Early Infant HIV Diagnosis (EID) and Entry to HIV Care Cascade: Seven-year Experience in Thailand

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Short title: Early infant HIV diagnosis in Thailand

Keywords: HIV, early infant diagnosis, dried blood spots, HIV care cascade, Thailand

Abstract

Background: Early infant HIV diagnosis (EID) is critical for timely initiation of antiretroviral treatment (ART) in HIV-infected children who are at high risk of mortality. EID using dried blood spot (DBS) was provided by the National AIDS Program (NAP), Thailand from 2007. We report outcomes after 7-years of roll-out.

Methods: DBS samples collected from HIV-exposed children were mailed to the Faculty of Associated Medical Sciences, Chiang Mai University. HIV-DNA was assessed using real-time DNA-PCR assay. Data of HIV-infected children were linked to the NAP database to ascertain ART and vital status.

Findings: During 2007-2013, 16,046 samples from 8,859 children in 364 hospitals were tested; 42%, 30% and 28% of samples were from small (≤120 beds), medium (121-500 beds) and large (>500 beds) hospitals, respectively. Median age at first DBS was 2·1 months [IQR;1·8-2·5]. Of 7,174 children with ≥2 DBS samples, 223 (3.1%) were HIV-positive (include 5 unconfirmed). Of 1,685 children with one DBS sample, 70 (4·1%) were unconfirmed positive. Of 293 HIV-positive children, 220 (68%) registered for HIV care and 170 (58%) initiated ART. Median age at ART initiation decreased from 14·2 [10·2-25·6] in 2007 to 6·1 months [4·2-9·2] in 2013 while the proportion initiating ART aged<1-year increased from 33% to 83%. There were 8.8% (15/170) mortality among children initiated ART and 32% (16/50) among children with no ART record.

Interpretation: EID using DBS had high uptake, particularly in primary care settings. Further improvement of linkage to HIV care is needed to ensure timely treatment of all HIV-infected children.

Word count: 249

Research in context

Evidence before this study

We searched PubMed using the terms “HIV”, “early”, “infant”, “diagnosis”, and “cascade” on 10th December 2015. Of 11 publications, only three included data on the cascade of care in HIV-exposed children receiving early infant HIV diagnosis (EID). One was a pilot study in Kenya assessing the benefit of mobile testing mothers on infant retention in care, one was a cross sectional study on uptake and turnaround times of EID in Malawi but did not include outcomes in terms of initiation of antiretroviral therapy (ART) in HIV-infected infants. One study, a cross sectional study from Burkina Faso included the full range of outcomes along the cascade of care for HIV-exposed infants but was restricted to data from one region of the country for one year.

Added value of this study

Our study is one of the first to report data from a national EID reference centre in Thailand, and is unique in its linkage with data from the National AIDS Programme to ascertain ART and vital status among HIV-infected children identified. The study covers a 7-year period (2007-2013) of EID scale up efforts and in 2011 represented approximately 40% of all EID tests performed in the country. We report improvements in EID uptake, turn-around time of reporting of results and highlight the need for further improvements in the cascade of care, particularly timely initiation of ART in HIV-infected children to minimize the high mortality observed.

Implications of all the available evidence

Studies on cascade of care in HIV-exposed infants often end with the rate of HIV transmission detected and does not sufficiently focus on treatment and clinical outcomes of the HIV infected child. Further studies are needed to identify and minimize leakages in the EID and ART cascade of care in infants.

Introduction

There has been dramatic scale up of interventions to prevent mother-to-child transmission (PMTCT) of HIV over the past decade, with the new goal of elimination of new paediatric infections by 2015.(1) However, despite improving coverage, there remains gaps in key regions and populations, with an estimated 240,000 children newly infected in 2013 alone.(2)

In the absence of antiretroviral treatment, up to half of perinatally HIV-infected children in resource-limited settings will die within the first two years of life.(3) Antiretroviral therapy (ART), initiated during the first 3 months of life, dramatically reduces mortality and disease progression among infants(4), and the World Health Organization guidelines recommend immediate initiation of ART in all HIV infected children aged less than 2 years(5), and in 2013 this was extended to all children under 5 years if feasible.(6) Yet ART coverage in children in low and middle-income countries continues to lag behind at 34% coverage of those in need of treatment as compared to 64% in adults.(7) Limited access to early infant HIV diagnosis (EID) is often cited as a critical barrier to increasing access to ART in children.(8, 9)

While there has been a number of EID scale up programmes, reports to date have highlighted operational issues relating to poor uptake, delays in turnaround time of test results and, in the few studies with follow up data reported, many of the HIV-infected infants failed to link to HIV care.(10-14) There remains scarce data on linkage of EID to the HIV care cascade and if this has improved over time, as well as the risks of mortality among untreated infected infants.

