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THE PERFORMANCE OF VIROLOGICAL TESTING FOR EARLY INFANT DIAGNOSIS OF HIV: A SYSTEMATIC REVIEW

D. Mallampati[1], A. Hannaford[2], N. Sugandhi[3], J. Markby[4], M. Penazzato[4]

[1]Harvard University, Harvard Medical School, Boston, USA, [2]Mount Sinai, Icahn School of Medicine, New York, USA, [3]Mount Sinai medical center, Institute of advanced medicine, New York, USA , [4]World Health Organization, HIV Department, Geneva, Switzerland

BACKGROUND AND OBJECTIVES

Scale up of more effective PMTCT interventions requires review of the existing testing algorithm to optimize infant testing in the context of wider exposure to ARVs as a result of maternal ART and infant prophylaxis. Knowledge of the performance of virological assays at different time points and in the context of ARV exposure is critical to inform such revision.This systematic review informed the revision of the World Health Organization (WHO) infant testing algorithm by assessing diagnostic accuracy for virological testing at birth and at 6 weeks in the context of ARV exposure.

METHODS

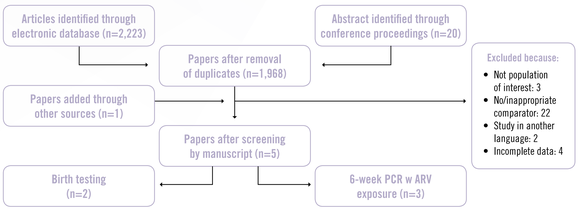
The search strategy used, aimed to consider studies published from 2009 (date of the most recent WHO guidelines on infant testing) and included the following search terms: HIV, HIV-1, HIV-2, AIDS, NAAT/NAT, PCR, whole blood, plasma, DBS, newborns, infants, children. PubMed, Embase, Cochrane Library, and LILACS as well as conference proceedings from CROI, ICASA, IAS, and the International Workshop on HIV Pediatrics were consulted. Studies were included if investigating performance of virological assays, against a standard comparator, in infants exposed to HIV and exposed to maternal ARVs or post-natal prophylaxis.

Two independent reviewers conducted the screening and a third reviewer was consulted to resolve discordance. Retrieval of missing information was sought by contacting authors. Summary estimate for performance were calculated. In order to assess the risk of bias the QUADAS-2 tool was used and the overall assessment of the quality of evidence was performed by using the GRADE approach.

RESULTS

A total of 2203 records were screened with final selection of 5 manuscripts. Three studies were included to assess the accuracy of PCR on DBS specimens and in the context of ARV exposure. The pooled sensitivity and specificity were 99.4% (98.27, 100) and 99.63% (99.11, 100) respectively. The risk of bias was judged as low yet the quality of the evidence, by using the GRADE approach, was considered low due to poor generalizability and small sample sizes.

Two studies were identified to assess PCR performance at birth compared to at 6 weeks of age. The calculated pooled sensitivity and specificity were 69.3% (61.1-77.4) and the specificity is 99.91% (99.55-100) respectively. The risk of bias in these studies was judged low but the GRADE quality of evidence for sensitivity was estimated to be low due to poor generalizability and small sample sizes.



A. Virological testing at Birth (compared to 6-week PCR)

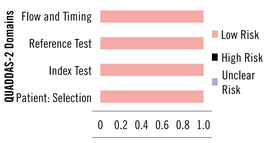
Study	Patient Characteristics	ARV Exposure	Index Test	Reference Test
Burgard et al 2012 (France)	Cohort of 1293 non-breastfeeding infants	Intrapartum prophylaxis: none, zidovudine, dual therapy, triple therapy	Amplicor or Cobas on plasma (RNA)	HIV RNA PCR on plasma at 6 months
		Intrapartum prophylaxis: None, IV ZDV, sdNVP + IV ZDV, sdNVP/other	HIV DNA PCR on PBMC (3 different methods)	
		Neonatal prophylaxis: ZDV, dual therapy, triple therapy		
Lilian et al 2010 (South Africa)	Cohort of 710 mother-infant-pairs who were breast-feeding	Maternal AZT from 28 weeks with sdNVP, infant AZT for 1 week, if suboptimal maternal prophylaxis, infant recieved 28 days AZT	HIV DNA PCR on DBS	DNA PCR on whole blood at 6w
			CAP/CT on DBS	
			Aptima on DBS	

