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# MPH dissertation

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Title: Analysis of HIV early infant diagnosis and linkage to care in the Western Cape: A laboratory perspective.

February 2012

University of Cape Town

## Contents:

1. Literature review
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3. Full article (include tables in figures)
4. Supplementary figures
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## **Literature Review of MPH dissertation**

**Dissertation title: Outcomes of HIV early infant diagnosis, a laboratory perspective**

### Introduction and purpose of the review

Prevention of mother-to-child transmission (PMTCT) of HIV is the cornerstones of HIV prevention programs. The principle of using antiretrovirals (ARV) to reduce the risk of transmission from mother to child is well established as a range of PMTCT regimens with varying efficacies have been widely studied and reviewed<sup>1</sup>. In South Africa and other Sub-Saharan countries, single dose Nevirapine, amongst other cost- effective regimens, have been adopted as part of the national HIV prevention program<sup>2</sup> since 2003.

The initiation of this lifesaving program, however, is only the beginning of a comprehensive care to combat paediatric HIV infection. The traditional PMTCT cascade focuses on the identification of HIV infected mothers and delivery of prophylaxis to mother and baby<sup>3:4</sup>. In order to minimise the morbidity and mortality of HIV- infected infants, a strategy for the care for all HIV exposed infants are required. Specifically, Infant diagnosis of HIV infection and linkage of HIV infected infant to care are among the top priorities of the care for HIV exposed infants. This review will outline the evolution of PMTCT regimens in the Western Cape Province and focuses on the various aspects of the paediatric HIV programme downstream from the provision of PMTCT. The aim is to provide a background to the dissertation which will focus on the outcomes of HIV early infant diagnosis (EID) and linkage to care in the province.

### Evolution of PMTCT regimens in the Western Cape Province

Following the landmark study in Thailand<sup>5</sup> where AZT given to pregnant mother from 34 weeks was shown to reduce the HIV transmission from 18.9% to 9.4%, the provision of AZT was piloted in two obstetrics units in Khayelitsha in 1999. This herald the start of pilot PMTCT programs in the Western Cape Province. AZT and other single-drug PMTCT such as the single dose Nevirapine<sup>6</sup> was rolled out to more pilot sites in Western Cape in the ensuing

years. It was not until 2003, forced by the constitutional court ruling, the single dose Nevirapine regimen was expanded to the rest of South Africa, including the Western Cape Province, making the standard of care in line with the WHO guideline<sup>7</sup> of single agent PMTCT at the time.

When the availability of highly active antiretroviral therapy (HAART) had become increasingly available in adult in 2004, the standard of care for women with advanced HIV (WHO stage 3 or 4 or CD4 count less than 200cell/mm<sup>3</sup>) was to receive HAART. For those who are not eligible for HAART, various multi-drug regimens of PMTCT were further rolled out in the province. AZT given to pregnant mother from 28 weeks followed by single dose Nevirapine at birth became available in the province in 2006. This regimen was subsequently adopted in the 2008 National PMTCT guideline<sup>2</sup>. By 2009 and 2010, the AZT was further extended to be given from 14 week during pregnancy and infant prophylaxis of Nevirapine to six weeks post partum (or after cessation of breastfeeding) in the latest iteration of the national PMTCT guideline<sup>8</sup>. These evolutions in the standard of care was in line with the revised 2010 WHO guidelines<sup>9</sup>.

Despite its very early exposure to PMTCT, the implementation and rollout of the PMTCT program in Western Cape is hindered by several factors. On the national level, the HIV denialism associated with the government at the time resulted in little political will to implement HIV prevention programs. The relative high cost of ARV in the context of resource limited setting is another important reason for the slow rollout of PMTCT nationally. On the program level, lower coverage of PMTCT in area where access to basic health services is a major problem<sup>10</sup>. This lack of access, due to a combination of skilled staff shortage and logistic constraints<sup>11</sup>, hampers all aspect of the PMTCT cascade from counselling and testing of mothers to reliable provision of ART for the purpose of PMTCT.

On a personal level, the fear of the diagnosis and the stigma associated with HIV<sup>12</sup> is among reasons that the uptake of counselling and testing service at the antenatal clinic is low.

#### PCR as a tool for HIV early infant diagnosis

Irrespective of the PMTCT program success, early infant diagnosis of HIV infection forms a critical part of the care of HIV exposed infants. Offered to infants that are HIV exposed, EID uses polymerase chain reaction (PCR) to detect viral genome. Conventional antibody based assays cannot be used to reliably diagnose HIV infection in infants if the mother is HIV infected. The trans-placental maternal antibody against HIV in the first 18 months of life necessitates a direct method of HIV detection.

PCR is both sensitive and specific<sup>13;14</sup> for the detection of paediatric HIV infection, but is relatively expensive, requires specialised laboratory equipment, and is technically demanding for the laboratory staff. PCR is also a time consuming assay. Despite recent improvement in PCR technology, most commercial PCR will take most of one working day to complete. This means EID is firmly in the domain of centralised specialist laboratories, and same day turnaround time is largely out of reach for the public sector of low and middle income countries<sup>15;16</sup>.

#### Importance of EID on paediatric HIV care

According to the 2011 World Health Organization/Joint United Nations Programme on HIV/AIDS/United Nations Children's Fund (WHO/UNAIDS/UNICEF) statistics, approximately 390,000 children acquired HIV infection in 2010. Majority of these HIV infections were acquired either perinatally or through breast feeding. Unlike the infection in adults, early infant HIV infection often progress rapidly, resulting in mortality of 50% in the first year of life<sup>17</sup>. Fortunately the high mortality associated with early HIV infection can be largely mitigated by the administration early antiretroviral therapy (ART)<sup>18</sup>. Thus early identification of HIV infection in infants is of individual and public health benefit, as it may

facilitate the timely and appropriate clinical management of disease, leading to improved quality of life and reduced infant morbidity and mortality<sup>19</sup>.

### Logistical issues around EID

The logistical factors are threats to an efficient EID service in sub-Saharan Africa. For laboratories to generate quality results, collection of infant blood samples and transport of the samples over long distances in a stable condition is critical. The Kenyan experience showed it can take up to three weeks from specimen collection to arrival at the laboratory. To this end, protocols of dried blood spot had played a major role in expanding the reach of EID<sup>20;21</sup>.

Equally, the timeous return of laboratory results to the health care worker in the absence of IT infrastructure is a major challenge. While studies in Botswana showed in an efficient setting, a 9 day delay from specimen collection to receipt of result at the facility<sup>20</sup>, other African studies of more remote rural settings indicate that it may take on average 3-6 weeks from sample collection to the return of the result to the health facility<sup>22;23</sup>.

### Return of EID result to caregiver

The biggest logistical challenge regarding EID is arguably the return of HIV PCR result to the mother or the caregiver of the child. As point-of-care testing is not currently available and same-day turnaround time for HIV PCR is not feasible since the caregiver will need to return to the facility at a later stage for the PCR result. Accessing health facilities can be a costly and time consuming exercise. Few available data in sub-Saharan Africa suggests that many caregivers elect not to return for the result of EID. A study conducted in Kwa-Zulu Natal<sup>24</sup> showed that 43% of the mothers never returned for their children's PCR result. A study in Tanzania showed that not only did 45% of the caregivers failed to return but 14% of the caregivers who received the positive PCR result had done so after their children had demised<sup>25</sup>. Thus it is not only important to make sure the EID result is returned to the child's

caregiver, in the case of a positive result, delay in returning result may prove to be fatal for the child.