In Thailand, EID was rolled out by the National Health and Security Office (NHSO) under the National AIDS Program (NAP) in 2006, initially requiring liquid blood samples which had to be transported to the laboratory within 24 hours, posing logistical and cost issues. Collection of samples as dried blood spots (DBS) overcomes these issues and

provides access to hospitals/clinics in more rural and remote settings.(14, 15) In 2007, the Faculty of Associated Medical Sciences, Chiang Mai University (AMS-CMU) became one of the 16 EID reference centres and the only centre until 2010 to provide EID on DBS, to hospitals across Thailand. We report herein the results of seven-years after roll out, including treatment and vital status of children diagnosed as HIV-infected.

Materials and Methods

Population

Children born to HIV-infected mothers in Thailand benefit from free-of-charge EID testing supported by the NHSO. In accordance to the Thai National guidelines, first EID test is recommended at 1-2 months of age, with repeat testing as soon as possible if positive, or after 4 months of age if negative.(16)

The Thai guidelines for PMTCT prophylaxis evolved over the duration of this study. In brief, from 2006 to 2009, HIV-infected pregnant women were recommended combination ART from 28 weeks gestation for women with CD4<200 cells/mm^3; and zidovudine (ZDV) from 28 weeks with single-dose nevirapine (NVP) at labour for women with CD4$\geq$200 cell/mm^3. Infants were recommended ZDV for one or four weeks.(17) From 2010 to 2014, the recommendations were for all pregnant women, irrespective of CD4 cell count, to receive combination ART immediately if CD4≤350cells/mm^3, and from 14 weeks gestation if CD4>350 cells/mm^3. Infant prophylaxis include ZDV syrup for four to six weeks. Infants whose mothers received no antenatal care were recommended four weeks of ZDV and lamivudine and one to four weeks of NVP syrup.(18) Infants were recommended exclusive formula feeding throughout.

Up to 2010, HIV infected children (with confirmed HIV DNA PCR if <18 months or antibody tests if aged>18 months) were recommended to initiate ART based on immune or clinical

criteria for age. From 2010, all infants aged<1 year were recommended immediate ART irrespective of immune or clinical status.(19)

Dried blood spots (DBS) preparation and transportation

DBS were prepared in small (≤ 120 beds), medium (121-500 beds) and large (>500 beds) hospitals. In small hospitals, medical team includes up to 3 non-HIV specialist practitioners and an HIV coordinator, usually a nurse, who ensures that all HIV-infected persons are followed appropriately. Hospital HIV coordinators were provided with free kits for DBS collection together with request forms and pre-stamped envelopes. Nurses and/or Medical Technologists at participating hospitals were initially trained for DBS preparation and transportation by the Clinical Microbiology Service Unit (CMSU) at the Faculty of Associated Medical Sciences, Chiang Mai University (AMS-CMU). Infant blood was drawn and spotted on filter paper (Whatman™ 903, GE Healthcare Ltd., UK). The filter papers were identified with an individual National AIDS Program (NAP) number and the request forms were filled accordingly. DBS were prepared as previously described(20) and shipped by conventional postal mail to CMSU laboratory. Along with the DBS preparation, the HIV-care team registered online the EID test through the NAP website.

HIV-DNA testing and reporting

Each DBS was tested at the ISO15189 accredited AMS-CMU laboratory for HIV-DNA using a validated in-house real-time DNA-PCR assay on DBS as previously described(20). The laboratory is quality controlled by the Qualitative HIV-1 DNA Diagnostic Proficiency Testing Program, Centre for Disease Control and Prevention, Division of Global AIDS (US-CDC). Children were considered to have confirmed HIV

status if they had two DNA PCR positive or negative test results from two separate samples taken on two different dates. Unconfirmed HIV status was defined as one DNA PCR positive or negative test result. Children with discordant test results are requested to send a third sample for confirmation testing.

DNA-PCR results were reported back to the clinic electronically through a dedicated secured NAP reporting system website. Access to the website was restricted to authorized HIV care teams using passwords. Results were also sent back by postal mail to the requesting physician. In addition, telephone calls, and more recently SMS messaging were used to alert the HIV care teams as soon as the results were uploaded online.

