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Is early HIV testing of infants in poorly resourced prevention of mother to child transmission programmes unaffordable?

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Summary

OBJECTIVES Paediatric HIV infection is predominantly vertically transmitted and 90% of the global burden is carried by Sub Saharan Africa. Diagnosis of HIV infection is important to ensure access to appropriate healthcare. Prevention of mother to child transmission (PMTCT) programmes in low resource settings fail to identify HIV-infected children because of high lost to follow-up rates by 12 months of age when HIV testing is performed. The cost of diagnosing HIV infection earlier in infancy was measured.

METHODS A prospective, longitudinal, descriptive study was conducted in a PMTCT clinic in Johannesburg, South Africa over an 18-month period. From a total of 300 HIV exposed infants enrolled in an infant diagnostic study, a convenience sample of 30 was enrolled in a costing sub-study. Patient and provider costs incurred in establishing the HIV status of an exposed infant were documented to determine the societal and provider cost of performing HIV testing at 6 weeks and 12 months of age.

RESULTS The average societal cost of an earlier diagnosis of HIV is R158 less per patient than current practice as determined from 123 (82%) questionnaires. On average, early diagnosis would cost the provider R8 more per patient. PMTCT clinic attendance figures predict that earlier testing would increase the number of infants diagnosed by almost threefold.

CONCLUSIONS A marginal additional investment by government to access an earlier HIV diagnosis for infants could triple the efficacy of PMTCT programmes in identifying HIV-infected children for medical management and improved quality and quantity of life. Early diagnosis offers societal benefits that extend beyond economic savings.

keywords cost analysis, human immunodeficiency virus, diagnosis, infant, prevention of mother to child transmission

Introduction

The majority of HIV exposed children worldwide live in low resource settings where prevention of mother to child transmission (PMTCT) programmes assume that early diagnosis of HIV infection is unattainable because of the requirement for costly and complex PCR testing (Gauteng Health Department 2001; ANECCA 2003; UNAIDS 2004). Instead, HIV exposed infants are followed clinically on co-trimoxazole prophylaxis to 12 months of age when an HIV ELISA test is performed to determine HIV status. Since persistent maternal anti-HIV antibodies can result in an infant's HIV ELISA test remaining falsely positive until 18 months of age, all positive 12-month HIV ELISA tests are repeated to exclude late seroreversion (CDC 1995; Gauteng DOH 2001; ANECCA 2003).

The HIV antenatal prevalence rate in South Africa in 2003 was 27.9% translating to about 280 000 HIV exposed children born annually (DOH 2004). The HIV transmission rate varies from 10% to 35% depending on the efficacy of the PMTCT programme and the prevalence of breastfeeding. Therefore between 182 000 and 252 000 of these 280 000 children requiring regular PMTCT follow up for a period of at least 12 months will be HIV uninfected. Over a 13-month period only 185 (15%) of 1234 vertically exposed children born at Johannesburg's Coronation Women and Children's Hospital (CWCH) presented for HIV testing at 12 months of age (Sherman *et al.* 2004). Similarly high lost to follow-up rates are experienced elsewhere in this and other developing countries (ANECCA 2003; Doherty *et al.* 2003). Consequently, the PMTCT policy for follow up of infants in low resource settings was described as 'largely unrealistic' (McCoy

2002). The policy fails to identify HIV-infected children for medical care and to establish HIV transmission rates for monitoring the efficacy of PMTCT programmes. The prospect of increased global access to antiretroviral therapy adds further impetus for identifying HIV-infected children.