#### HIV disease and early antiretroviral therapy in infants

The main purpose of EID is to triage HIV exposed infants for early intervention. Prior to the early HAART era, the WHO recommend<sup>26</sup> HIV infected children would received co-trimoxazole prophylaxis until such time that they are either symptomatically or immunologically eligible for ART. This rationale was the convention used for adult ART, where ARV was deferred due to both program cost constraint and the intention to limit drug toxicity in those that does not yet require ARV. However, the first year of life is a perilous period for a peri-natally infected child. A randomised study conducted in Zambia indicated that the use of co-trimoxazole prophylaxis had resulted in 43% reduction in mortality in the first 19 months of life<sup>27</sup>. Despite this effective intervention, the mortality rate in the co-trimoxazole arm was 28%. Pneumonia, diarrhoeal illness, failure to thrive, BCGosis and tuberculosis are amongst the commonest opportunistic illness that present in these children<sup>28-</sup><sup>30</sup>. The investigating team of the children with early antiretroviral therapy (CHER) study challenged the paradigm of deferred antiretroviral in children, arguing that the immature immune system of a newborn is at high risk of HIV disease progression and that early HAART may reverse the mortality seen in the early infant life.

The outcome of CHER study showed that by initiating ART as soon as HIV diagnosis is made in the infant (early ART), there was 76% reduction in early mortality and 75% reduction in HIV disease progression<sup>18</sup>. This dramatic effect prompted the release of the new WHO paediatric treatment guideline<sup>31</sup> in 2010 where early ART is recommended in all children less than 24 months of age.

#### The South African National guideline on EID and early ART

The local guideline in South Africa was similarly adjusted to include children under one years of age in the eligible criteria<sup>32</sup>. In South Africa, in order to encourage the caregiver of

HIV exposed infant to return, the EID visit coincides with the early immunization visit at 6, 10 and 14 week<sup>8</sup>. This integration of service makes a lot of sense logistically as it reduces the number of postnatal follow ups and allows time for the delay between getting the blood sample to the laboratory, HIV PCR testing in the laboratory and returning of result to the health facility. The local guideline also stipulated that a confirmation of HIV PCR in the form of baseline HIV-1 RNA viral load should be performed at the first ARV visit. Thereafter, HIV viral load should be monitored at 6 months and one year after the initiation of HAART. For HIV infected infants, the interval between testing and receiving result may be too long which results in delay of ART initiation. Some of these children often present at district hospitals or even tertiary hospitals with opportunistic infections. In these health facilities, HIV PCRs are often performed as part of symptomatic HIV diagnosis. If the HIV diagnosis is made in the first year of life, according to the 2010 National guideline, ART should be rapidly initiated in these facilities.

#### Linked to HIV care

Key barriers such as staff training need to be addressed before a smooth paediatric ARV program can be delivered. Paediatric ARV had always been initiated by specialised paediatricians. In order for early HAART to be widely available, primary health care staff, supported by specialists, should be able to initiate and manage infant ARV. Efficient referral systems from EID/immunization clinics should be in place so that the delay between diagnosis of HIV infection and the initiation of ART is minimised. This may be difficult to achieve as recent data from Malawi found that only 320 (30%) of 1084 infant tested HIV PCR positive had enrolled in subsequent HIV care<sup>33</sup>. Despite good EID turnaround time in the Botswana study<sup>20</sup>, only 65% of PCR positive infant were linked to care. These studies were conducted at a time where the paediatric guidelines were in the process of revision. More recently, study conducted in four resourced-limited countries<sup>34</sup> demonstrated the

difficulties related to linkage to care. The proportion of PCR positive children linked to care for Senegal, Uganda and Cambodia were 22%, 37% and 38% respectively. Lack of efficient referral service and poor integration of services are two reasons the proportion of linkage to care is low. Further studies in the era of the new guideline will be required to assess whether interventions to improve linkage to care is necessary.

### Conclusion

Ciaranello et al<sup>35</sup> suggested that the delivery of early infant diagnosis in the resourced-constraint setting should be viewed as a cascade where four levels of the service deserves individual attention. Firstly, HIV testing should be offered to infants that requires them regardless of known HIV exposure and history of PMTCT. Secondly, the specimen must be collected, transported and processed effectively. Thirdly, the result must be returned to the health care provider, the patient and caregiver promptly. Finally, children should be referred to appropriate service for intervention. Currently, there is little published data evaluating the performance of the PMTCT and EID program in South Africa. Grimwood and colleagues looked at the outcomes of PMTCT at 58 antenatal clinics in three provinces<sup>36</sup>. The result is encouraging. Proportion of PCR positive infant was reduced by 75.2%. However, little systematic data is available on the linkage to care of PCR positive infants. The questions remain whether the system is able to delivery the result to the caregiver and refer the infected children to care.

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**Title: Analysis of HIV early infant diagnosis and linkage to care in the Western Cape: A laboratory perspective.**

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**Abstract:**

**Introduction:**

Prevention of Mother-to-Child Transmission (PMTCT) is a well established HIV prevention strategy that had prevented countless infant HIV infection and mortality in sub-Saharan Africa. Despite its wide implementation, few studies and surveys are able to effectively measure its progress. Centralized laboratories that perform early infant diagnosis of HIV are at a unique position to gather data on the progress of PMTCT.

**Method:**

We conducted a retrospective cohort study analyzing archived demographic and laboratory data from the national pathology service provider, National Health Laboratory Service. All test requests of HIV PCR as part of early infant diagnosis program between 2005 and 2011 were extracted and analysed to monitor progress of program. HIV viral load test requests were further extracted with the purpose of linking positive PCR result to subsequent virological testing, a proxy for referral to care.

**Results:**

A total of 83698 first time early infant test requests were extracted. Overall, 6322 (7.6%) of infants tested PCR positive. The proportion of PCR-positive children declined steadily from 12% in 2005 to 3% in 2011. Our matching algorithm yielded 4105 (65%) children with matching positive PCR and viral load testing episodes. The proportion of matched PCR-VL improved from 54% in 2005 to 71% in 2010 and the delay between match PCR-VL was reduced from 146 days in 2005 to 33 days in 2010.

**Discussion:** Our data suggest there had been substantial improvement in both the effectiveness of PMTCT services and the capacity for referral of infected infants to care. However, the large proportion of PCR-positive children who do not appear to be enrolled into subsequent HIV care and treatment services is of concern, and warrants further research. Although using laboratory data to evaluate program progress has some limitations, it is an efficient and readily available resource to monitor HIV programmes and inform health policies in wider settings.

## **Introduction:**

Prevention of Mother-to-Child Transmission (PMTCT) programmes are one of the most effective means of preventing HIV infection<sup>1</sup>. In South Africa where an estimated 29.4% of pregnant mothers are infected with HIV<sup>2</sup>, mother-to-child transmission of HIV is associated with a large burden of morbidity and mortality. Prior to the implementation of PMTCT programmes, early infant mortality was high and a peak in the 2-3 month age group was partly attributed to the HIV infection among infants<sup>3</sup>. Thus PMTCT plays an important role in the overall HIV prevention program.

In order to assess the impact of the PMTCT program, direct measures of PMTCT programme outcomes are required. However until recently, very little data were available on the efficacy of PMTCT in South Africa. An evaluation of 58 antenatal clinic showed the HIV infection rate was on the decline<sup>4</sup>. In a recent study, Goga and Dinh et al<sup>5</sup> conducted a facility- based survey of PMTCT efficacy using data from immunization clinics in South Africa. These authors found that the mother to child transmission rate to be 3.3% for the Western Cape Province and 3.5% for South Africa overall.