Data collection and analysis

Data prospectively collected at CMSU were: hospital name and location, individual NAP number, date of blood draw, date of DBS mailing, date of reception at CMSU, date of online result reporting. Results of HIV DNA PCR were analysed by year of birth. Data are described using number and percentage with 95%confidence interval for categorical data and using median with interquartile range (IQR) for continuous data. All data analyses were performed using STATA™ version 10·1 software (Stata Corp, College Station, TX).

NAP number was used along with children birth date and hospital name to link with antiretroviral treatment data and vital status of children diagnosed as HIV infected. Vital status data collected until March 2015 were used.

Role of the funding source

The study received no funding. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results:

Uptake of EID services

Between April 2007 and October 2014, 16,046 DBS samples were collected from 8,859 children, born in 2006-2013. Of 12,555 DBS with information on blood source, 10,193 (81%) were prepared from venous blood, 2,187 (17%) from heel prick and 175 (1.4%) from finger pricks. Samples were sent from 364 hospitals throughout Thailand; 42% of samples were from small hospitals (mostly with 10-60 beds), 30% from medium and 28% from large hospitals. In 2011, this accounted for approximately 40% of all EID tests performed in Thailand.(21) EID access expanded to reach all provinces across Thailand by 2012 (Figure 1), the Central region of Thailand with 86 hospitals accounted for the largest proportion of DBS samples, 25·3% of 16,064 samples collected during the course of this study.

The median duration from blood collection to DBS reception at CMSU was 8 days [IQR;6-12] and between DBS reception to online result reporting was 6 days [IQR;4-9]. Results were reported at a median of 15 days [IQR;11-21] after blood collection (Figure 2). Results were available online within 7 days after DBS reception for 62·6 % of samples and 8-14 days for 30% of samples. Overall, the median age at first blood draw was 64 days [IQR; 55-76] and at second blood draw was 128 days [IQR;123-144], as per the 2nd and 4thmonths recommended in the national guidelines.

EID results

Of 8,859 children tested, 7,174 (81%) had two or more DBS samples, of whom 223 (3·1%) tested HIV-DNA positive. Eleven infants had discordant test results, all with an initial negative result (DBS at age 0-2.1 months) followed by a positive test result (DBS at age 2.2-5.7 months). All were requested to provide a third DBS sample for confirmation testing, six

children were confirmed positive, the remaining five children did not send a third sample and were classified as unconfirmed positive. Of the 1,685 children with only one DBS, 70 (4·1%) tested positive and considered unconfirmed positive.

The proportion of children with confirmed EID results increased over time from 79·0% in 2007 to 83·3% in 2013 (p=0·02). When including all children (with confirmed and unconfirmed results), the overall transmission rate was 3·3%, the rate decreased over time from 7·5% (95%CI; 5·2-10·5) in children born in 2006-2007 to 1·3% (95%CI; 0·8-2·1) in those born in 2013 (Table 1). The median age at first positive test result was 2·3 months [IQR 2-3·9] among children with confirmed positive result and 3·4 months [IQR 2-4·9] among those with unconfirmed positive result. Eighty-five children (29%) had their first positive DBS aged ≤ 2 months, the remaining 207 (71%) positive infants had their first positive test aged>2 months (one child had no date of birth recorded)

Of 293 HIV-positive children, 288 were documented as Thai nationals and therefore eligible for free ART. Information of 91% of children (267/293) were retrieved from the NAP database, 75% (220/293) were registered for HIV care, 58% (170/293) initiated ART, while 25% (73/293) were lost to follow up or could not be detected by NAP program prior to linkage to HIV care and had unknown vital status. Among the 220 children linked to HIV care, 16 (7·3%) died prior to ART initiation, median age at death was 6·6 months [IQR, 5·5-17·2]. Overall, 89 children (30% of 293) died or were lost to follow up prior to start of ART (Figure 3). Of the 170 initiated on therapy, median time from first positive test to ART was 150 days [IQR 74-345] among children with a confirmed positive result (n=139), as compared to 68 days [IQR 21-206] (n=31) among those with unconfirmed positive result. Fifteen children (8·8%) died after start of ART, the median age at death was 9.2 months [IQR, 4·7-13·3]. The proportion of children registered for HIV care was significantly higher among children with confirmed HIV infection than those with unconfirmed HIV (83% vs 52%, P<0·001). Once children entered HIV care the proportion initiating ART were similar, 77% vs 79%.

