

What is the effectiveness of highly active antiretroviral therapy among children HIV-infected living in resources-limited settings?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the effectiveness of highly active antiretroviral therapy among children HIV-infected living in resources-limited settings?*

INTRODUCTION

The UNAIDS "AIDS epidemic update 2008" estimated that globally the numbers of children living with HIV increased from 1.5 million in 2001 to 2.5 million in 2007. However, estimated new infections among children declined from 460,000 in 2001 to 430,000 in 2007. Deaths due to AIDS among children has increased from 330,000 in 2001 to 360,000 in 2005, but have now begun to decline to an estimated 330,000 in 2007. Sub-Saharan Africa remains the most affected region in the global AIDS epidemic. More than two out of three (68%) adults and nearly 90% of children infected with HIV live in this region, and more than three quarters (76%) AIDS deaths in 2007 occurred there [1].

Most of the studies and clinical trials on the efficacy of highly active antiretroviral therapy (HAART) have been conducted in adult populations. Although the clinical efficacy of HAART in children and adolescents has been well documented in industrialized countries, there are few data from the resource-limited settings (RLS), in which it is estimated that less than 5% of HIV-positive children have access to HAART.[2]

Important obstacles to scaling up HAART in children living in RLS include: (a) lack of human capacity and limited training and experience in treating children; (b) lack of practicable, acceptable and available paediatric antiretroviral formulation; (c) no fixed-dose combination, nor practicable paediatric antiretroviral formulation (d) high cost of paediatric antiretroviral medications; and (e) lack of affordable and simple HIV-diagnostic testing technologies for children under 18 months of age [3, 4].

The aim of this systematic review was to summarize the evidence available for effectiveness of combination antiretroviral therapy for HIV-infected children living in resource-limited settings. The primary objective of this review

was to determine the rate of survival of among children using HAART. The secondary objectives were to assess the rate of viral suppression and to evaluate the immune restoration by the increase of CD4 absolute cells count or percentage. We also describe some features of the study groups such as age, baseline CD4 count and viral load, prior use of ARV drugs and nutritional status.

METHODOLOGY

Initially, we searched the Cochrane Reviews for systematic reviews on HAART among children in RLS but there were no reviews. We further used PubMed as reference to perform this review followed by search in others Electronic Databases.

Criteria for considering studies for this review:

Types of studies

All experimental, quasi-experimental and observational studies using antiretroviral therapy for HIV-1-infected children in RLC were included.

Types of participants

Studies comprising infants, children and adolescents HIV infected from birth to 18 years of age were evaluated. We included studies with all-age children infected by mother-to-child transmission and other routes (sex or blood). Studies including adult HIV infected were excluded.

Types of interventions

The intervention required was the use of antiretroviral therapy including at least 3 drugs from two or three classes of the antiretroviral drugs (NRTIs, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors and PI, protease inhibitors).

Types of outcome measures

The first outcome measured was the survival of HIV-infected children, as the proportion of alive children at the end of the follow up (in weeks).

The second outcome measured was the proportion of children with HIV RNA viral load below of detection level. There are different levels of detectability threshold depending on the type of the assay used. For analysis we allocate the levels on two

groups (< 500/400 copies/ml or < 50/40 copies/ml) over time (weeks of follow-up).

The third measured outcome was the absolute T CD4+ lymphocyte cells count or percentage increase compared with the baseline values.

Search strategy for identification of studies

Firstly, an electronic search was made in distinct databases (see below). Secondly, the reference sections of identified papers were examined for additional publications. Finally, for every study we made a summary table to assist reviewers' analysis and evaluation.

Electronic searches

Electronic Databases used in the search strategy were: Cochrane Library, PubMed and SCIELO. First, we searched for: "HAART or highly active antiretroviral therapy", "efficacy or effectiveness", "HIV-infected child or children", "pediatric or paediatric" and "developing countries or resource-limited settings". In addition, we limited the search by age group, considering all children (0 < 18 years) and type of article: clinical trial, review, randomized controlled trial. The search was not limited by language and was done until May 31, 2008.

Other Sources

The primary search was supplemented with an exploration in AIDSSEARCH and AIDSINFO with the aim to identify other reference lists.

1. Selection of Studies

All titles and abstracts that included clinical trials or observational studies were retrieved if the main outcome variable was the rate of survival or the viral suppression rate under HAART (using either viral load < 500/400 copies/ml or ≤ 50/40 copies/ml). To study immune restoration scope, we included studies with the increase of CD4 cells count or percentage from baseline value. The citations identified had their full text articles selected for potential inclusion.

2. Data extraction, data management and assessment of methodological quality of included studies

The data extraction was resumed in a table composed for every study using the PICO analysis (clearly structured question constructed to search for evidence in the literature). Prospective observational studies were assessed by detailed description of the study design and the experimental studies were assessed by using the CONSORT (Consolidated Standards of Reporting Trials). Study quality was completed by two independently reviewers (ES and CM).

We created a table containing the authors' identification of the citations retrieved, number of participants, median age, follow up period and measurement of viral load detectability threshold, baseline CD4 count, type of HAART combination, viral load level of detection, the year of publication and type of study design. Two reviewers independently evaluated the methodological quality of studies, disagreements were resolved by discussion of criteria when required. The studies were scrutinized for methodological quality, bias, internal and external validity.

3. Measures of survival rate, viral suppression rate and immune restoration

The measures of survival was the proportion of children alive at the end of the follow up. The measure viral suppression rate achieved after HAART was the proportion of patients with

detectable level under either < 500/400 or < 50/40 copies/l. The measure of CD4+ lymphocytes cells count or percentage increase was the difference between baseline and end-point values.

