Time to first positive DNA PCR test in non-breastfed infants with HIV-1

June 05, 2023

Outline

Pathways of Mother–to–child Transmission of HIV

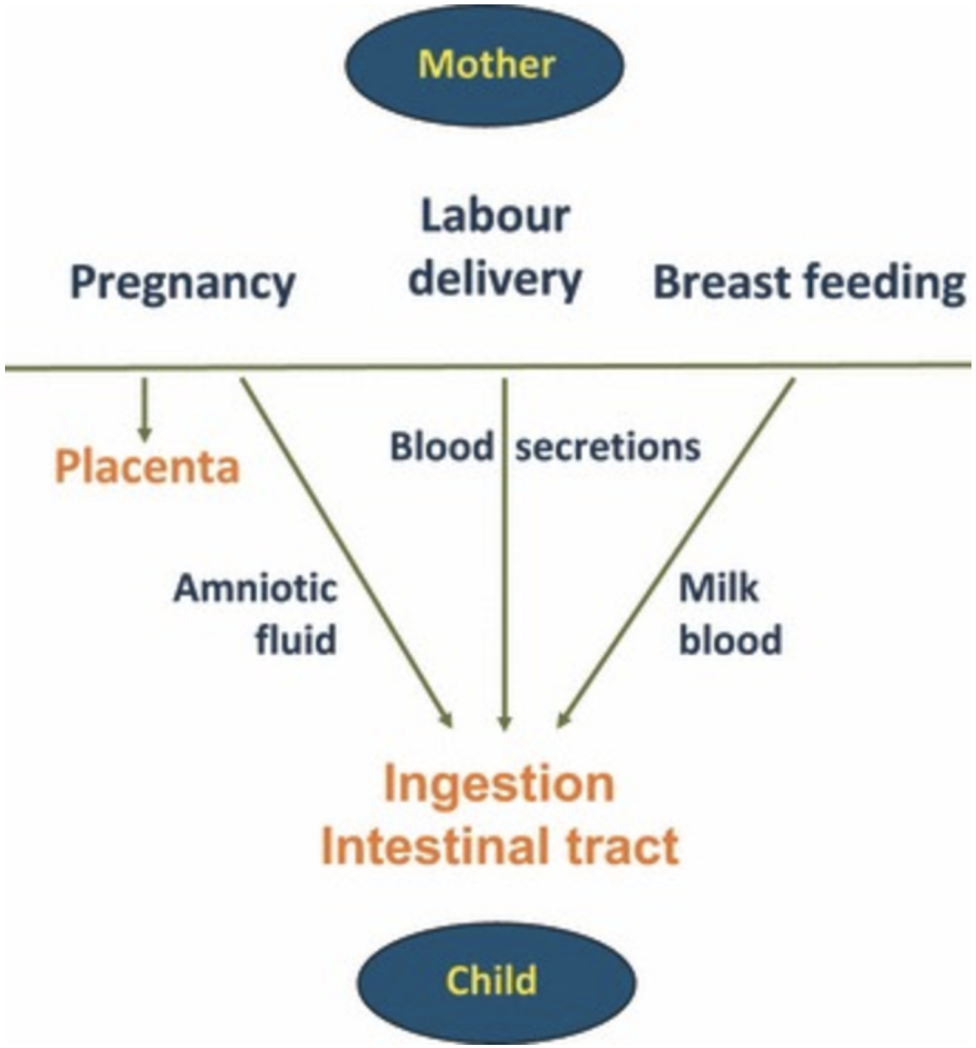

Figure 1: Cavarelli, M. et al., Journal of Internal Medicine, 2011

Global burden of Mother–to–child Transmission of HIV

- An estimated 1.3 million women and girls living with HIV become pregnant each year (WHO 2019).
- In the absence of treatment, transmission rates range from 15% to 45% (WHO, 2018).
- Transmission rate can be reduced to below 2% with effective intervention (combined antiretroviral therapy, cART) during the periods of pregnancy, labor, delivery and breastfeeding[1].