Early infant diagnosis (EID) of HIV by polymerase chain reaction (PCR) is a direct measure of PMTCT effectiveness. PCR testing is necessary because in infants below 18 months of age, maternal antibodies render the conventional rapid test difficult to interpret. Whereas a positive rapid test identifies the infant as HIV exposed, a positive PCR identifies the infant as HIV infected. This early diagnosis of infant HIV infection allows rapid referral to care. In these cases, early initiation of Antiretroviral Therapy (ART) is critical. Violari and colleagues demonstrated in the Children with Early Antiretroviral Therapy (CHER) study that while HIV infection in the first year of life is associated with high mortality, this can be largely mitigated by the administration of early ART<sup>6</sup>.

For both EID and the subsequent immunological/virological monitoring of infected infants, specialised laboratory staff and equipment are required. The prerequisites place EID firmly in the domain of a few centralized specialist laboratories. By analyzing laboratory testing data for EID, one could gain useful insight into the efficacy of PMTCT and health system issues relating to referral to early infant ART. However, there is little published data on the use of specialist laboratory data to describe the implementation of early infant diagnosis and subsequent referral of HIV-infected infants to paediatric HIV care and treatment services.

The PMTCT and early infant diagnosis program had been provided through a range of primary and tertiary health facilities by the provincial Department of Health in Western Cape Province since 2001. The provision of the deferred ART was initially based on the 2004 WHO recommendation on antiretroviral drugs for treating HIV infection in infants in resource-constrained settings<sup>7</sup>. The early infant diagnosis is performed at well baby clinics in primary care facilities. Once diagnosis is made, the child is referred to central facility for follow up and initiation of ART once eligible. Following the outcome of CHER study in 2008, early ART gradually became available in the province through the paediatric services in their academic centres and their outreach programmes. Baseline HIV viral load was performed in all PCR positive infants enrolled into the ART programme. This baseline viral load serves as a confirmation of the positive PCR result.

National Health Laboratory Service (NHLS) is a South African national pathology organization that provides pathology service for the entire public sector in South Africa.

NHLS was thus the sole provider of HIV PCR and HIV viral load testing for the provincial PMTCT and ART programme. All patient details including health facility data, date of testing, demographic detail and test requested were captured from the laboratory request form onto the laboratory information system by laboratory clerk prior to testing. This accuracy process is monitored by internal reviewing 5% of all test requests. The corporate data warehouse (CDW) of NHLS has routinely archived all demographic and laboratory testing data from the laboratory information system since 2005. We retrieved data from the archive of NHLS CDW on all episodes of HIV PCR and HIV viral load in the Western Cape from January 2005 to July 2011.

### **Methods:**

This study was a retrospective cohort study to evaluate the early infant HIV diagnosis (EID) service in the Western Cape Province of South Africa using routine laboratory data. We examined the trends in PCR-positive test results and the subsequent referral of infected infants based on the availability of HIV viral load test results. The turnaround time between PCR diagnosis and subsequent viral load was also assessed in this study.

Yearly data for HIV PCR and HIV viral load were concatenated and non-diagnostic testing episodes such as external quality assurance samples were removed from the analysis. Any duplicate data were tagged and removed. For HIV PCR, tests with missing results were recoded to positive/negative/equivocal, based on best available information in the extracted laboratory data or removed from the analysis because the test could not be performed. Serial testing of the same individual was identified using a combination of identical folder number, surname and/or date of birth. These episodes were tagged and ordered by the date of testing and only the first episode of each individual from children less than 2 years of age and the HIV viral load results from children less than 5 years of age were included in the analyses. Any positive testing episodes that is not the first test is considered repeat testing and therefore not included in the analysis to prevent duplication. The facility number allocated to each of the infants in western Cape are unique and thus duplication in facility number is not a result of different patients in different clinics.

In order to identify the HIV infected infants that were followed up and enrolled into the ART programme, we used linked, subsequent HIV viral load testing as a proxy because all infants in the ART program in the province received a baseline HIV viral load testing immediately prior to commencement of ART. PCR and viral load from the same individuals were linked by common personal identifiers. In order to have a both sensitive and specific linkage process, we chose to link the first PCR and viral load episodes with combinations of the hospital folder number, full name and date of birth in an iterative manner..

In a sensitivity analysis, we derived two separate data sets representing (i) definitive and (ii) probable HIV PCR and HIVVL links in order to assess how the linkage algorithms may have influenced the study findings. An identical full surname or hospital folder number in combination with an identical date of birth were considered definitive match. Any combinations of partial surname date of birth and hospital folder number was considered probable matches (see supplementary figure 3). All successfully linked data were checked and any viral load that preceded the HIV PCR was removed from the final merged dataset. The delay in days between the first PCR and the first viral load was considered the approximate turnaround time for referring a PCR positive child to ART. PCR positive children that did not have a subsequent HIV viral load were considered non-retention in care.

Statistical analysis was performed by statistical software StataSE (version 10.0, Statcorp, Texas, USA). Continuous variables were described using median and interquartile range (IQR) while proportions/percentages for were calculated for categorical variables. Odds ratios (OR) with 95% CI were calculated to demonstrate associations between categorical variables and stratified analyses were used to assess the effect of confounding. The study was approved by the Research and Ethics committee of the Faculty of Health Sciences at University of Cape Town.

## **Results:**

### HIV PCR results

The search of NHLS CDW archive yielded 97235 electronic records of HIV PCR testing in the Western Cape Province. After removing duplicate records, non-diagnostic episodes, insufficient samples and unresolved tests, 94186 episodes remained. Of these remaining episodes, 2989 (3%) were performed on children two years or older and 7499 (8%) were repeat tests of previously tested children. The proportion of repeat testing increased from 317/8653 in 2005 (4%) to 1163/10446 (11%) in 2011. Of the 83698 episodes of first time PCR from children less than 2 years of age, 6322 (7.6%) tested positive, 76956 (91.9%) tested negative and 418 (0.5%) had equivocal PCR results, (supplementary figure 1). The breakdown of the PCR results by year, gender, location and age is shown in table 1.

In 2005, 303 health facilities were the sources of HIV PCR testing. This number rose to 341 facilities in 2010. The turnaround time of the HIV PCR from date taken to date of test completion was reduced from 6 days (IQR 5-8days) to 2 days (IQR 1-2 days). While the number of HIV PCR testing gradually increased from 8000 to 16,000 per year, the proportion of PCR positive children had steadily declined from 12% in 2005 to 3% in 2011. The median age of first time HIV PCR testing was reduced from 4 months (IQR 3.1-5 months) in 2005 to 1.5 months (IQR 1.4-2.1 months) in 2011. Thirteen percent of PCR testing came from tertiary hospitals where specialist paediatric services were available and 69% of PCR tests were from health facility in urban sub-districts in the City of Cape Town. No significant changes in the proportions of tertiary and urban PCR testing were observed over the 5 year study period. Infants from tertiary centres were much more likely to be PCR positive (OR 5.6, 95% CI 5.3-5.9).

### HIV VL result

The HIV viral load test requests extracted were put through a similar cleaning process as HIV PCR (supplementary figure 2). Only 34 140 of the 445 629 total electronic episodes of HIV viral load were completed diagnostic HIV VL for children less than 5 years of age. Of these, 22487 were follow-up testing and thus only 11653 episodes were the first HIV viral load test of each child. Only these episodes were included in the PCR-VL linked analysis. The number of facility that test HIV viral load rose from 91 in 2005 to 220 in 2010.