Established diagnostic protocols, requiring at least two HIV DNA PCR tests per infant, are prohibitively expensive in low resource settings and require adaptation to 'minimize cost and maximize accuracy' lest they continue to deny the majority of HIV exposed children worldwide access to an HIV diagnosis (CDC 1995; UNAIDS 1997). The early diagnostic protocol advocated here is adapted for local conditions and originates from an infant diagnostic study to determine an affordable, accurate HIV diagnostic protocol for infants (Table 1). The Amplicor^{TM} HIV-1 DNA Version 1.5 test (Roche Diagnostic Systems, Branchburg, NJ, USA) is a highly accurate test for infant diagnosis (Dunn *et al.* 1995; Sherman *et al.* 2000; Benjamin *et al.* 2001) and a single HIV PCR test at 6 weeks of age was 100% sensitive and specific in diagnosing perinataly acquired HIV in the infant diagnostic study compared to gold standard diagnostic protocols (Sherman *et al.* 2004). Six weeks is the earliest age at which a PCR test would detect virtually all perinatally transmitted HIV infections (Dunn *et al.* 1995; Benjamin *et al.* 2001; Benjamin 2002) and coincides with the timing of the first post-natal and immunization visit of infants. Clinical examinations at 6 weeks and 3 months of age in conjunction with the single PCR test provide additional safeguards for early diagnosis of HIV (Benjamin *et al.* 2001). Bayes' theorem, based on the CWCH–HIV prevalence and the HIV PCR test being 99% sensitive and specific, predicts that the probability of this early diagnostic protocol missing an HIV-infected child is 1.8 per 10 000 children tested (Benjamin 2002; Sherman *et al.* 2004). HIV PCR testing of dried blood spots (DBS) collected on filter paper enhances accessibility of PCR testing without compromising accuracy (Cassol *et al.* 1991; Biggar *et al.* 1997; Sherman *et al.* 2005). DBS are suited to low resource settings because they have simple transport and storage logistics and skills for venesection of young babies are not required.

This study is the first to measure the cost of diagnosing an infant's HIV infection status in the current South African PMTCT programme and to compare it to the cost of establishing an earlier diagnosis of HIV. The findings are that earlier diagnosis substantially reduces the overall societal cost of the PMTCT programme and that it improves identification of HIV-infected children.

Materials and methods

All infants born at CWCH to HIV-infected women were eligible to participate in the infant diagnostic study to determine an accurate, affordable HIV diagnostic protocol (Sherman *et al.* 2004). Approval was obtained from the University of the Witwatersrand's Ethics Committee. The diagnostic study enrolled 300 mother-infant pairs between January and October 2002. Seven 6-week-old infants were enrolled per week. Each week, the first 1–2 participants already enrolled in the diagnostic study that agreed to participate in the costing exercise were enrolled in the cost analysis sub-study. Enrolment rates were limited by the capacity of the study team. A costing questionnaire was administered by a single investigator to a convenience sample of 30 patients at five consecutive study visits when the infant was 6 weeks, 3, 4, 7 and 12 months of age (Table 1). The informants were adults, mostly mothers of the infants.

The provider and societal cost of each diagnostic option was determined. Financial costs incurred by the provider

Table 1 Schedule of clinic visits for the *infant diagnostic study*, the suggested protocol for early diagnosis (*Option 1*) and the currently recommended PMTCT follow-up visit schedule for low resource settings (*Option 2*). The visits correspond to the age of the infant. When repeat HIV ELISA testing is performed at 15–18 months of age, an additional counselling visit* is required

	6 weeks	3 months	4 months	7 months	12 months	13 months	15–18 months
Diagnostic study visits	X PCR	X PCR	*	X	X ELISA		
(n = 123)	(30)	(28)	(17)	(26)	(22)		
Option 1							
Early diagnosis protocol (HIV PCR testing)	X PCR	X *					
Option 2							
Current PMTCT follow up (HIV ELISA testing)	X	X		X	X ELISA	*	X (ELISA)

X, clinical examinations performed; PCR, HIV DNA PCR performed; ELISA, HIV ELISA performed; (ELISA), repeat HIV ELISA testing required in approximately 48% of children; (n), number of completed questionnaires available per study visit.
* Mother counselled regarding the HIV infection status of her infant.

(e.g. drugs, HIV tests) and the patient (e.g. travel fare, refreshments) were measured. The financial costs, reflecting actual money spent, were further qualified into economic costs by incorporating opportunity costs. Opportunity costs recognize the value of additional resources used like the wages forfeited by mothers when they take infants for follow-up clinic visits (Creese & Parker 1994). Economic costs incurred by both the provider and the patient were added to obtain an overall cost to society of each of the diagnostic options. It is emphasized that not all costs of each diagnostic option are measurable (e.g. the anxiety experienced by mothers awaiting the HIV status of their infants).