[1] **cooper2002combination**.

Early Detection of HIV in infants

- Virologic assays (HIV RNA or HIV DNA nucleic acid tests [NATs]) that directly detect HIV must be used to diagnose HIV in infants and children aged <18 months.
- HIV antibody and HIV antigen/antibody tests should not be used in infants as antibodies are passively transferred from mother-to-child, leading to false positive results.

Primary hypothesis

Do potent, combination therapies (cART) for preventing the mother-to-child transmission of HIV delay HIV detection among infants with HIV?

Is the earliest age at which HIV is detectable in an infant delayed when the infant is exposed to cART?

Why is this important?

- Early infant diagnosis of HIV is a critical issue in the clinical management of infants born to HIV positive mothers.
- Early ART treatment initiation for infants with HIV is associated with significantly better health outcomes
- Current guidelines for diagnostic tests from CDC[2] do not consider infant's treatment exposure.
- Our hypothesis suggests that these guidelines should depend on treatment exposure.

[2] https://clinicalinfo.hiv.gov/en/guidelines/perinatal/diagnosis-hiv-infection-infants-and-children

Data

- Cohorts
  - The Women and Infants Transmission Study[3] (WITS) was carried out at obstetric/gynecologic and pediatric clinics in Boston, Chicago, Manhattan, Brooklyn, San Juan, and Houston.
  - The Perinatal AIDS Collaborative Transmission Study[4] (PACTS) was conducted in 4 US cities (New York City, 1986; Baltimore, 1989; Atlanta, 1990; and Newark, 1990).
- Inclusion Criteria
  - Non-breastfed infants with HIV-1;
  - Infant has at least one DNA-PCR test before age 3 months.

[3] sheon1996women.

[4] kapogiannis2011mortality.

Data

WITS	PACTS	Total
129 infants 126 mothers	299 infants 298 mothers	428 infants

Mother-infant pairs with HIV in PACTS and WITS

Primary Exposure: Maternal ARV

Figure 2: Maternal ARV categorized based on **most complex ARV (Antiretroviral Therapy)** received in the 3rd trimester and at the time of labor/delivery. Potency of treatment increases from left to right.

NRTI: Nucleoside Reverse Transcriptase Inhibitors
cART: combination antiretroviral therapy with 3+ therapies including NNRTI +/- PI

