

# Modeling of the Timing of Mother-to-Child HIV-1 Transmission as a Function of Zidovudine Treatment Duration in Mothers and Infants

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## ABSTRACT

**Background:** To optimize antiretroviral prevention strategies, determining the time in which mother-to-child HIV transmission (MCTC) occurs is of major importance. In the absence of breastfeeding, the timing of transmission must be deduced through a limited number of viral detection but results provided by the infant during the first weeks of life. We analyzed the influence of the duration of zidovudine (ZDV) prophylaxis on the timing of MCTC.

**Methods:** Data were collected for PPTCT 1, a clinical trial comparing the efficacy of different ZDV treatment durations in mothers and infants to prevent HIV-1 transmission. Mothers were given ZDV 300 mg twice daily starting at 28 to 35 weeks of pregnancy, followed by a 300-mg dose of ZDV every 3 hours (oral loading dose) from onset of labor until delivery. Infants were given ZDV 2 mg/kg every 3 hours for 3 days to 6 weeks. Mothers and infants were classified according to actual treatment duration (mothers: long > 7.5 weeks, short ≤ 7.5 weeks; infants: long > 4 weeks, short ≤ 4 weeks, provided adherence > 75%). The studied sample consisted of 1321 mother-infant pairs and 93 infected infants. A hierarchical model in a Bayesian framework (Markov process for viral marker evolution, timing of transmission as a mixture of 3 distributions associated with early, late in utero and intrapartum transmissions) was developed to back-calculate the time of transmission according to ZDV treatment duration. The decrease in transmission rate during a given period from 1 to another, in other words, to determine the last 2 weeks before birth from mother to short long treatment duration, when infants received a short treatment, was estimated as avoided transmission rate.

**Results:** When mother treatment was long compared to short, 1 to 2% transmission occurred more than 2 weeks before birth were avoided, independently of infant's treatment duration; a 4 to 5% transmission occurring during the last 2 weeks of pregnancy were avoided by mother long treatment as compared to short treatment, whereas no effect of mother treatment duration was found when infants received a long one; 1 to 4% transmission occurring during the last 3 days of pregnancy were avoided by infant long treatment as compared to short, but only when mother had received a short treatment.

**Conclusions:** These results may help optimize personal HIV prevention strategies, especially in women whose ZDV treatment is initiated late in pregnancy.

## INTRODUCTION

The progress achieved in the prevention of MCTC by using prophylaxis with antiretroviral drugs has been remarkable. Among preventive treatments, zidovudine (ZDV) remains an attractive drug due to its efficacy, even when used as a monotherapy, and due to the rare occurrence of drug resistance in treated women and infants. The determination of when and how many transmissions occur under a specific prophylaxis regimen is an essential step to better understand the mechanisms of prevention of MCTC, which may in turn help to optimize prevention strategies.

Since it is not possible to observe the exact timing of transmission, the latter has to be deduced from the analysis of a limited number of results of PCR tests performed during the first weeks of infant's life, using assumptions on the time necessary for a contamination to become a detectable infection.

The purpose of this work was to analyse the influence of the durations of ZDV prophylaxis in mothers and infants on the timing of MCTC through a modeling bayesian approach.

## MATERIAL AND METHODS

### 1. SOURCE OF DATA

- We used the data of the clinical trial PPTCT 1 in Thailand;
- Mothers received a 300 mg ZDV tablet twice a day starting from either 28 or 35 weeks of pregnancy and 300 mg oral ZDV every 3 hours from onset of labour until delivery.
- Infants received ZDV orally 2 mg/kg of body weight every 6 hours for 3, 4, or 6 weeks.
- DNA PCR tests for HIV detection in the infant were to be performed shortly after birth, and at approximately 6 weeks, 4 and 6 months after birth.
- An infant was defined HIV-1 infected if PCR tests were positive on 2 successive occasions or non-infected if negative on 2 successive occasions after 1 month.