An ingredients-based approach was used to measure individual patient costs. Resources used, by both the provider and the patient in the process *of obtaining a diagnosis* for HIV infection status, were determined. The questionnaire documented direct costs incurred by the patient as a result of the clinic visit; personnel costs by recording the time spent with various categories of personnel by each patient at every clinic visit and the medication dispensed. To identify additional resources used by the clinic the investigators spent 3 days observing staff working in the PMTCT follow-up clinic. Resources such as consumables, medication and diagnostic tests were valued using average 2003 prices obtained from suppliers. Personnel time was valued using total cost to company packages including overtime. Although the general practice in economic costing is to exclude overtime and fringe benefits in calculating human resource costs, overtime payments were included in this instance because they are built into the basic salary. A step-down allocation process was used to allocate non-specific patient costs to equipment, furniture and buildings. The costs for capital items, excluding buildings, were calculated for the entire programme and then allocated on a per-patient basis. Building space was measured and costs based on replacement value for equivalent space at existing standard rates provided by the Centre for Scientific and Industrial Research. Capital costs were annualized to obtain annual-equivalent amounts. A discount rate of 6%, currently used by the National Treasury Department to discount public expenditure, was used to annualize all capital costs.

Costing of the HIV PCR test was done assuming DBS collection. In calculating the cost of the HIV ELISA test it was assumed that 48% of all children would test positive at 12 months of age and require repeat HIV ELISA tests (Sherman & Jones 2005). All positive HIV ELISA tests are automatically retested in the laboratory to confirm the result (UNAIDS 1997). If the HIV ELISA test is negative at 12 months of age no further testing is performed. If the HIV ELISA test is positive at 12 months of age, the cost of the test is tripled for HIV negative infants and quadrupled in HIV-infected infants because the initial positive test is retested and a subsequent specimen submitted at

Table 2 The provider costs incurred by each identified input

Recurrent costs		Capital costs	
Personnel (basic salary + overtime)		**Buildings** (e.g. waiting rooms, counselors' rooms, consultation cubicles, offices, supplies, storage space)	R2.17 per visit
Nurse assistant (R0.40 per min)	R2.00 per visit*		
Medical officer (R1.84 per min)	R27.61 per visit*		
Paediatrician (R2.13 per min)	R21.30 per visit*		
Pharmacist	R1.55 per visit		
Supervision of PMTCT programme	R0.21 per visit	**Equipment** (furniture including examination beds, double steps, filing cabinets, otoscopes and scales, etc.)	R0.71 per visit
Medication (total cost of prescription)			
Consumables (swabs, needles, gloves and syringe, etc.)			
Serum collection: HIV ELISA test	R11.06 per collection		
Plasma collection: HIV PCR test	R10.7 per collection		
DBS collection: HIV PCR test	R6.49 per collection		
Laboratory HIV tests		**Total capital cost per patient**	R13.73
HIV ELISA test	R36.00 per test		
HIV DNA PCR test	R245.25 per test		

The difference between the consumables cost for collecting plasma and serum is attributable to the difference in the cost of the collection tubes. DBS, dried blood spot.
* Average cost per visit.

15–18 months of age (Table 2). Since perinatal HIV transmission rates vary, the number of HIV-infected children who would incur the highest cost is difficult to establish. The assumption was made that 48% of patients would need three HIV ELISA tests and the remainder would require a single test erring on underestimating costs.

Results

Questionnaires were completed for 123 of the scheduled 150 visits (Table 1). Of the 27 unavailable questionnaires, 19 were not completed despite patients attending their clinic visits. This occurred predominantly at the 4-month visit, a counselling visit for which too few study personnel were initially allocated (Table 1). The remaining eight unavailable questionnaires were due to patients being lost to follow up. The costing sub-study sample was representative of the infant diagnostic study sample as HIV transmission, lost to follow up and maternal unemployment rates were similar between the two groups. All reported costs are in South African rands (R1 = US $0.17), and time periods represent averages.