DNA PCR test results

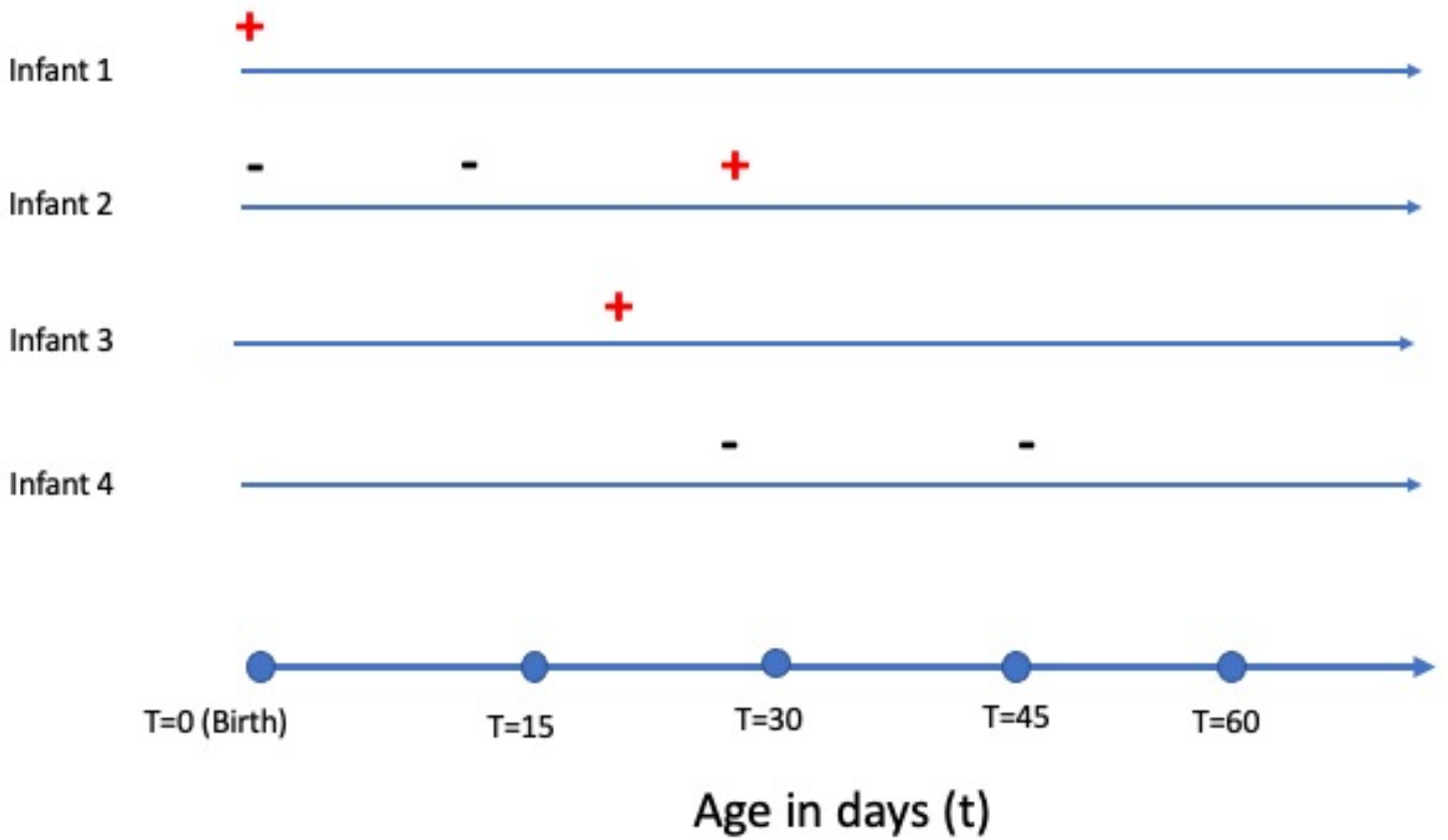

Figure 3: Observed data structure

1. Background
2. Data
3. Analysis
   - Overview
   - Mixture model
   - Other approaches
4. Results
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Outcome

T=Time to first positive DNA PCR test in infants with HIV

Origin time ($T = 0$) corresponds to time of birth

Goals

- Estimate distribution of time to first positive DNA PCR by maternal ARV.
- Adjust for covariates including mother's viral load, CD4 count, mode of delivery, gestational age and infant birth weight.

Challenges

- T (time to first positive DNA PCR test) is a mixture distribution.
- Interval censored and right censored observations.
- Adjust for covariates.
- Goodness of fit of parametric assumptions.
- Observational data (not randomized).

Mixture distribution for T (time to first positive DNA PCR test)