### Linking PCR to VL episodes

Using the definitive matching algorithm (dark grey boxes of supplementary figure 3), we found 3414/6322 (54%) children with first HIV PCR that had a matching episode of HIV viral load. Even with the expanded search criteria, we were only able to link a further 691 probable matches (11%) resulting in 4105 (65%) total linked PCR-VL episodes (appendix figure 3). The relatively small proportion of probable links maintained its trend over the study period (figure1). We decided to proceed to further data analysis including all definite and probable matches.

### Analysis of linked vs unlinked episodes

The breakdown and number of linked versus unlinked positive PCR episodes are shown in table 2. Over the study period, the proportion of linked HIV PCR-VL episodes had increased from 54% in 2005 to 71% in 2010. Despite only contributing toward 13% of all PCR tests requested, the tertiary centres were responsible for 45% of the linked episodes. In particular, Cape Town's largest paediatric hospital contributed 25% of all linked episodes. The linked rate of the tertiary centre (69%) was greater than that of the primary care centres (58%).

The urban centre linkage rate (68%) is substantially better than the rural (50%) counterparts as well. The difference remained significant even after taking into account that the urban centres had more tertiary centres.

Children greater than 2 months of age appeared to be less likely to be linked (OR 0.73, 95% CI 0.64-0.81) compared to younger infants. However, this association was likely confounded by the year of testing because after stratifying by year of testing, the proportion of linked children was very similar regardless of the age of the children.

### Characteristics of the PCR-positive children referred for HIV care and treatment

The median delay between PCR and VL decreased from 146 days in 2005 to 33 days in 2010. A notable decrease was observed in 2008. The delay was halved from 81 days in 2007 to 39 days in 2008. Overall, 66% and 85% of the PCR-VL delays were less than 150 days and 365 days respectively. In 2010, 83% of the PCR-VL delays were less than 150 days compared to the 50% in 2005. Two thirds of the PCR-VL delays in 2005 were less than 1 year. This figure was improved to 99% in 2010.

The two major academic centres, Red Cross Children's Memorial Hospital and Tygerberg Hospital, had much shorter delay between the testing of PCR and viral load. The median delays of children from these two hospitals were 13 days (IQR 5-68 days) compared to the rest of the children who had a median delay of 87 days (IQR 28-287 days). The overall trend of reductions in delays over calendar years was similar for the two academic centres and the rest of the facilities. The major reduction in delay during the 2007/2008 period was similarly observed in tertiary centres and non-tertiary centres.

The median age of children undergoing their first HIV viral load testing was 96 days over the entire study period (IQR 50-169 days). This age had steadily decreased from 119 days in 2005 to 60 days in 2010, with 2007/2008 being the year of the most significant decrease (from 103 days in 2007 to 73 days in 2008). However, the reduction in median age of HIV viral load was mainly observed outside the two academic centres (Figure 3). The age of first HIV viral load in Red Cross Children's Memorial Hospital and Tygerberg hospital remained constant over the study period.

## **Discussion:**

### Improved PMTCT and EID

Our data showed that the number of tested infant doubled over the six year period but the PCR positive rate was reduced from 12% to 3%. This steady decline speaks of the success of PMTCT in the province. Furthermore, the increased number of PCR testing facilities and reduction in laboratory turnaround time clearly demonstrated that the capacity of testing was

substantially improved. With access to more facilities, the median age of children tested was reduced to 1.5 months in 2011.

The few tertiary paediatric hospitals contributed to a high proportion of the total HIV PCR tests requested. As hospital in-patients are mostly children with severe disease, our stratified analysis showed that infants from tertiary centres were 5.6 times much more likely to be PCR positive. When focusing on non-tertiary centres cases only, the reduction in HIV infection remained significant (from 8.2% in 2005 to 2.8% in 2011). Similar significant reductions were seen in rural centres when urban facilities are excluded from the analysis. Therefore the effect of improved PMTCT and EID is not limited to the well resourced areas. The increased PCR positive proportion seen in older children is a result of different use of the HIV PCR. In the older children where the test is exclusively used for HIV diagnosis, the probability of PCR test being positive is much higher, representing children who previously missed EID and currently presenting with clinical illness.

However, the increased testing capacity also resulted in increasing number of repeat testing within individual infants. The reason for the repeat HIV PCR tests is unclear, but may point towards a potential problem in returning the laboratory result to the caregiver of the infant and health care worker. Studies conducted in other parts of Africa showed that delay in the return of EID results to the clinics and failure of the caregivers to return for EID result is common<sup>8-11</sup>.

#### Poor linkage of PCR positive infants to care

Our linkage of HIV VL to PCR-positive test results shows that less than two-thirds of children testing positive go on to be enrolled in further HIV care and treatment services, as indicated by a subsequent HIV viral load. This proportion did not change appreciably even when the linkage criteria had been made less stringent (raising the possibility of false-positive linkages). However, this proportion increased over the 5 years study period with 71% of the HIV infected infants in 2010 had a subsequent HIV viral load.

There are several possibilities which could result in the non-retention of PCR positive infants. First, the infant could have demised before the caregiver had an opportunity to attend a clinic where ART could be given to the infected infant. A Tanzanian study showed that 14% of caregivers received the EID result when their child had already demised<sup>10</sup>. Our manual search revealed that many of the HIV PCR positive episodes had other hospitalizations where additional inpatient investigations such as bacterial culture, TB cultures and tests for opportunistic infections were done. This symptomatic HIV disease was reflected even in the linked episodes where 45% originated from tertiary paediatric services. Second, the non-retention could be due to the migration of infants and their mothers/caregivers. Due to better health infrastructure in the Western Cape, many pregnant mothers elect to travel from neighboring provinces, especially the Eastern Cape Province for the delivery and post natal services. It is possible that after the early infant testing, the HIV-positive results were never received and the subsequent follow up of HIV infection was done in another province. However there is little evidence that the levels of migration could account for the magnitude of the non-retention seen here. Third, multiple facility/folder numbers may be created of each infants and this would hamper the linking of the PCR to subsequent VL, resulting in under-estimation of linked infants. Although this may potentially be an issue, the use of combinations of two further patient identifiers should capture any duplicate tests from the same infant, despite different facility numbers.

The time delay between HIV PCR and first HIV viral load decreased across calendar year. This is compatible with the change in WHO recommendation of infant treatment and steady increased access to ARV facilities. For the latter, the increase number of sites that submit HIV viral load request more than doubled over the study period, pointing towards increasing capacity for paediatric treatment. However, the median delay was still more than 1 month. Several factors contribute towards this long delay. First, although the median laboratory turnaround time of HIV PCR had been reduced to 2 days, this delay would still require the mother to return to the clinic to receive the result. Further to this, the clinics that provide ART is often separate from the ones that provide EID. This means visits to two clinics on at least three separate occasions are required before infected infants can be started on HAART. Even in the setting of urban Western Cape, transport cost to and from the clinics remain a significant financial constraint. A same day turnaround time EID and intergrated clinic service that provides PMTCT, EID and early infant ART would greatly reduce the delay. Second, because early ART is a relatively new service and the number of HIV infected infants is few, staff experience of providing ART to small infants may be limited. As capacity to provide early ART is increased, we can expect further reduction in the linkage to ART care due to increased paediatric ART sites.

Interestingly, the reduction in the median age of infants undergoing first HIV viral load testing is mainly observed in the non-academic setting. The reduction in these non-academic primary care centres is explained by early ART initiated in asymptomatic newly diagnosed infant. The HIV viral load testing in the academic centres clearly represent a group of infants that either cannot gain access to PMTCT, EID or ART. The relative constant age of infants receiving HIV viral load testing at tertiary setting reflects the age in which infected children present to hospitals with their first manifestations of HIV.