The cost incurred by the patient to attend five visits was R251 (range: R38–861) at R50 per visit (range: R31–66) (Figure 1). Of the 30 mothers interviewed, 17 (57%) were unemployed for the duration of the study. On average 47% of mothers attending at each of the five study time-points were unemployed. The total time spent travelling per visit was 1 h 9 min (range: 10 min–9 h). The inconvenience of long distance travel is another opportunity cost that cannot be measured in financial terms.

The personnel cost per patient at each visit remained fairly constant ranging from R36 to 47 (Figure 2). Nursing assistants spent 5 min per visit with a patient and an additional 6 min if blood was collected (Table 2). Patient visits were equally shared between medical officers ($n = 64$) and paediatricians ($n = 59$).

The medical officer spent 15 min per patient visit, 5 min more than the more highly paid specialist. The 4-month counselling visit was comparatively long at 25 min per patient. Predictably, co-trimoxazole was the predominant medication prescribed (Figure 2).

The total cost of the two diagnostic options to the provider and society is represented in Table 3. The provider cost of the two diagnostic options is essentially the same; but the cost to society of the current PMTCT diagnostic protocol is substantially more than the PCR option. A sensitivity analysis assuming 35% of infants tested HIV ELISA positive at 12 months of age reduces the cost of Option 2 by R16 (Chantry *et al.* 1995; Moodley *et al.* 1995). A reduced HIV PCR test price will decrease the cost of Option 1 rand for rand.

The CWCH–PMTCT clinic attendance figures reveal that 39% of infants are available for early HIV testing as

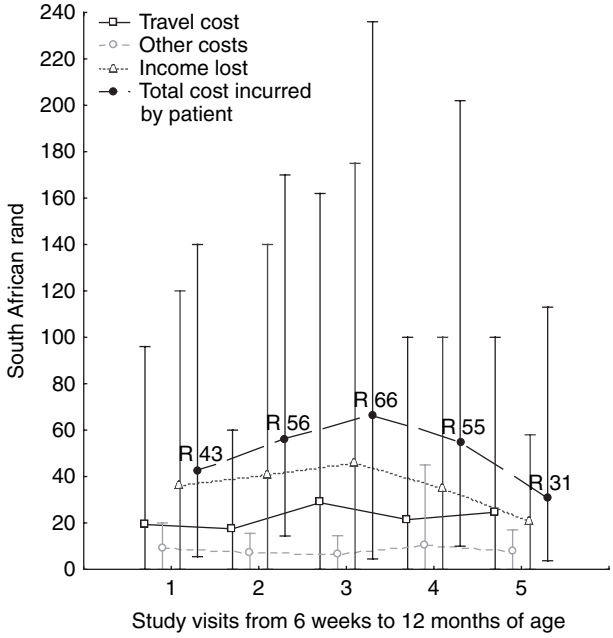

Figure 1 The average, minimum and maximum cost incurred by the patient to attend the five clinic visits. The total cost is the sum of the travel fare, income lost and other costs (e.g. child care services for children left at home and refreshments). The lowest and highest cost incurred by a patient for a single visit was R3.70 and 236.00, respectively.

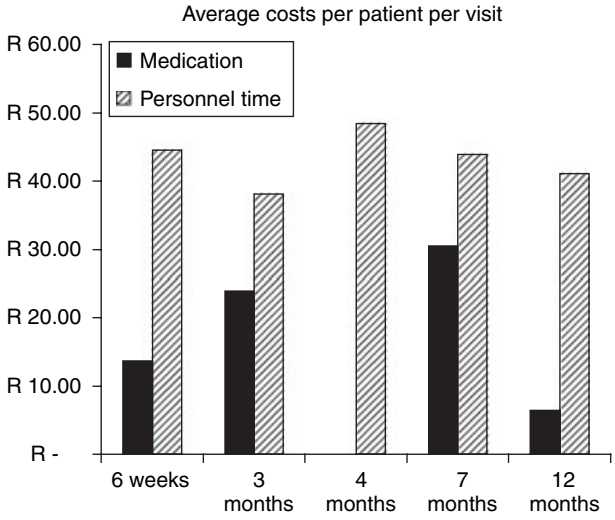

Figure 2 Average personnel and medication costs at the five study visits. The increased dose of co-trimoxazole required with age accounts for the rise in medication costs except at 12 months when prophylaxis is discontinued in most infants (Gauteng DOH 2001).

