

# What is the role of HIV antigen testing in infants less than 12 months old?

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

This review addresses the question: *This review addresses the question: What is the role of HIV antigen testing in infants less than 12 months old?*

The **WHO Pocketbook of Hospital Care for Children** states that viral testing is the most reliable method for determining HIV infection less than 18 months of age and is becoming increasingly available in developing countries. (Pocketbook 8.1.3, page 204)

## Introduction:

With the increasing availability of antiretroviral drugs in resource poor countries, there is a vital need to develop a straightforward, cost-effective laboratory method for the early diagnosis of infant HIV infection. Immunoassays for HIV antibodies provide a simple and cost-effective diagnostic test for children over 12 months. The Prevention of Mother to Child Transmission (PMTCT) programmes in low resource settings therefore require all exposed children to be followed to 12 months of age or older before their HIV infection status can be determined [1]. In South Africa, over 280,000 children per year are being monitored for over 12 months, 90% of whom will prove to be un-infected but will have received prophylactic treatment [2]. These costly inefficiencies have been addressed in the United Nations Development Goals which seek to prioritise the need for a straightforward and inexpensive HIV diagnostic test in children.

The current WHO guideline for diagnosis of HIV infection in infants less than 12 months is DNA/RNA virology which is neither cost-effective nor easily accessible.

HIV-1 p24 antigen testing, whilst more cost effective, was originally trialled with discouraging results. In 1996 a new amplification boosted procedure was established, the Ultrasensitive p24 assay. This review intends to answer the question: Can the newer antigen marker linked techniques be effectively used in the diagnosis of HIV in the infant population?

## Methodology

The Cochrane database was searched for reviews and randomized trials and a search of the 1966-2007 Medline database of the US National Library of Medicine was conducted. The PubMed clinical search strategy used was 'HIV Antigens'. The search was limited to 'human', 'published in the last 10 years' and 'Infant birth -23 months'. The search was conducted on 19/11/08.

Papers were excluded if they did not relate to the Ultrasensitive p24 assay techniques, did not relate to diagnosis, were non-comparative, if they failed to clearly define our comparison groups, if they failed to identify/control for known confounders or if the sample sizes were too small. Papers were only included if they contained data relating to infants specifically less than 12 months old. If papers incorporated infants up to the ages of 24 months, they were included if relevant data could be extracted.

Methodological quality of included papers was at least type 2b according to the criteria of the Oxford Centre for Evidence-Based Medicine.

## Results

Our search criteria retrieved 138 results including 4 reviews. All abstracts were read: if there was any doubt as to the relevance of the article, the full text was sourced. Citations listed in relevant trials were also hand searched and reviewed. The exclusion criteria applied left a total of 6 papers for review. See Table 1

The primary outcome assessed was the sensitivity and specificity of the Ultrasensitive p24 antigen assays for the diagnosis of HIV in infants between 0-12 months old. Positive and negative likelihood ratios were calculated where possible.

## Costing

A detailed analysis by Sherman et al highlights the huge cost inefficiencies of the currently employed PMTCT programme of prophylactic treatment until antibody diagnosis at 18 months. The study suggests that this cost could be reduced by 25% if a diagnosis was reached earlier (using PCR virology) so that only those infected were treated [1]. Further, studies have shown that the Ultrasensitive p-24 antigen test is cheaper to conduct than PCR virology, suggesting a major advantage of this technique above all others suggested for the diagnosis of HIV in infants less than 12 months old.

According to Zijenah et al in Zimbabwe, the Ultrasensitive p24 assay costs US\$10 in contrast to US\$50 per DNA PCR test. These figures include equipment costs, reagents and personnel training [6]. Sutthent et al state that in Thailand, p24 testing costs only \$3 compared to \$30 for in-house DNA PCR analysis [4]. A detailed breakdown of these costs was not available.

According to Nadal et al in Switzerland, the market costs for HIV diagnosis via an Ultrasensitive p24 assay is around \$23 per test whereas RNA PCR analysis costs \$132 [5].

## Discussion

The Ultrasensitive p24 assay technique has been shown to produce sensitivities of greater than 91.7% for infants younger than 18 months across the studies, with the exception of one study which related to a considerably small sample size. The majority of studies yielded sensitivities of over 98%, supporting the use of the Ultrasensitive p24

assay technique in the screening of infants for HIV.

The specificities associated with Ultrasensitive p24 assay technique were extremely high with the majority being above 98.5%, highlighting the new technique's useful role in ensuring there is a low proportion of HIV negative infants who are exposed to unnecessary treatment.

The positive likelihood ratios range from 10 to 74 thus providing strong evidence for the validity of a positive HIV diagnosis based on the Ultrasensitive p24 assay technique. The majority of negative likelihood ratios are less than 0.1 thus providing strong evidence for the validity of a negative HIV diagnosis based on the Ultrasensitive p24 assay technique. One study indicated a higher negative likelihood ratio of 0.51.

