height, body mass index, etc. Fourth, which growth charts should be used: e.g. if a multinational trial is conducted on different continents, should growth charts by country (or region) be used, or should a clinical trial employ one uniform growth chart for the trial? Fifth, if other aspects of growth and nutrition (e.g. severe malnutrition) are more closely related to HIV-related death, should some aspect of growth velocity still be used as an endpoint? Specifically, is growth velocity an important enough component of paediatric health and development that impairments of growth velocity be considered a part of the paediatric HIV composite endpoint?
These and other questions may be addressed in future research in growth velocity and paediatric HIV in prospective cohort studies. Such research might also provide recommendations for other aspects of the composite endpoint for paediatric HIV trials conducted in resource-poor countries. These cohort studies should further evaluate and refine our understanding of both laboratory and clinical endpoints and the relationship of those endpoints to HIV disease progression in children globally.

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References