The proportion of HIV infected children referred to HIV care and initiating ART increased over time and the proportion initiated ART before one year of age increased from 33% (5/15) in 2007 to 83% (10/12) in 2013 (Figure 4). The median duration between EID reporting to ART initiation decreased from 9·5 months [IQR;5·8-23·1] to 2·5 months [IQR;1·5-3·7] in children born in 2006-2007 and 2013, respectively. The median age at ART initiation decreased from 14·2 months [IQR;10·2-25·6] in children born in 2006-2007 to 6·1 months [IQR;4·2-9·2] in 2013 (Table 1).

Discussion

Thailand was one of the first developing countries to implement a national PMTCT program for all pregnant women from 2000. Since 2007, EID testing at 1-2 and 4-6 months was added to Thailand's PMTCT program under the universal health coverage scheme, and these results represent the outcomes of one of 16 national EID reference centres, and the only one centre providing EID services using DBS in 2007-2010.

Over seven years, our services has reached 364 hospitals throughout Thailand; mostly small (42%) and medium (30%) size hospitals from where transportation of whole blood to specialized EID testing laboratory within 24 hours with cold chain requirement is not possible. In 2011, our reference centre accounted for approximately 40% of all EID tests performed in Thailand.(21) Most diagnoses were performed on DBS samples collected at the time-points recommended in the Thailand national guidelines for EID testing and the majority of results were reported within 2 weeks of blood collection.

We report a dramatic decrease in the rate of perinatal infection, reaching less than 2% in 2013, reflecting the efficacy and efficiency of the PMTCT program. We have also observed a 3 fold reduction in the median duration from EID reporting to ART initiation (9·5 month in 2007 vs 2·5 months in 2013) and a halving of the median age at ART initiation (14·2 months in 2007 and 6·1 months in 2013), which may have been partly due to the revised Thai guidelines in 2010 recommending immediate ART in all infants less than 12-months at any

CD4 level.(19) Nonetheless, 8.8% of children who initiated ART died, comparable to previous reports of mortality on ART in children in Thailand, mostly due to advanced disease progression at ART start(22). As the age at ART initiation reduces over time, we hope the mortality rate will decline to the low levels reported in the CHER trial where all children initiated ART aged<3 months, while asymptomatic.(4)

Linkage between EID and HIV care cascade needs to improve further to enable this, and critically, to improve on the proportion of children tested DNA positive who initiate ART, which remains unacceptably low, ranging from 47 to 73% across calendar years, similar to those observed in other settings.(13, 14) This highlights important 'leakages' in the EID to HIV cascade of care and the need to address potential institutional barriers such as timely communication of positive results to the parents/caregiver, coordinated transfers to ART clinics as well patient-level barriers such as nondisclosure to family, fear of stigma/discrimination etc.

Study limitations

There are some important study limitations to highlight. Firstly, the study presents outcomes of children who accessed EID, we do not have the denominator of all HIV-exposed children born in the participating hospitals to accurately estimate EID coverage. Such numbers are difficult to estimate as mothers do not always return to their hospital of delivery/antenatal care for EID. National annual estimates of HIV-infected pregnant women in Thailand ranged from 5,900 in 2008 to 4,936 in 2011. (23) Based on these estimates, the number of children receiving EID at our reference centre accounted for approximately 16% of all HIV-exposed infants born in 2008 (957/5900), and rose to 35% in 2011 (1738/4936) suggesting increased uptake over time. However, the total number of infants who received EID aged≤2 months of age across Thailand (including all reference centres) was estimated at 73% in 2011. (2) There remains a sizeable proportion of infants who fail to access timely EID as per recommendations and further study is needed to minimise this gap.

Secondly, the risk of lost to follow up following EID and prior to linkage to HIV care was high in earlier calendar years prior to WHO and Thai guidelines recommended immediate start of ART in the first year of life. Some of these children may have died prior to confirmation test/referral to HIV care or could not be detected by NAP program and lead to an underestimation of pre-ART deaths. Factors associated with lost-to-follow-up were not examined in this study and warrants further investigation. Third, some children may not be eligible for ART under the NHSO universal coverage system, but may have accessed ART through private hospitals, charities and non-governmental organizations or health insurance systems which may have led to an underestimation of number initiated on ART. There have been efforts to increase access to HIV services for migrant workers (MW) through a network of field outreach workers and MW health volunteers. In June 2014, the Government and the Ministry of Public Health launched the Health Insurance System for MW which includes access to ART. However, effort will be required to ensure this system works smoothly and efficiently.

Fourth, the EID service performance reported here relies primarily on a functioning mailing system which some countries may not have and therefore the findings may not be generalizable. However, numerous studies have reported alternative systems for transportation of DBS from primary care facilities via courier/transporters already in place for delivery of ART/laboratory supplies (25, 26). Such settings may benefit from some of the lessons learned here, although must be adapted to their own settings.