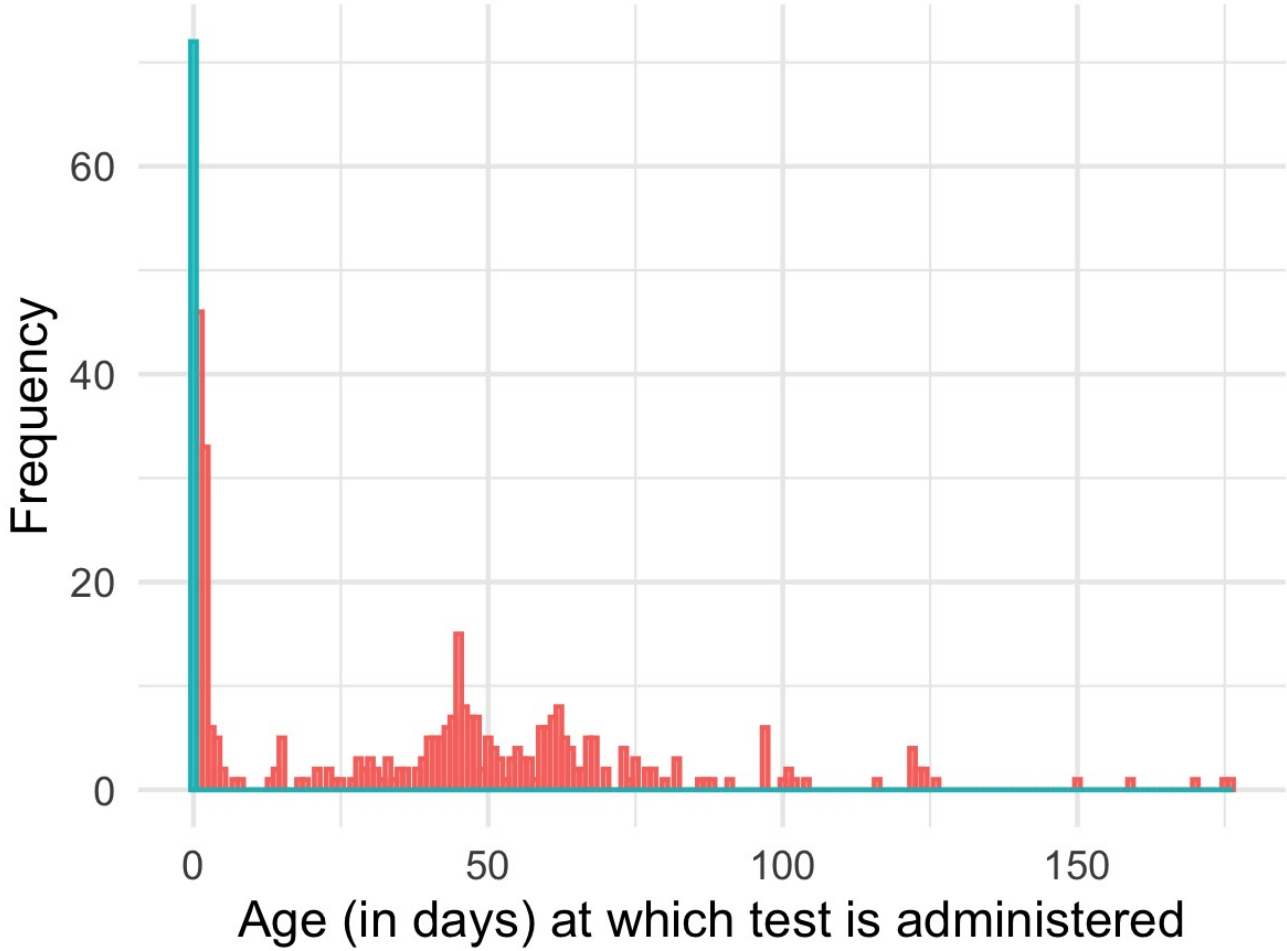