### Limitations

The differences between the probable and definitive linkage proportions were constant over the 5 calendar years points towards a systematic data linkage issue. The robustness of the PCR-viral load linkage process is entirely dependent on the quality of data written on and captured from the laboratory request forms. Although there were spelling errors and erroneous entries of personal identifiers, we believe our refined methodology would have captured a significant proportion of truly linked episodes of PCR and viral load. Unless totally non-matching personal identifiers are commonly used for the early infant diagnosis and subsequent HIV care, we do not believe this factor would account for much of the non-retention.

The time delay between PCR diagnosis and referral to care is likely a combination of delay in providing results to caregiver and delay in referral to care. Our methodology is unable to disentangle these two issues and review of individual patient folders or clinic registry is necessary for determining the true delay in referral to care.

### **Conclusion**

Despite its limitations, routine laboratory data is an important data source to evaluate PMTCT and infant ART program success. It is cost effectiveness and can be used to detect temporal trends in the background of changing international and local guidelines. It is a useful adjunct to cohorts data and routine district data collected by health facilities. Individual testing data from public pathology laboratory service can be used to validate the hypothesis generated from small pilot cohorts. From the EID perspective, our study confirmed that although the

proportions of HIV infected infants are decreasing dramatically, linkage of the infected infants to care remains a challenge. Further study to examine the cause of the low retention rates is required.

**Acknowledgement**

We would like to acknowledge the NHLS for providing the data for the study.

University of Cape Town

Table 1 Factors influencing HIV PCR result amongst first time testing of HIV exposed children

		HIV PCR			OR (crude)	95%CI
		positive	negative	% positive		
Year	2005	1057	7594	12%	ref	
	2006	861	6193	12%	1	0.91-1.10
	2007	1170	11416	9%	0.74	0.67-0.80
	2008	1097	13279	8%	0.59	0.54-0.65
	2009	1035	14640	7%	0.51	0.46-0.56
	2010	793	14931	5%	0.38	0.35-0.42
	2011	311	8903	3%	0.25	0.22-0.29
Gender	female	3215	36648	8%	ref	
	male	2848	36289	7%	0.89	0.85-0.94
Tertiary site	no	3757	68605	5%	ref	
	yes	2567	8351	24%	5.61	5.31-5.93
Cape Metro	no	1994	23545	8%	ref	
	yes	4330	53411	8%	NS	
Age	<2 months	1962	40823	5%	ref	
	2-3 months	1608	16570	9%	2.02	1.89-2.16
	4-5 months	1134	11765	9%	2.01	1.86-2.16
	6-8 months	563	3586	14%	3.27	2.96-3.61
	9-11 months	433	1998	18%	4.51	4.03-5.05
	12-17 months	449	1711	21%	5.46	4.87-6.12
	18-24 months	175	503	26%	7.24	6.06-8.65

Table 2 Factors influencing referral to care as demonstrated by linked positive HIV PCR and Viral Load tests in HIV infected children less than five years of age in the public sector health facilities in the Western Cape Province of South Africa between January 2005 and December 2010

		HIV PCR linked VL		Total	% linked	OR (crude)	95%CI
		Linked	Not linked				
Year	2005	576	481	1057	54%	ref	
	2006	483	378	861	56%	1.07	0.89-1.28
	2007	662	508	1170	57%	1.09	0.92-1.29
	2008	758	337	1095	69%	1.88	1.57-2.24
	2009	703	332	1035	68%	1.77	1.48-2.11
	2010	566	227	793	71%	2.08	1.71-2.53
Gender	female	1924	1134	3058	63%	ref	
	male	1715	994	2709	63%	1.02	0.91-1.13
Specialist Hospitals	no	2061	1488	3549	58%	ref	
	yes	1687	775	2462	69%	1.57	1.41-1.75
Urban facilities	no	954	936	1890	50%	ref	
	yes	2794	1327	4121	68%	2.07	1.85-2.31
Age at time of PCR	<2 months	1230	592	1822	68%	ref	
	>2 months	2518	1671	4189	60%	0.73	0.64-0.81
	2-3 months	949	585	1534	62%	0.78	0.68-0.90
	4-5 months	637	474	1111	57%	0.65	0.55-0.75
	6-8 months	320	217	537	60%	0.71	0.58-0.87
	9-11 months	249	167	416	60%	0.72	0.58-0.89
	>=12 months	363	228	591	61%	0.77	0.63-0.93

Figure 1. Proportion of first PCR referred for subsequent viral load and the median delay between PCR and linked viral load (VL)

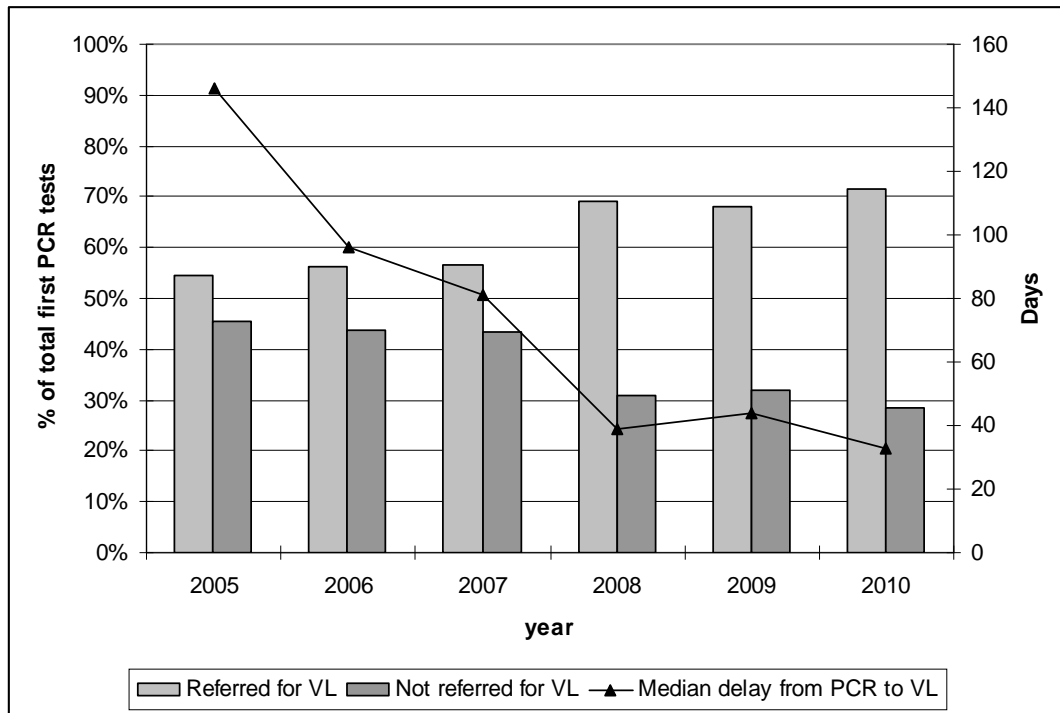
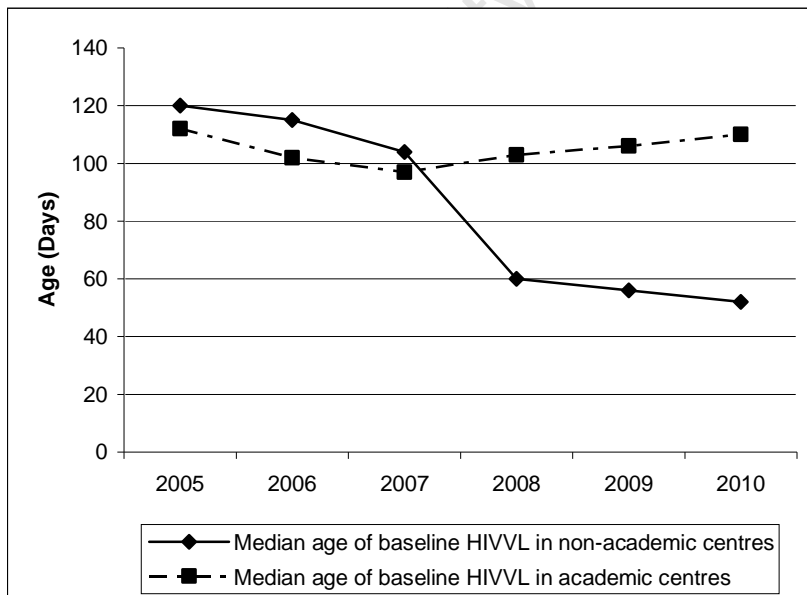