Thailand has embarked on the “Getting to Zero, 2011-2015 Strategy” and since 2014 it is recommended to treat all HIV-infected individuals irrespective of their CD4 count. The PMTCT program has been very successful and the rates of MTCT are very low except for HIV-infected pregnant women presenting late for antenatal care (ANC) or have no ANC during pregnancy and thus receive a short or no PMTCT course.(23) There is now an

attempt in Thailand to test for *in utero* HIV infection by testing DBS collected at birth (within the first 2-7 days of life). Although EID has been shown to be cost-effective in the Thai setting, despite declining MTCT rates,(28) the cost effectiveness of birth testing has yet to be evaluated and will need to take into account the lower “sensitivity” of DNA PCR tests conducted on samples collected at less than 4 weeks of age.(29) Ongoing studies are assessing the feasibility and effectiveness of this approach.

The experience of CMSU shows that diagnosis within 2 weeks of blood collection is feasible in routine care settings, and is critical for the early identification of HIV-infected infants. This enables infant PMTCT prophylaxis to be switched to ART regimens without interruption as soon as HIV diagnosis is confirmed and minimise risk of mortality.

With improved life expectancy of HIV infected patients on ART, (30) more HIV-infected women will conceive initial and subsequent pregnancies on ART in low- and middle-income settings with varying levels of virological monitoring. In these settings, EID programmes will remain critical in assessing perinatal outcomes over time.

In conclusion, our study shows that EID testing using DBS has high uptake, particularly in smaller hospitals and is a critical step for infected children to be identified and enter the HIV care cascade. As MTCT rates continue to decline, EID may move towards targeted birth testing to enable early ART, although improved linkage between the EID services and HIV care teams is needed to ensure that all HIV-infected children are followed and ART initiated immediately after diagnosis.

Contributors

WS, IC, PL, and NN conceived and designed the study. WS, WK, AP, SC, and TS analysed the data. WS, NN, IC, and TS wrote the first draft of the paper. All authors provided a critical review of the manuscript and approved the manuscript for submission: All (WS, WK, IC, AP, PL, SC, NN, TS)

Declaration of interests

We declare no competing interests.

Acknowledgments

The authors wish to thank the National AIDS Program (NAP), Health Security Office (NHSO) who provided children data. We thank all hospitals HIV teams responsible for care of children born to HIV-infected mothers.

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Figure and Table captions

Figure 1. Coverage of EID service in 2007 (A) and 2012 (B) by the Clinical Microbiology Service Unit (CMSU), Chiang Mai University and number of hospitals accessing EID per province.

Figure 2. Median turnaround time of EID service at the Clinical Microbiology Service Unit (CMSU) during 2007-2013.

Figure 3. Cascade of care among HIV-positive children born between 2006 and 2013.

Figure 4. Total number of HIV-infected children diagnosed, number initiated ART and number initiated ART within 1 year of age, by calendar year of birth.

Table 1. Summary of number of children received EID and HIV positive children received ART by calendar year of birth.