4. Unit of analysis issues

Some studies had multiple treatment groups. We only extracted and included data of the treatment groups using HAART with 3 or more classes of drugs: 2 nucleoside reverse transcriptase inhibitors (NRTIs) + non nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitor (PI).

5. Dealing with missing data

Some of the selected studies had not all the outcome measures included in this review. Some of them had the rate of survival but not the viral suppression, other had CD4+ lymphocyte cells count and not percentage. However, all studies were included for subgroup analysis. Studies with missing descriptive and analytical statistics were excluded.

6. Data synthesis

Statistical analysis was performed using version 9.2 of STATA software. The Chi-square test or Fisher exact test was used to compare categorical data. Logistic regression analysis was used to determine if the duration on follow-up were associated with survival rate. A p-value of < 0.05 was regarded as statistically significant.

RESULTS

The initial broad search yielded a total of 1808 references, but only 334 met the inclusion broad criteria. This number was reduced to 151 (refined criteria) and after quality control procedure to 18. Reasons for study exclusion included: some studies used data from earlier publications on the same participants, used only on-treatment analysis and do not have rate of survival viral or load threshold as an outcome variable. A summary of the characteristics of all included studies is showed at Table 1 [3, 5-21].

Thirteen out of 18 (72%) studies had survival as primary outcome. Additionally, fourteen out of 18 (78%) studies had viral suppression rate as second outcome with different threshold level of viral detectability assays. All of studies, except one (94.4%), had as secondary outcome the increase of CD4+ lymphocyte cells count or percentage.

Description of the studies:

1. Included Studies

The included studies had the follow profiles:

Study design and publication year: from the 18 papers included, 11 (61.1%) papers were retrospective observational studies, 7 (38.9%) were prospective studies; 3 out of 18 (16.6%) were experimental studies. Eleven (61.1%) out of 18 studies were published at 2007.

Patient population: a total number of patients included in all studies was 8,519 (median 473 patients/study, range: 26-4,875). The median age when starting HAART was 85 months (range: 23 - 156 months).

At baseline, in 12 out of 18 studies, median viral load was 5.34 log₁₀ copies/ml (range: 4.84 – 6.1) and in 13 out of 18 studies, patients median CD4 percentage was 9% (range: 3.5% - 20.1%), while in 12 out of 18 studies, CD4 count was 239.5 (range: 46 – 584).

Interventions: Highly Active Antiretroviral Treatment (HAART) consisted of 3 drugs of 2 or 3 classes: 2 NRTIs + NNRTI (61%) or PI (11%), NNRTI+PI (28%). The median follow-up period was 20.2 months (range: 6 - 48). According to a pre-exposure to antiretroviral drugs: 11 (61.1%) studies had included only naïve patients and 7 (38.9%) studies had both naïve and ARV experienced patients.

Outcomes: the median rate of survival was 92.2% (range: 80% – 100%) during a median follow up period of 20.2 months. No significant difference was observed in term of mortality between children receiving a NNRTI-based regimen and those receiving a PI-based regimen (p = 0.917).

To demonstrate virological decay, the majority of the studies (8/13) used the percentage of decrease of copies/ml, while others studies used percentage of individual under the lower level of detection assay. The studies that had as outcome viral load suppression (14/18), all demonstrated a statistical significant decrease on percentage of plasma HIV-1 RNA load. However, only 7 studies used the lower limit of assays detection as outcome, 4/18 (11.1%) studies used a limit of 400 copies/ml assays showed mean rate of viral suppression of 61.5 (37.9 to 81.0) and 3/18 (16.6%) studies used a limit of 50 copies/ml assay showed mean rate of viral suppression of 73.7 (67.7 to 83.3).

In regard to immune restoration, data described in the studies differed in many ways. Of the 17 studies that displayed median CD4 cell count or percentage, all of them demonstrated statistical significant increase compared with baseline values, but according to the increase of percentage of CD4 cells, only 2 (11.1%) studies used setpoint above 25% as absence of immunodeficiency, while the median increase of the CD4 cells count, calculated for 7 studies, was 445.3 (range: 329 – 699.8).

2. Excluded Studies

The characteristics of the excluded studies were: missing statistics and failure to measure the primary and secondary outcomes, i.e. survival or viral suppression.

DISCUSSION

Most studies were published in 2007 (61,1%) and included a substantial number of individuals (8,519 patients). The median age of starting HAART was 7 years and did not differ when compared with other studies. [22,23] Patients baseline immunological and virological characteristics before starting HAART are according with WHO and international guidelines, i.e. evidence of immunodeficiency (median CD4 + cell percentage and absolute count) and viral load > 100.000 copies of HIV-RNA/ml. [24-27] The elevated median rate of survival (92.2%) was similar to the overall probability of survival found in a studied that include HIV-infected children from 14 countries form Africa and Asia. [28]

The major proportion of regimens using NNRTs and the short median follow-up period might be due to more recent access to drugs and might reflect the high median survival rate (92,2%). However, both NNRTI-based regimen and PI-based regimen showed to be equally effective.

In this resource-limited setting, HAART was effective for HIV-infected children despite initiation of treatment during the advanced stage of disease or treatment of antiretroviral experimented subjects. Furthermore, the rates of HIV suppression measured by viral load tests showed similar to the rates found in international collaborative studies including developed and undeveloped countries [29,30].

Finally, the effectiveness of HAART use among children living at resource-limited setting should encourage global efforts to make ART available for all HIV-infected children in poor countries.

SUMMARY

Combination antiretroviral therapy for HIV-infected children living in resource-limited settings showed to be effective in reducing mortality, control burden of HIV viral replication and leading to immune restoration in the majority of patients.

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