Figure 2. The difference in age of baseline HIVVL children between specialist hospitals and the rest of the health facilities in Western Cape



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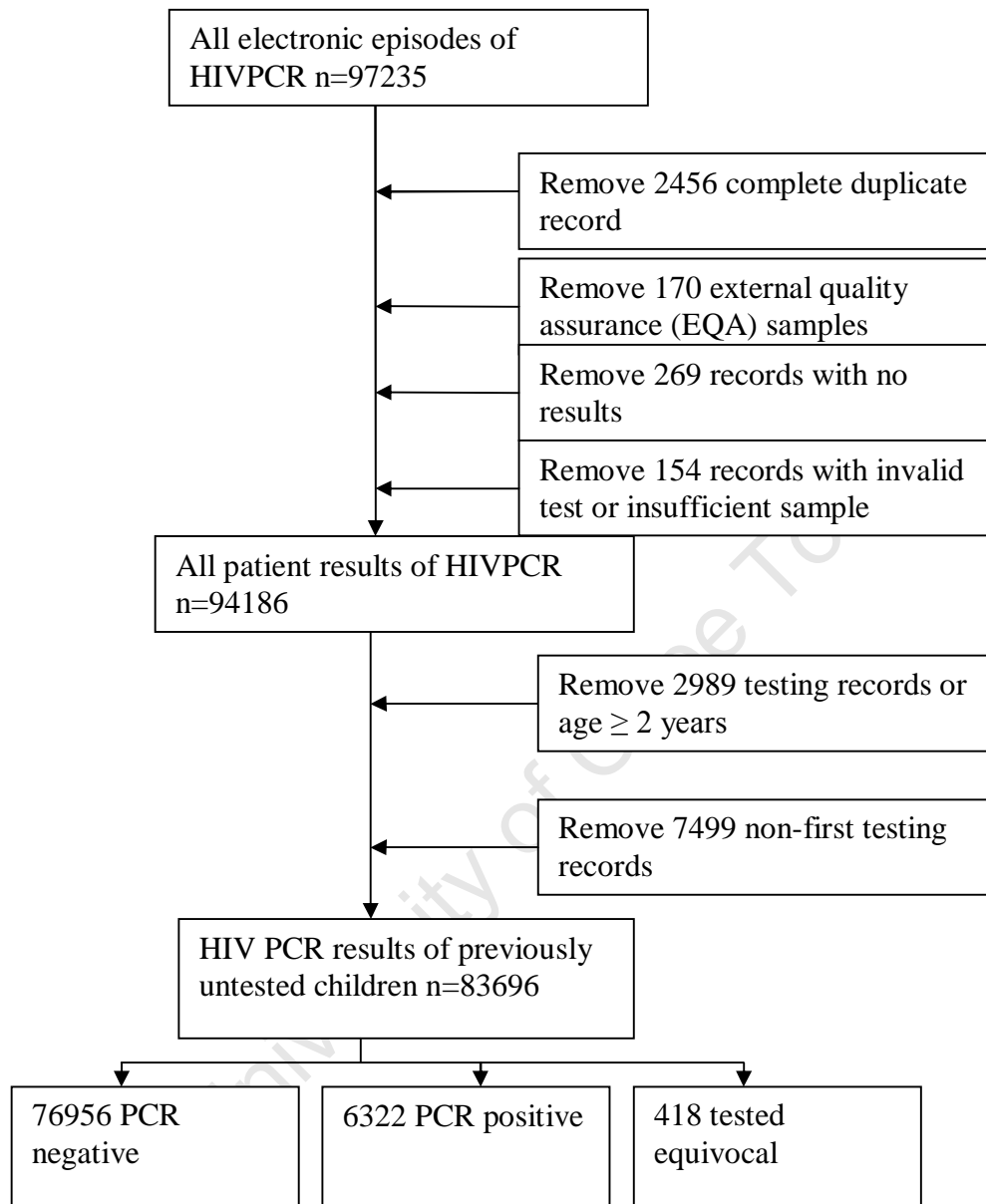
Ref Type: Conference Proceeding

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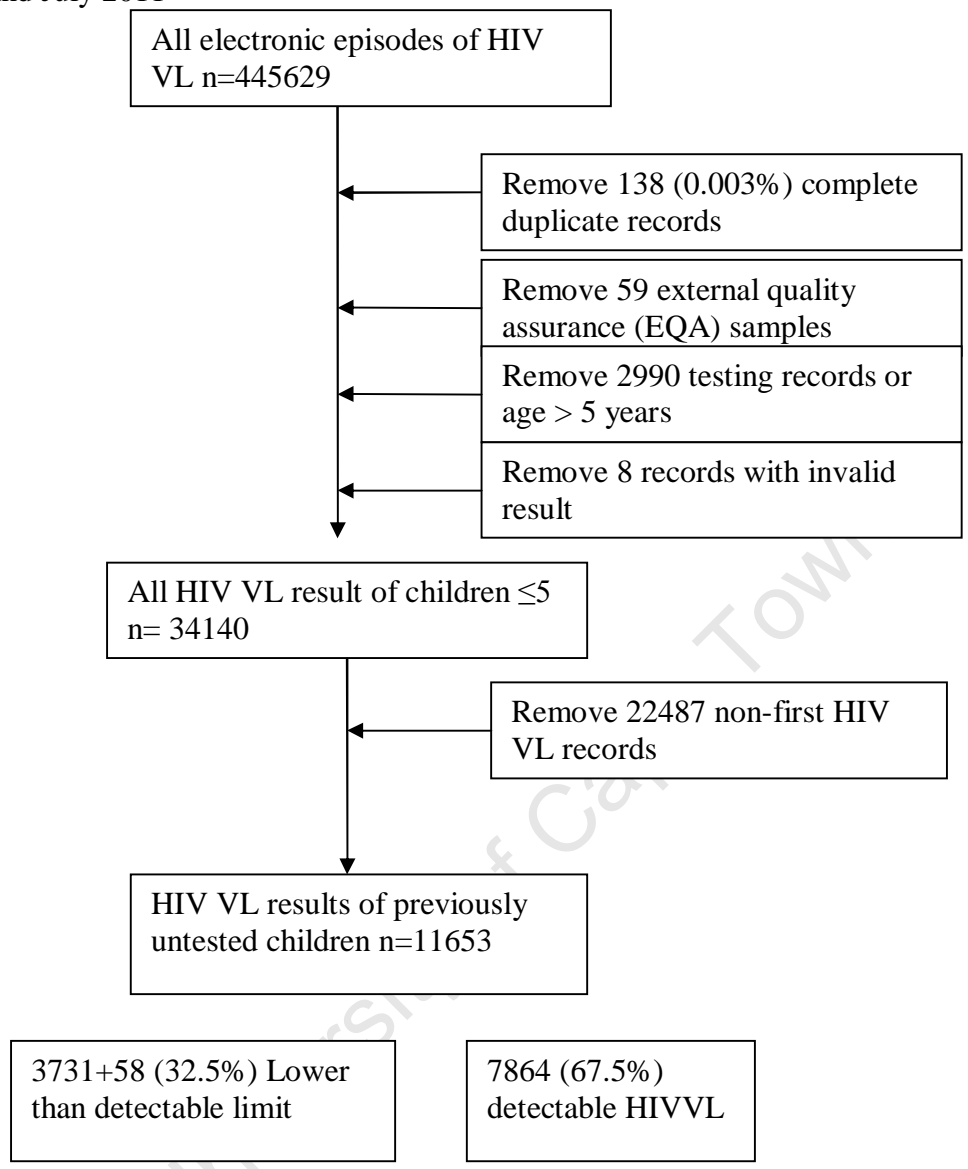
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Supplementary Figure 1. Processing and breakdown of HIV PCR testing episode between Jan