Figure 1
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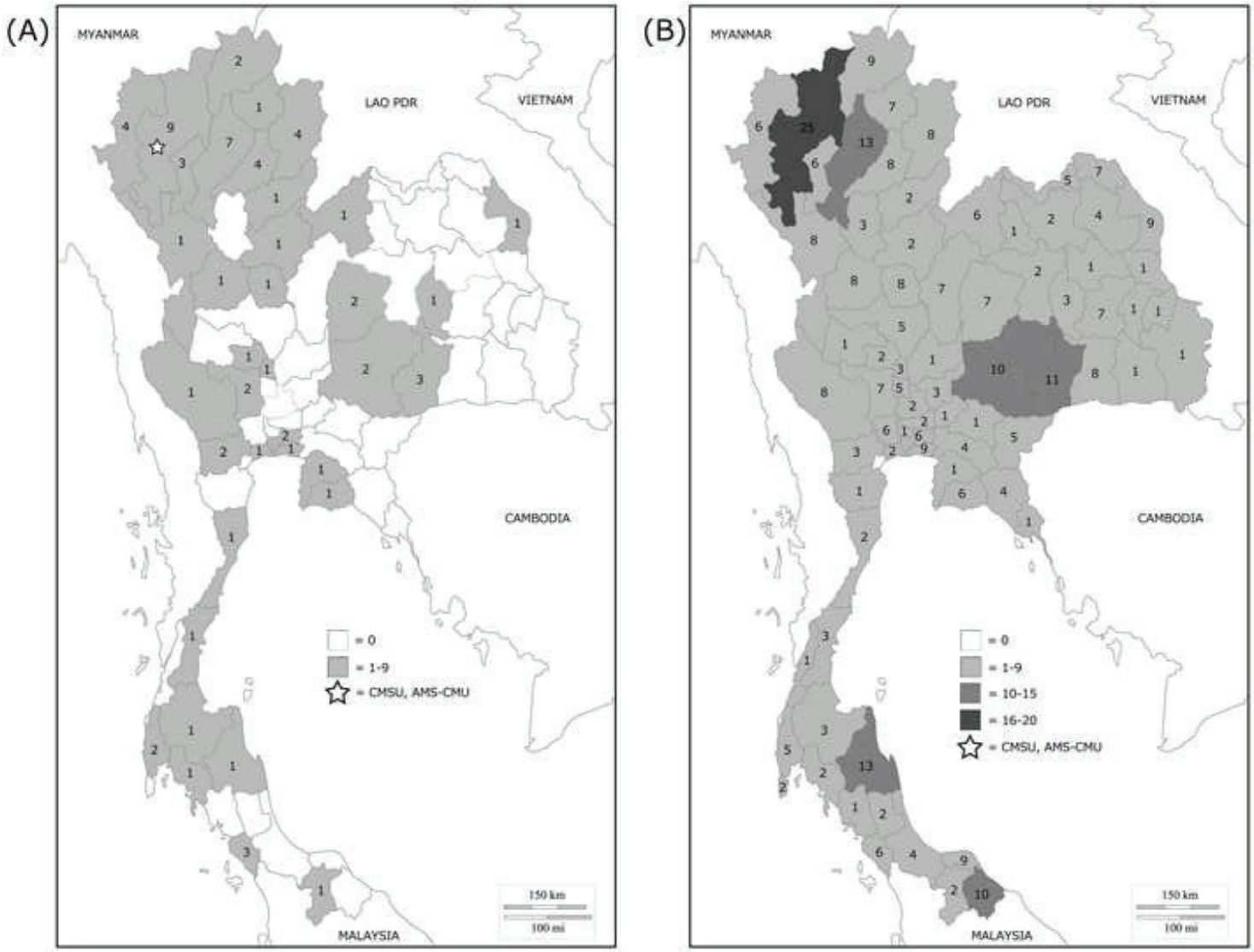

Figure 2
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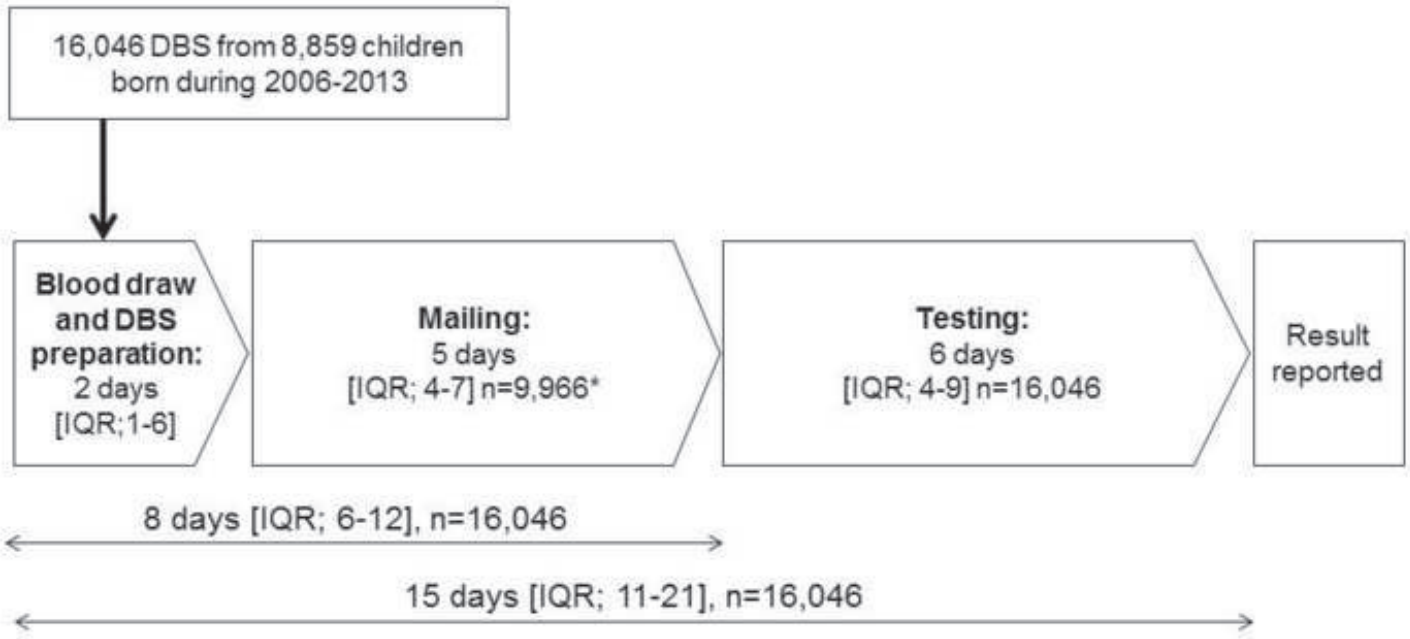