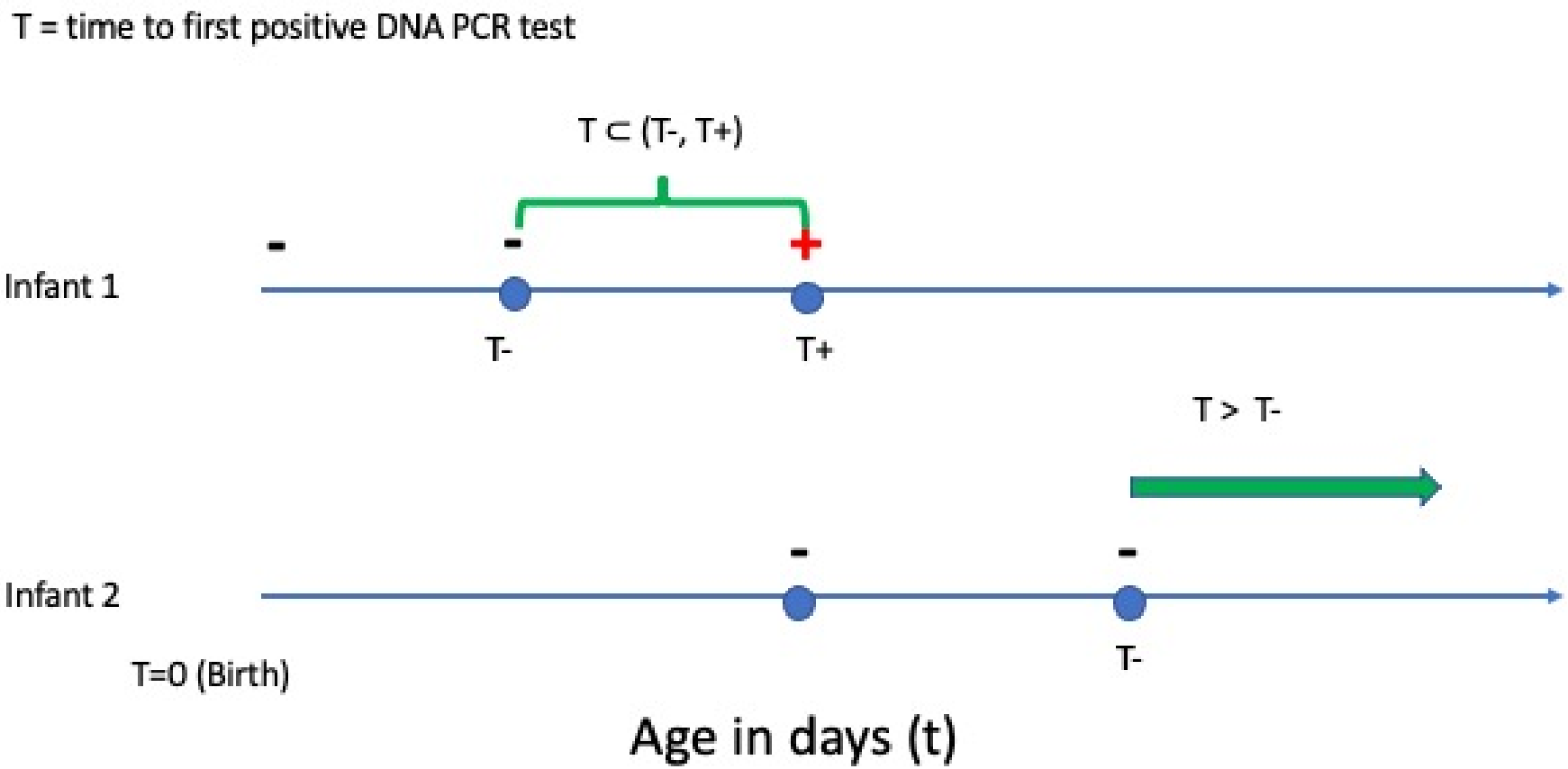


