

Where HIV antigen testing is unavailable, what is the validity of starting antiretroviral therapy in children less than 18 months who are HIV antibody positive with 'presumptive stage 4' disease?

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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: *Where HIV antigen testing is unavailable, what is the validity of starting antiretroviral therapy in children less than 18 months who are HIV antibody positive with 'presumptive stage 4' disease?*

The **WHO Pocketbook of Hospital Care for Children** recommends that for children aged 12-18 months who are HIV (antibody) positive, with symptoms and in whom HIV is strongly suspected on clinical ground, it may be reasonable to start ART. (Pocketbook pg 209)

Introduction:

HIV/AIDS is an immense problem facing the practice of pediatrics globally. As of 2007, 2.5 million children under 15 were infected with HIV and the annual pediatric death toll from AIDS has reached 330,000. [1] With the up-scaling of antiretroviral (ARV) therapy, some have reported concern that children are being left behind in access to life-saving ARV medicines. [2] Lack of HIV testing for children has been identified as a major barrier to improving access to children

[3] - a particular problem faced in infants under 18 months as maternally acquired HIV antibodies produce false positive tests on traditional rapid antibody testing techniques. As a result time consuming and expensive antigen tests are used for laboratory confirmation of HIV infection in infants, however these tests remain largely inaccessible in resource limited settings. Due to the rapid progression to AIDS and death in children, lack of diagnostic testing prevents the use of life-saving ARV medicines in this most needy group. [4] The revised guidelines for increasing ARV access for children use a population-based public health approach, produced by the World Health Organization (WHO) in 2007, [2] these guidelines aim to integrate the limitations of services in many settings within their clinical protocols. Acknowledging the lack of diagnostic resources for infants in resource limited settings, the new guidelines advise starting antiretrovirals in infants presenting with clinical symptoms and signs of severe stage 4 disease – either an AIDS indicator condition, such as Pneumocystis pneumonia, or at least 2 of: oral thrush, severe pneumonia, or severe sepsis. This review intends to answer the question *Where HIV antigen testing is unavailable, what is the validity of starting antiretroviral therapy in children less than 18 months who are HIV antibody positive with 'presumptive stage 4' disease?*

Methodology

A literature search was conducted of the PubMed, Embase and Cochrane databases. No prior Cochrane review had been done on this topic. Searches were performed using a combination of MeSH and text word searches on 'infant', 'antigen', 'antiretroviral', 'serodiagnosis' and 'resource poor' or 'resource limited'. Bibliographic lists were also consulted. This search was completed in March 2008. The PubMed database search yielded 85 hits, the Embase database search yielded 50 hits (many repetitive) and the Cochrane database yielded no hits. A review of the Cochrane Register of Controlled Trials revealed no currently active studies on this subject area.

Further review of papers for relevance resulted in final consideration of 2 meta-analysis papers, 5 systematic and non-systematic review papers, 4 policy analysis papers, 1 controlled trial, 9 cohort trials and 1 correspondence.

Results & Discussion

Diagnosis of HIV

Infants acquire maternal antibodies to HIV if their mother is positive, however only a minority of infants of HIV positive mothers also become infected with HIV - the transmission rate is 25-48% in Southern Africa [3]. In developed countries, HIV DNA PCR is the preferred test for confirming the diagnosis of HIV infection in children less than 18 months of age. Some clinicians use HIV RNA PCR to further confirm the diagnosis [1]. As there is a small risk of false negative results in young children, in well-resourced countries PCR testing is therefore repeated several times throughout the first year of life. [1] However, in resource-limiting settings a single HIV DNA PCR test is very accurate for diagnosing HIV infection in children < 18 months of ageⁱ. The average time to seroreversion (the loss of maternal antibodies) varies from 7 to 13.3 months in various studies [2]. Lack of access to PCR testing has been identified as a major barrier to treatment of pediatric HIV - in one study in Kenya, there was no PCR testing available outside institutions for research purposes [2]. While antibody testing has a high false positive rate in infants under 18 months, a negative test in this group may be a useful screening tool for excluding HIV. [2] Laboratory technicians are often in short supply, to compound financing

restrictionsⁱⁱ. The costs of diagnosis and monitoring of HIV in infants could outweigh the costs of antiretroviralsⁱⁱⁱ.

Benefits of ARV therapy in infants in a resource limited setting

ARV has been successful in slowing progression and reducing mortality rates for children and infants in developed countries. [12] Studies in well-resourced environments have shown a significant decrease in AIDS-associated illness and encephalopathy in infants treated with early antiretrovirals, rather than those deferred to 6 months. [13] However, a large number of studies have been published in the last few years also showing significant improvements in mortality for children and infants in resource limited settings. [14-22] However, these studies disproportionately included older children, and little direct evidence is available from studies of antiretrovirals in infants in resource limited settings. While most of these studies had access to PCR for diagnosis, the decision to initiate treatment was based on clinical and CD4% guidelines, generally using the WHO classifications for advanced or severe disease. The study by Cowburn et al. [23] based in a Pediatric Intensive Care Unit amongst critically unwell children showed good long-term outcomes amongst those who survived to start ARV treatment. Recent research has focused on the issue of when to start antiretrovirals in infants. Previously, ARV therapy would not be started in asymptomatic children due to concerns regarding drug toxicities, however new studies have shown significant improvements in survival for infants started on ARV therapy before 12 weeks. The CHER study was presented at the 4th IAS conference in 2007 [24] and showed a 75% reduction in early mortality for infants commenced on ARV therapy before 12 weeks, as compared to those started when CD4% <20% (or <25% if under 1 year) as per WHO guidelines. This, and similar studies, will likely profoundly impact the treatment of pediatric HIV with early treatment. Already, the American guidelines have been changed to recommend early ARV treatment [5], and revisions are being made to the WHO guidelines. preventing opportunistic cryptococcal infections.