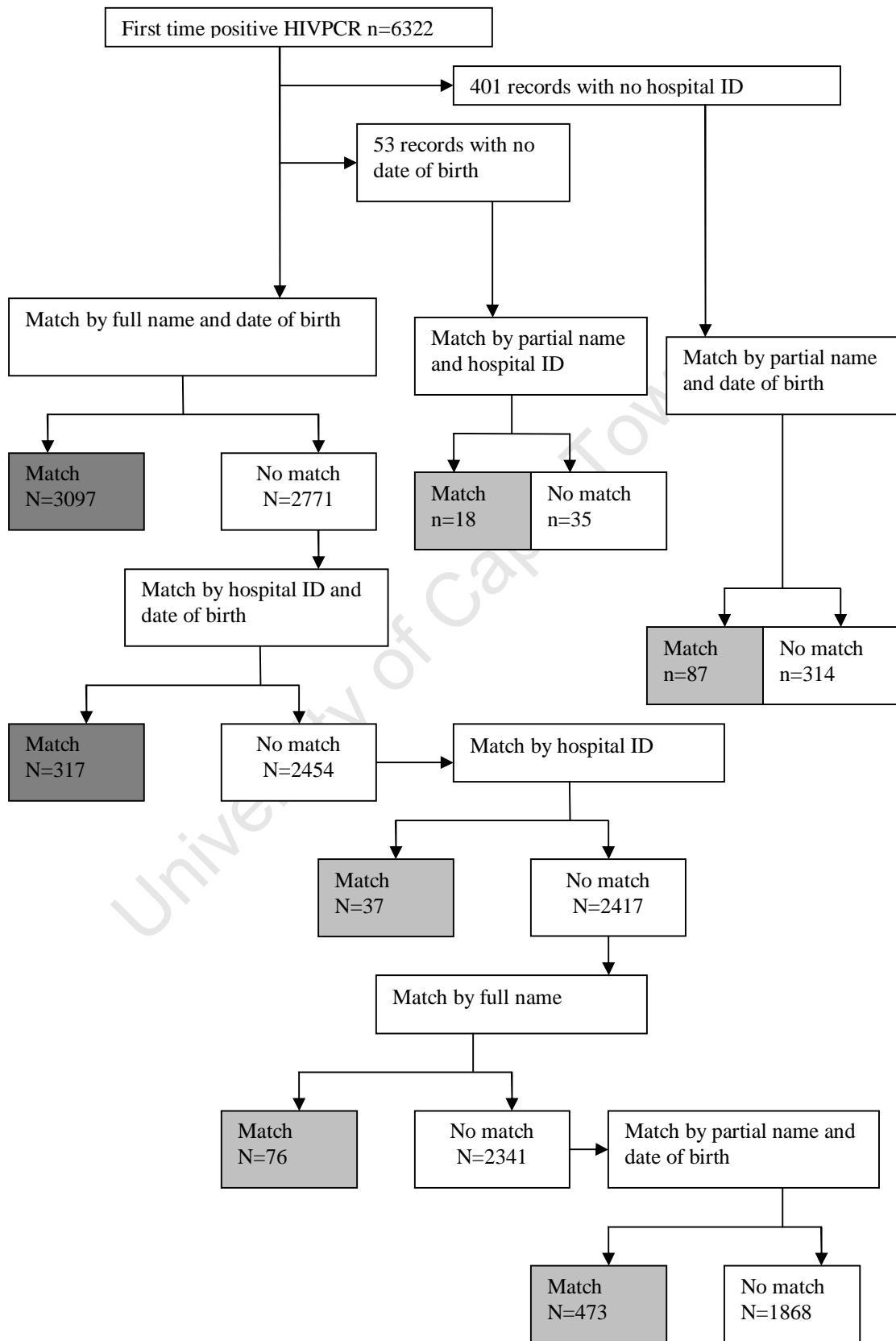
2005 and July 2011



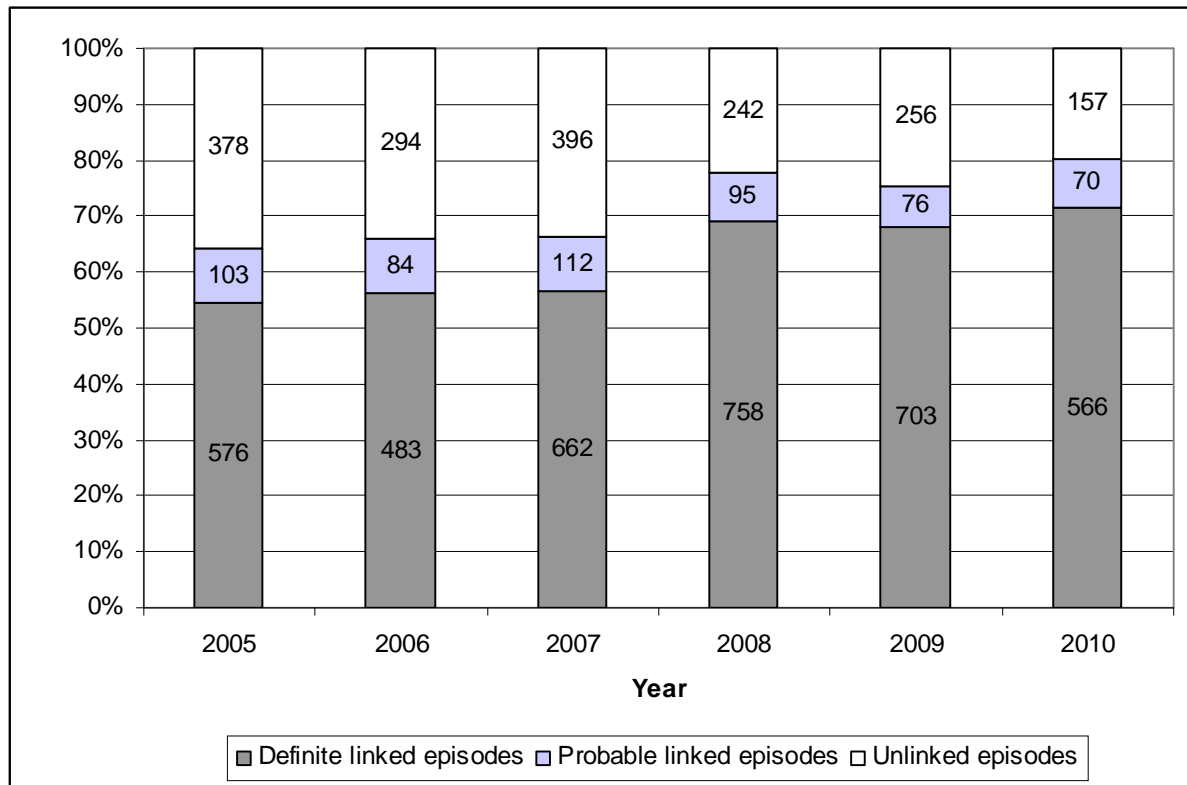
Supplementary Figure 2. Processing and breakdown of HIV VL testing episode between Jan 2005 and July 2011



Supplementary Figure 3. Processing of matching HIV PCR and HIV VL episodes. Dark grey boxes represent definite matches and light grey boxes represent probable matches.