As well as its accuracy we have also discussed how the Ultrasensitive p24 assay is significantly more cost and resource effective than its rivals. Other advantages to p24 testing are that it is relatively quick to produce results, taking around 6 hours [8].

## Summary

This review has shown that the new Ultrasensitive p24 assay is as accurate as PCR virology, significantly cheaper and less resource demanding when used to diagnose HIV in infants less than 12 months old.

## References

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2. Sherman, G.G., G. Stevens, and W.S. Stevens, Affordable diagnosis of human immunodeficiency virus infection in infants by p24 antigen detection. *Pediatr Infect Dis J*, 2004. 23(2): p. 173-6. [Medline]
3. Fiscus, S.A., et al., Ultrasensitive p24 antigen assay for diagnosis of perinatal human immunodeficiency virus type 1 infection. *J Clin Microbiol*, 2007. 45(7): p. 2274-7. [Medline]
4. Sutthent, R., et al., p24 Antigen detection assay modified with a booster step for diagnosis and monitoring of

human immunodeficiency virus type 1 infection. *J Clin Microbiol*, 2003. 41(3): p. 1016-22. [Medline]

5. Nadal, D., et al., Prospective evaluation of amplification-boosted ELISA for heat-denatured p24 antigen for diagnosis and monitoring of pediatric human immunodeficiency virus type 1 infection. *J Infect Dis*, 1999. 180(4): p. 1089-95. [Medline]

6. Zijenah, L.S., et al., Signal-boosted qualitative ultrasensitive p24 antigen assay for diagnosis of subtype C HIV-1 infection in infants under the age of 2 years. *J Acquir Immune Defic Syndr*, 2005. 39(4): p. 391-4. [Medline]

7. Lyamuya, E., et al., Performance of a modified HIV-1 p24 antigen assay for early diagnosis of HIV-1 infection in infants and prediction of mother-to-infant transmission of HIV-1 in Dar es Salaam, Tanzania. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1996. 12(4): p. 421-6. [Medline]

8. Rouet, F. and C. Rouzioux, The measurement of HIV-1 viral load in resource-limited settings: how and where? *Clin Lab*, 2007. 53(3-4): p. 135-48. [Medline]

Reference	Sample Size	Gold standard for diagnosis	Sensitivity	Specificity	+ve Likelihood Ratio	-ve Likelihood Ratio
Sherman [2]	203 samples from 90 infants aged 0-7 months	DNA PCR	98.10	98.70	74.00	0.02
	85 samples from 6 week old infants		95.70	100.00	$\alpha$	0.04
	82 samples from 3 month old infants		100.00	100.00	$\alpha$	0.00
	5 samples from 4 month old infants		100.00	100.00	$\alpha$	0.00
	31 samples from 7 month old infants		100.00	92.00	12.00	0.00
Fiscus [3]	802 specimens from 582 infants aged 0-180 days	DNA PCR	91.70	98.50	61.13	0.09
	114 samples from infants aged 0-7 days		$\beta$	99.90	$\beta$	1.00
	180 samples from infants aged 8-30 days		90.00	98.01	69.23	0.10
	367 samples from infants aged 31-90 days		93.30	98.00	46.65	0.07
	141 samples from infants aged 91-180 days		94.10	97.70	40.91	0.06
Sutthent [4]	242 samples taken from infants aged 1-6 months	DNA PCR	100.00	100.00	$\alpha$	0.00
	121 samples taken from infants aged 1-2 months		100.00	100.00	$\alpha$	0.00
	121 samples taken from infants aged 4-6 months		100.00	100.00	$\alpha$	0.00
Nadal [5]	643 samples from 246 infants and children	DNA PCR	85.37	98.80	70.85	0.14
	12 samples from infants aged 0-10 days		50.00	98.65	37.00	0.51
	10 samples from infants aged 11 days - 3 months		100.00	98.28	58.00	0.00
	19 samples from infants aged 3-6 months		100.00	100.00	$\alpha$	$\alpha$
Zijenah [6]	164 infants aged between 0-18 months	DNA PCR	96.70	96.10	24.79	0.03
	85 infants aged 0-6 months		98.10	96.90	31.65	0.02
	79 infants aged between 7-18 months		89.50	91.10	10.06	0.12
Lyamuya [7]	231 samples from infants aged 0-30 months	DNA PCR	98.40	100.00	$\delta$	0.02
	18 samples from infants aged 1-8 weeks		100.00	$\Delta$	$\delta$	$\delta$
	36 samples from infants aged 9-26 weeks		97.20	$\Delta$	$\delta$	$\delta$
	40 samples from infants aged 27-52 weeks		100.00	$\Delta$	$\delta$	$\delta$
	25 samples from infants aged 13-18		96.00	$\Delta$	$\delta$	$\delta$

	months				
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$\alpha$	There are no false +ve's or false -ve's in this data
$\beta$	Author stated the data set was too small for accurate analysis
$\gamma$	Author states sensitivities and specificities but does not state likelihood ratios or the raw data
$\delta$	Author only gives raw data for children who tested +ve for HIV