Table 3 The average provider and societal cost of the PMTCT programme per patient for the two diagnostic options

	Provider cost	Range	Societal cost	Range
Option 1	R375.33	(R310.96–458.93)	R474.63	(R330.86–R768.93)
Option 2	R366.95	(R218.85–R478.85)	R632.42	(R271.69–R1354.59)
Difference	R8.38		R−157.79	

Current practice represents an average saving of R8 per patient to government but the societal cost of the programme is currently R158 per patient more in comparison to introducing an HIV DNA PCR test.

compared to 15% by 12 months of age (Sherman *et al.* 2004). During the 13-month period when 1234 infants were enrolled, only 17 (15%) of an anticipated 111 HIV-infected children were identified by HIV testing at 12 months of age. Earlier testing at 6 weeks of age would have identified 43 (39%) infected infants. On a national scale and based on testing of all exposed infants, the additional provider cost for PCR testing for 280 000 HIV exposed infants per annum would be R2.4 million but the societal saving would amount to R44 million with more efficient identification of HIV-infected children. Introduction of earlier HIV testing into the current national PMTCT programme would allow approximately 110 000 infants access to an HIV diagnosis, reaching about 70 000 more infants per annum than is presently being achieved.

Discussion

The cost of diagnosing HIV infection in exposed infants was measured in the context of current recommendations for PMTCT follow-up programmes in low resource settings. The cost of an alternative diagnostic strategy, which could realistically be achieved under local conditions, was established for comparison. In delivering healthcare, a government has the responsibility to consider the cost to society of a programme despite being directly responsible only for the provider cost of the programme (Creese & Parker 1994) and to provide an equitable and accessible service. Earlier HIV testing of infants would reduce the societal cost of the current PMTCT follow-up programme by 25% whilst marginally increasing the provider cost. The saving is attributable to reduced patient costs by sparing a population of predominantly HIV-uninfected children additional clinic visits. Paradoxically, the reduction in societal cost would increase the efficacy of identifying HIV-infected children almost threefold. Access to an earlier diagnosis is likely to increase this rate further.

To our knowledge, this study is the first to assess the cost of infant diagnosis in the context of a PMTCT follow-up programme in a low-middle income country. The data is vital for informing policy in low resource settings where follow-up care of HIV exposed children remains suboptimal (McCoy 2002; ANECCA 2003; Doherty *et al.* 2003; Sherman *et al.* 2004). The study sample, although small, was representative; thus the costs are likely to reflect the true situation in this urban PMTCT clinic (Sherman *et al.* 2004).

Regular clinical monitoring contributes to improved healthcare of children, especially those in vulnerable circumstances, like HIV affected children. The current PMTCT follow up of HIV-exposed infants occurs in isolation of other infant medical services like immunization, growth monitoring and treatment of acute illnesses which is likely to contribute to the high lost to follow-up rates. Research on restructuring PMTCT follow-up care is necessary to achieve early identification of HIV-infected children for HIV specific medical care and to capture HIV exposed but uninfected children within the general child healthcare service.

The requirement by current infant diagnostic protocols for at least two HIV PCR tests is a luxury poorly resourced PMTCT programmes cannot afford. Although highly accurate, a single HIV PCR test is not expected to be infallible and additional clinical examinations and HIV testing in selected children will be necessary where misdiagnosis is suspected and particularly where post-natal transmission has occurred. Ongoing evaluation of infant diagnostic protocols adapted for local settings and incorporating new technology is essential. Monitoring the efficacy and cost of a restructured programme is imperative to optimize health care for all infants according to resources expended.

Current PMTCT follow-up programmes for infants in low resource settings are ineffective because of high lost to follow-up rates. Identification of HIV-infected children is critical because healthcare delivery is known to improve their quality and quantity of life. This data dispels the notion that early diagnosis of HIV, employing an accurate diagnostic protocol adapted to suit local circumstances, is unaffordable in low resource settings. Early HIV testing would triple identification of HIV-infected children at virtually no additional cost and the benefit to society would exceed significant economic savings.

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