Supplementary figure 4. Proportion of unlinked, probably linked and definitely linked PCR positive infants from January 2005 to December 2011.



## Research Proposal

Title: Impact of infant HIV diagnosis and referral to care: an audit of NHLS laboratory testing data.

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### Background:

South Africa's HIV prevalence is amongst the highest of the world's. The 2009 South African antenatal survey conducted by department of Health estimated that overall, 29% of mothers attending the antenatal clinics in South Africa were HIV infected. Prior to the antiretroviral therapy (ART) era, HIV infection amongst newborns result in significant burden of disease. This burden was indirectly observed in the high mortality of children under 5 and increased service demands in many secondary and tertiary paediatric care institutions.

Risk of transmission to foetus and infant can be effectively reduced by using ART to temporarily suppress HIV viral replication. This intervention is commonly known as prevention of mother-to-child transmission, or PMTCT. In its simplest form, a single dose of Nevirapine given to the mother and her newborn child is able to reduce the HIV transmission by 47%. Western Cape had been in the forefront of implementing various PMTCT regimens. These programs had been quite effective in reducing the incidence of HIV infections among infants in the province. However, failure of this intervention does occur occasionally and despite the existence of a national PMTCT program, some infants does become HIV infected.

Laboratory testing forms an important part of the PMTCT program because it is the most direct measurement of program success. Early infant diagnosis of HIV using polymerase chain reaction (PCR) allow us to identify the cases of PMTCT failure, and make sure the HIV infected children received the optimal care. According to archived NHLS laboratory data, approximately 30 HIV infections were detected in infant less than 3 month during the month of March in 2011. Prior to 2009, the South African guideline recommended that ART should only be started in these HIV infected children when disease progression had occurred. This recommendation was challenged by Violari and colleagues in the CHER study, as the study concluded that delaying ART in the perinatally infected children resulted in significant mortality. Thus the early ART strategy was adopted by the new national guideline in 2009 and HIV infected infants, diagnosed by HIV PCR, would be fast track to ART.

The implementation of this guideline is met with two major logistic difficulties. Firstly the timeous return of HIV PCR result to the mothers can be difficult in the resource poor setting. Infrastructure issues such as transport of specimen and speedy delivery of results to clinics/patients remain a concern in the Western Cape. Secondly, following diagnosis of HIV infection in the infant at the mother-child clinic, there is delay in referral to sites where ART could be initiated. In order to improve these services, data on the current program is essential. NHLS central data warehouse (CDW) archived data of all laboratory testing requests around the country and this represents a largely untapped resource of systematic information that can

be used to evaluate health programs. In this study we propose to use the CDW data to evaluate the performance of the PMTCT between 2005 and 2011.

**Study Aim:**

To evaluate the evolution of PMTCT between 2005 till 2011 in the Western Cape from the laboratory testing perspective.

**Objective:**

To describe trends in HIV PCR testing of infants from 2005-2011 according to: time period, test result and facility from which specimens were received

To describe the proportion of PCR positive infants who subsequently initiate ART and the delays from PCR positive test result to ART initiation, during the years 2005-2011

**Pilot data/proof of concept study**

Children who had HIV PCR testing in Jan 2010 were reviewed and their subsequent HIVVL testing data was sought in this pilot study. The findings are as follows:

Total children <18 months PCR pos	56
Red Cross/Somerset/GRS/MOW PCR pos	31
	[56-
<u>Of the PHC with pos PCR</u>	31=25]
HIVVL at same clinic	6
HIVVL at different PHC clinic	3
HIVVL later at a hospital (symptomatic)	6
no further HIVVL done (LTF or died)	10

As of Jan 2010, most HIV PCR positive children are still being diagnosed late in the tertiary hospital setting (31/56 are at hospital setting). This may reflect the presence of major gaps in PMTCT coverage in Western Cape and perinatal/postnatal HIV transmission is taking place.

Of the PHC diagnosed positive result, only 9/25 had HIVVL at primary level subsequently. The rest either lost to our system or presented later at a hospital (mostly RXH) with opportunistic infection and then HIVVL was requested.

**Methodology:**

This is a part service audit part descriptive study of the infant tested for HIV PCR in the Western Cape between 2005 and 2011. The Western Cape HIV PCR and HIV viral load testing data stored in NHLS central data warehouse (CDW) will be extracted. For individuals with positive or equivocal HIV PCR, searches will be performed in the HIV viral load database to determine whether these individual had been enrolled into HIV care at the same site or elsewhere.

**Data analysis:**

Describe the infant population tested for HIV PCR in Western Cape with regards to:

- 1) Numbers of tests over time
- 2) site of testing (primary vs tertiary care setting)
- 3) age of infants tested at time of diagnosis (PCR testing) and treatment initiation

## (HIVVL)

Describe the testing and results of HIV PCR's in Western Cape, specifically:

- 1) turnaround time from sample taken to authorization of result
- 2) proportion of positive result
- 3) proportion of equivocal/indeterminant results

Follow up positive HIV PCR results with HIV viral load data to identify

- 1) The proportion of PCR positive children who have a subsequent HIV viral load (suggesting successful initiation of ART)
- 2) The time delay from positive PCR result until first baseline HIV Viral load was performed
- 3) How these proportions and delays vary according to (a) time period and (b) the site of testing and/or (c) the site of ART initiation (as indicated by subsequent viral load testing), with a broad distinction between tertiary hospitals and primary care settings

### Procedures

Data will come from the CDW stored Western Cape ARV rollout program data between Jan 2005 to June 2011, specifically HIV PCR and HIV viral load tested at Groote Schuur and Tygerberg Laboratories. All laboratory information captured by Disalab will be extracted, including laboratory of testing, laboratory number, patient name, date of birth, gender, location of request, date of request, test performed, date of test completion, and test result. Data will be managed in excel spreadsheet for searching purposes. A final dataset consisting of only relevant data merged on patient name and date of birth will be imported into STATA for data analysis.

### Ethics

The proposed audit represents minimal risk to patients. All study data will be kept in password protected files, stored on limited-access computers behind firewall-protected servers on the UCT and NHLS networks. The routine datasets received from CDW will contain minimal patient identifiers (patient name, folder number, date of birth) required to identify subsequent viral loads taken on PCR positive children and to link maternal and infant specimens. However once the matching (of PCR and viral load data among infants, or maternal and infant results) is complete, we will strip the dataset of all identifiers prior to beginning data analysis. While there is no direct benefit to participants, there is potential indirect benefit of improved health care services for HIV-infected mothers and children that may emerge as a result of this research.

### Timelines

June 2011 – submission of protocol to UCT ethics committee

July 2011 – Receive ethics approval and submit the data request to CDW

August 2011- obtaining the database of HIV viral load and CD4 from NHLS CDW and start the data search and data capturing process

October – complete data analysis

### Budget

We anticipate minimal costs associated with this research. Minor office costs will be paid from other funds by the Depts of Virology and Public Health.