B. Virological testing at 6 weeks with DBS (compared to whole blood)

Study	Population Characteristics	ARV Exposure	Index Test	Reference Standard
Leelawiwat et al 2009 (Thailand)	Cohort of 162 paired samples at 2 months. Non-breastfeeding	Monotherapy of short-course ZDV OR combo short course ZDV and sdNVP	Amplicor HIV-1 DNA v1.5	Whole blood
			NucliSens RNA	
Lilian et al 2010 (South Africa)	Cross-sectional study of 125 infants (4-8 weeks). Unknown breastfeeding	sdNVP to mother and infant	NucliSens RNA	DNA PCR on whole blood
Yapo et al 2013 (Cote d'Ivore)	Cross-sectional within cohort of 71 infants (4-8 weeks). 49/71 were breastfeeding	Maternal Regimen: NVP pre partum followed by ZDV/3TC post partum (3), ZDV/3TC/NVP (13), TDF/FTC/NVP, D4T/3TC/NVP (9), ZDV/3TC/ABC (1)	Biocentric (DNA)	Biocentric DNA Kit on cell pellets
		Infant prophylaxis: ZDV/3TC/NVP (11), TDF/FTC/NVP, ZDV (3), unspecified (3)	Amplicor DNA v1.5	
			HIV RNA Cell Kit	

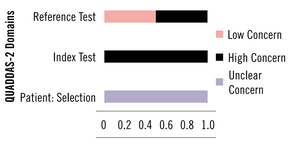
Risk of bias

Proportion of studies with low, high, or unclear risk of bias (n=2)



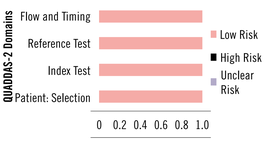
Applicability

Proportion of studies with low, high, or unclear concernes about applicability (n=2)



Risk of bias

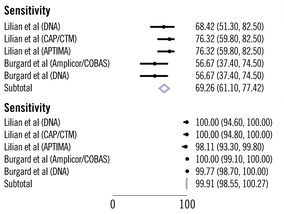
Proportion of studies with low, high, or unclear risk of bias (n=3)



Applicability

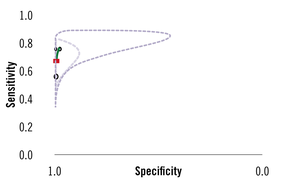
Proportion of studies with low, high, or unclear concernes about applicability (n=3)

Sensitivity

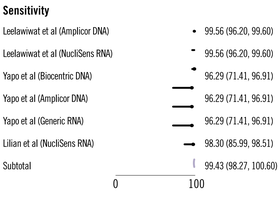


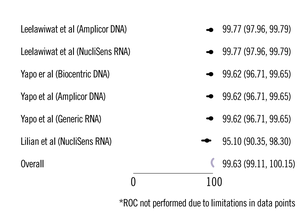
Sensitivity

ROC curve (Receiver Operating Characteristic)



Sensitivity





*ROC not performed due to limitations in data points

CONCLUSION

Our systematic review shows that there is currently no evidence to suggest that virological assays on DBS have poor performance when infants are exposed to ARVs. However only few subjects in the studies were infants exposed to triple maternal ART and postnatal prophylaxis.
The performance of PCR at birth demonstrated low sensitivity and high specificity. However, this may reflect the inability of PCRs to detect intrapartum infections rather than a lack of accuracy of the assays used. Sensitivity of PCR at birth may therefore vary depending on the transmission dynamics that are influenced by the PMTCT intervention provided.
Further research to assess accuracy of PCR at different time-points and in the context of more effective PMTCT interventions is urgently needed.

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