Figure 4: T (time to first positive DNA PCR test) follows a mixture distribution.

Censored observations of T



Analysis approaches

- Mixture model for T, parametric assumptions
- Nonparametric Turnbull estimator for interval censored observations.
- Parametric Weibull, proportional hazards survival analysis.

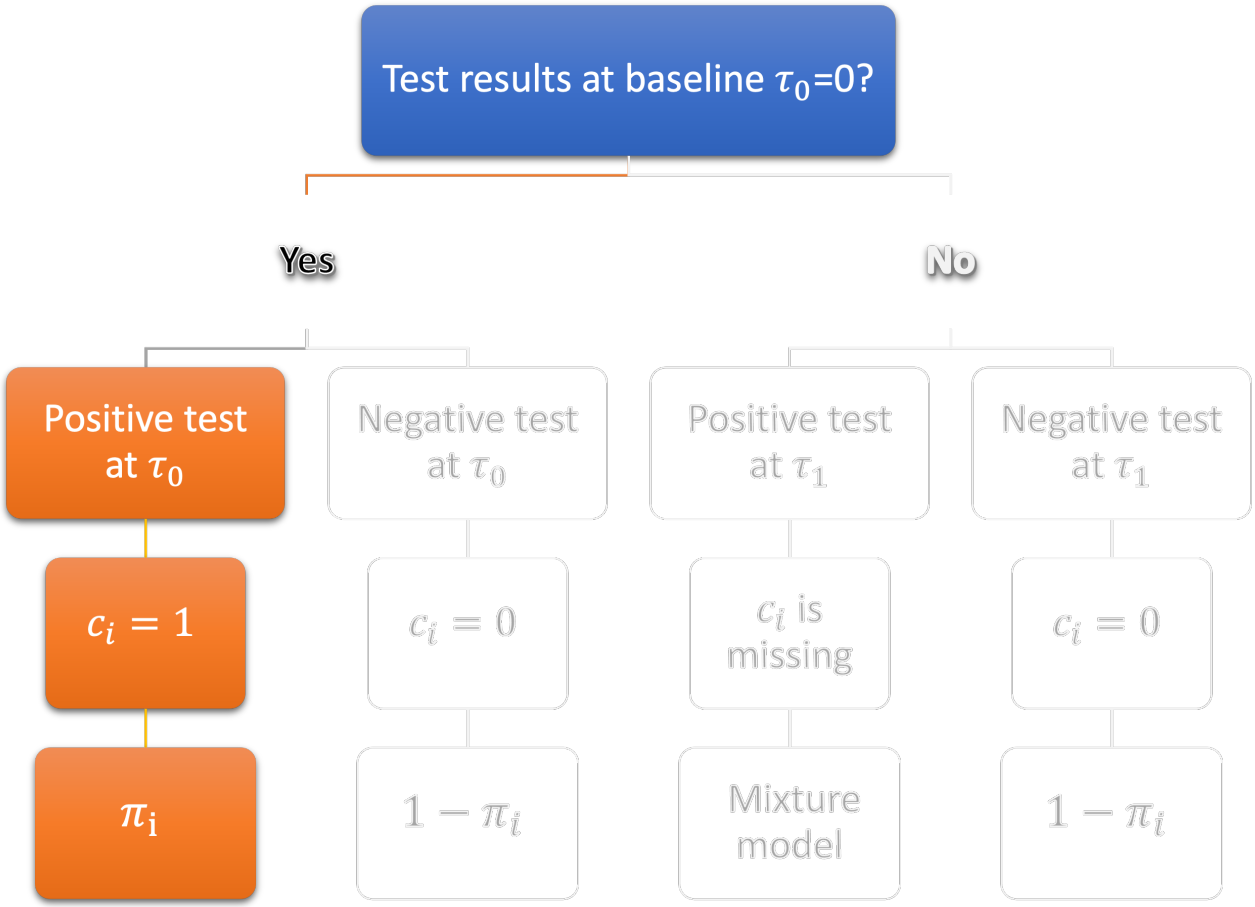
Notation

- T is the unobserved time to first positive DNA PCR test.
- $S(t)$ is the survival function.