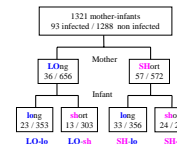
### 2. SAMPLE AND DATA USE:

Mothers and infants were classified according to actual treatment duration and selected on adherence (see below). There were no other reports of breastfeeding.

### Classification and selection

#### ➤ Actual treatment duration

- Mother:
  - LOng > 7.5 weeks
  - SHort ≤ 7.5 weeks
- Infant:
  - long > 4 weeks
  - short ≤ 4 weeks
- More than 75 % compliance



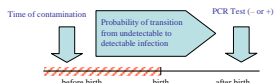
### 3. MODEL USED TO ESTIMATE THE TIMING OF TRANSMISSION:

The rationale of the modeling is shown in Diagram 1.

We developed a hierarchical model in a Bayesian framework to estimate from the results of the PCR tests the time necessary for contamination to become detectable using:

- 1) a Markov process for viral marker evolution;
  - 2) a mixture of 3 distributions associated with early in utero, late in utero and intrapartum transmissions describing the delay between contamination and birth
- We estimated by back-calculation the timing of MCTC as a function of ZDV treatment durations.

### Diagram 1 Hypothesis on the timing of contamination



## MATERIAL AND METHODS (continued)

### 4. DYNAMICS OF VIRAL MARKERS

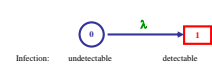
Diagram 2 Shows Markov process from contamination to two possible states of infection,

- 0 : undetectable and 1 : detectable

The probability of transition from undetectable to detectable infection is constant by time unit,  $\lambda$ , where the probabilities of transition from state 0 to state 0 or to state 1 at time interval  $\Delta t$  are

$$P_{0/0}(\Delta t) = e^{-\lambda \Delta t} \text{ and } P_{0/1}(\Delta t) = 1 - e^{-\lambda \Delta t}$$

### Diagram 2 Model of time from undetectable to detectable infection



### 6. BAYESIAN INFERENCE AND IMPLEMENTATION

The bayesian approach was used to estimate model parameters (Diagram 3).

Principle of bayesian inference:

$$P(\text{Knowledge}|\text{Data}) \propto P(\text{Knowledge}) \times P(\text{Data}|\text{Knowledge})$$

Posterior distribution = Prior distribution Likelihood function

- The prior distributions were chosen according to the study by Choquet et al<sup>1</sup> and Kourouk et al<sup>2</sup>.

- The likelihood function of observed infection status at PCR tests over all N infants is

$$L = \prod_{i=1}^N P_{0/0}(Z_i) \cdot P_{0/1}(I_i)$$

where  $I_i$  being the date of the last PCR-negative and  $Z_i$  the date of the first PCR-positive tests of infant  $i$ .

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### 5. TIMING OF TRANSMISSION

The unknown time interval from contamination to birth ( $Z_i$ ) assumed to follow a mixture of 3 Gamma distributions as shown on Figure 1.

Figure 1 Model of time interval from contamination to birth ( $Z_i$ )

A mixture of 3 distributions (with proportions  $P_1, P_2, P_3$ ) of

$f_{i/0}(t)$  : integration transmission (m/0)

$f_{i/1}(t)$  : late in utero (m/1)

$f_{i/2}(t)$  : early in utero (m/2)

$f_{i/3}(t)$  : early in utero (m/3)

$f_{i/4}(t)$  : early in utero (m/4)

$f_{i/5}(t)$  : early in utero (m/5)

$f_{i/6}(t)$  : early in utero (m/6)

$f_{i/7}(t)$  : early in utero (m/7)

$f_{i/8}(t)$  : early in utero (m/8)

$f_{i/9}(t)$  : early in utero (m/9)

$f_{i/10}(t)$  : early in utero (m/10)

$f_{i/11}(t)$  : early in utero (m/11)

$f_{i/12}(t)$  : early in utero (m/12)

$f_{i/13}(t)$  : early in utero (m/13)

$f_{i/14}(t)$  : early in utero (m/14)

$f_{i/15}(t)$  : early in utero (m/15)

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