* Note: Date of mailing was recorded in only 9,966 of 16,046 DBS samples.

Figure 3
Click here to download high resolution image

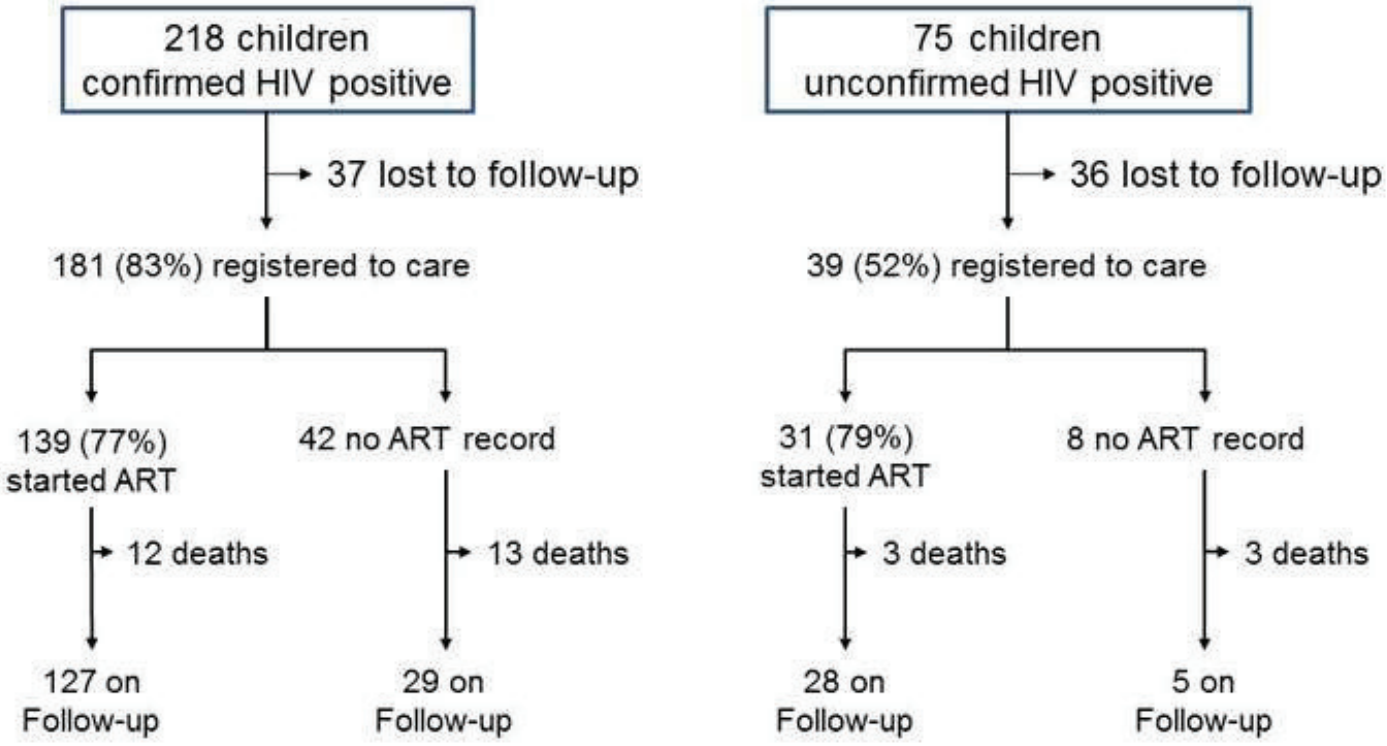

Figure 4
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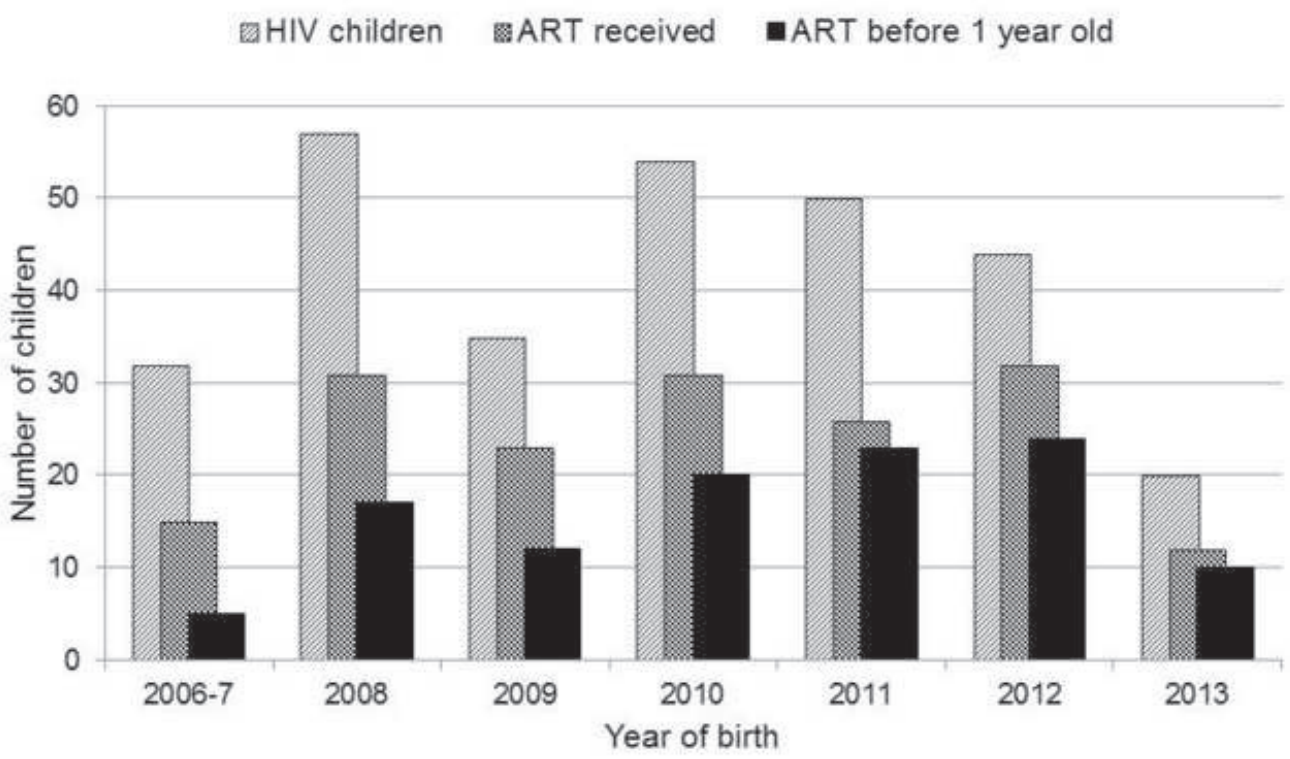

Table 1

	Year of birth							
	2006-2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Overall**
Number of children tested (EID)	425	957	1160	1416	1738	1639	1485	**8,859**
Number of HIV positive children	32 (7·5%)	57 (6·0%)	35 (3·0%)	54 (3·8%)	50 (2·9%)	44 (2·7%)	20 (1·3%)	**293 (3·3%)***
Number initiated ART	15 (47%)	31 (54%)	23 (66%)	31 (57%)	26 (52%)	32 (73%)	12 (60%)	**170 (58%)**
Median duration from EID report to ART initiation, months [IQR]	9·5 [5·8-23·1]	6·9 [3·7-23·7]	5·7 [2·9-24·2]	5·1 [1·8-13·0]	3·1 [1·3-5·0]	2·8 [1·9-6·4]	2·5 [1·5-3·7]	**4·6 [2·2-10·9]**
Median age at ART initiation, months [IQR]	14·2 [10·2-25·6]	11·4 [8·6-26·5]	10·1 [1·8-26·5]	7·6 [4·7-18·4]	6·8 [5·4-9·1]	7·0 [5·2-11·6]	6·1 [4·2-9·2]	**8·6 [5·9-14·9]****

Note: *Include confirmed and unconfirmed positive results. **One child had no birth date recorded,