Role of Clinical Algorithms in HIV diagnosis

Clinical severity scores have been used to assess progression and mortality risk in children with

laboratory confirmed HIV [25] , and work has been done expanding these prognostic clinical algorithms into diagnostic algorithms. Clinically directed screening algorithms have been trialed to identify a high-risk cohort for HIV testing. In one study, Ojukwu & Ogbu [26] looked at 8 risk factors associated with HIV infection, and found the highest correlation between HIV seropositivity and oral candidiasis (38.2%) followed by severe malnutrition (33.8%) and generalized lymphadenopathy (31.4%). The presence of 2 of the 8 risk factors increased the relative risk of HIV seropositivity to 9.1. Another study, Richardson et al. [27] looked at the odds ratios of HIV infection with various clinical risk factors. In all children, rash (OR 1.8), failure to thrive (OR 1.9) and lymphadenopathy (OR 2.5) were associated with acute HIV infection. In infants \geq 2 months of age pneumonia (OR 3.2) and dehydration (OR 6.0) were also associated with acute HIV infection. These studies looked at individual risk factors for HIV infection, rather than develop a clinical algorithm.

The first study assessing the validity of a clinical algorithm for the diagnosis of HIV was done by Horwood et al. [28] , using the Integrated Management of Childhood Illness (IMCI) guidelines of South Africa, comparing clinical diagnosis with laboratory results. This study found a sensitivity of 56.1% and a specificity of 85.0% for the algorithm. This result was consistent for infants less than <11 months and \geq 11 months. Correspondence on this study criticized some versions of the IMCI guidelines for HIV diagnosis for their low sensitivity. In the Bulletin of the World Health Organization, Jones et al. [29] discussed a study they had undertaken in South Africa using a structured questionnaire based on the CDC guidelines amongst infants attending a PMTCT clinic. This study had a sensitivity for HIV infection of 56% at 6 weeks and 93% at 12 months. They concluded that the lack of sensitivity of these clinical algorithms was of concern and advocated research for alternative laboratory diagnostic techniques. Knowledge of maternal HIV status is an important factor in considering pre-test probability of HIV infection in infants [30], and this may explain the difference in results between a PMTCT clinic and a general pediatric clinic.

The WHO clinical case definition for pediatric AIDS was designed to replace HIV laboratory testing in resource-limited settings. However, validation studies demonstrated a low sensitivity. The Horwood study also looked at the validity of the WHO clinical definition of pediatric AIDS and found a low sensitivity (8.5%) but a very high specificity (98.7%) for diagnosing AIDS, addressing concerns that children who were not HIV positive would receive potentially harmful treatment. The 1989 study by Lepage et al. [31] in Rwanda using earlier WHO case definitions for pediatric AIDS also found a high specificity of 92% and a low sensitivity of 41%. They found that individual signs had the same positive predictive value as the WHO case definition: chronic diarrhea (47%), respiratory distress from lower respiratory tract infection (50%), oral candidiasis (53%) parotitis (67%), lymphadenopathy (88%) and herpes zoster infection (100%). These children were older than the Horwood and Jones studies. The Otieno et al. [32] study in Kenya involved a small younger cohort, more similar to the Jones study. This study found the WHO pediatric AIDS definition to have a sensitivity of 60% and a specificity of 94%. From these results on clinical algorithms for both HIV and AIDS diagnosis we can see that these tools have poor sensitivity despite their high specificity and so new laboratory technologies are being developed to find a low-cost HIV diagnostic test for infants. Also, in light of the new research showing a survival benefit for infants started on antiretroviral therapy before 12 weeks, waiting for a presumptive clinical diagnosis of AIDS would delay treatment and adversely affect mortality rates.

Alternative Diagnostic Tests in Infants

Due to the technical restrictions and high costs of traditional HIV antigen testing using PCR, research has been undertaken to validate alternative tests for HIV in infants.

New PCR collection techniques have also been developed to address testing limitations. The development of dried blood spot tests for HIV PCR reduces the transportation and collection limitations associated with traditional PCR [33], however currently there is a higher associated reagent cost [8]. A Reverse Transcriptase test using a modified ELISA test also shows promise [34], however the cost per test is still over \$25 [35].

p24 assays have been shown to be a sensitive and cheap alternative to PCR testing. A study by George et al. [36] from Haiti demonstrated a sensitivity of 93-95% for p24 assays with a cost for a commercial kit of \$7. Another study by Zijenah et al., from Zimbabwe showed a higher sensitivity of 96.7% and a specificity of 96.1% in infants under 18-months [37]. CD4% counts may also be an important measure of when to start treatment, and showed a sensitivity of 87.1% in a case control study in Cote d'Ivoire [33].

Summary

Due to the limitations of definitive HIV laboratory diagnosis in infants, the WHO recommendations for the start of antiretrovirals in infants with advanced disease balances the importance of an accurate diagnosis with life-saving antiretroviral therapy. ARV treatment has shown significant improvements in mortality in children in resource limited settings, however there are concerns that children are being left behind in programs to roll out wider ARV access due to a series of barriers to treatment, including limited access to laboratory diagnosis in many settings with both limited resources and high HIV prevalence. Where HIV antigen testing is unavailable, clinical algorithms have been shown to be highly specific in diagnosing HIV infection; however they often have low sensitivity, resulting in research to identify an alternative cheaper diagnostic test than HIV PCR.

When a child presents with features meeting the WHO clinical definition of AIDS they are very likely to be HIV positive, as this is a highly specific tool for diagnosing AIDS. However, it is less effective as a screening tool as many infants with symptomatic HIV will not be detected under the clinical definition as it has poor sensitivity.

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