For subjects $i, i = 1, \ldots, N$,

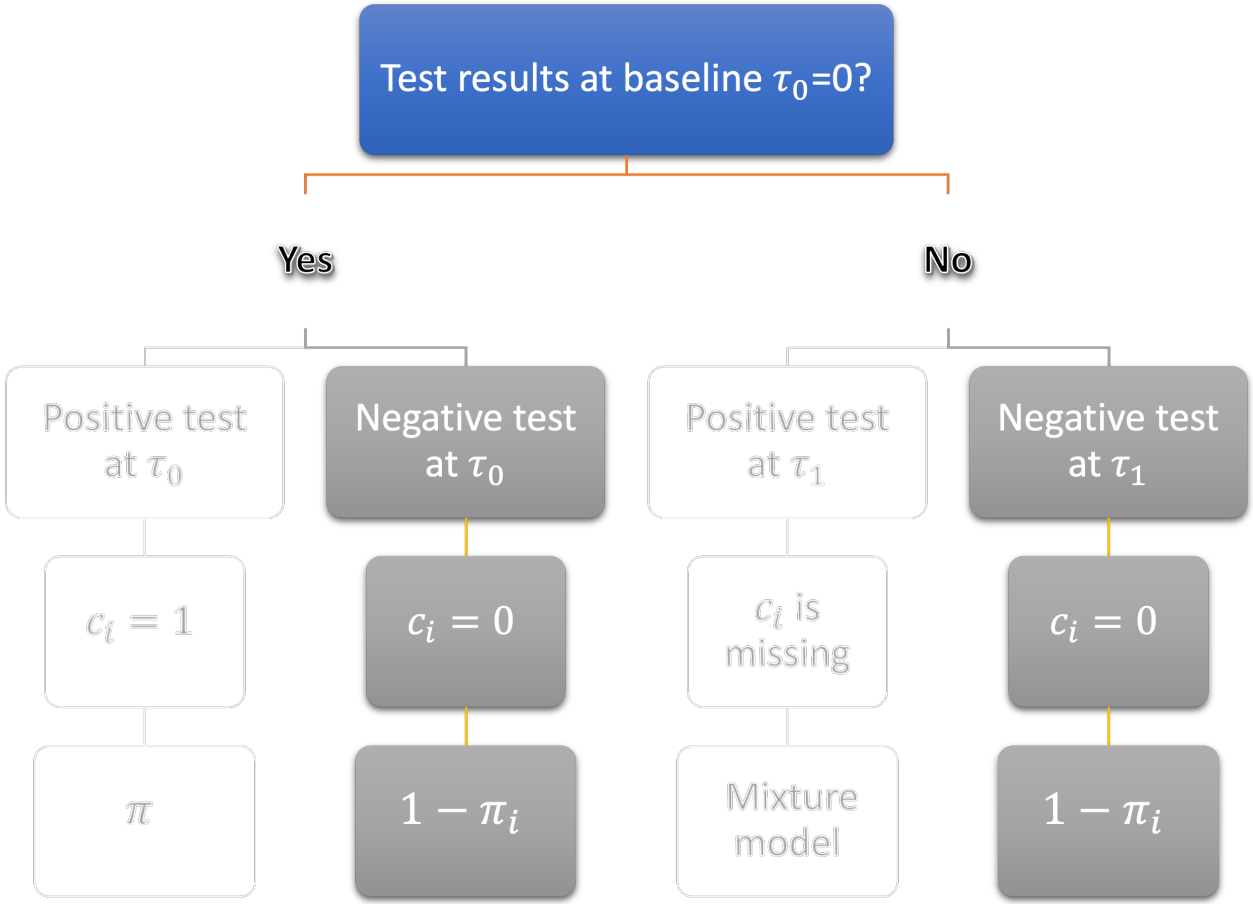
- Let c_i be the indicator of T=0.
  - $c_i = 1$ if time to first positive test is at birth, $Pr(c_i = 1) = \pi_i$,
  - $c_i = 0$ if time to first positive test is after birth, $Pr(c_i = 0) = 1 - \pi_i$,
  - *Note: c_i is missing for a subset of infants in the data*.
- Let L_i be the time of the last negative DNA PCR test.
- Let R_i be the time of the first positive DNA PCR test.

Diagram of Mixture Model



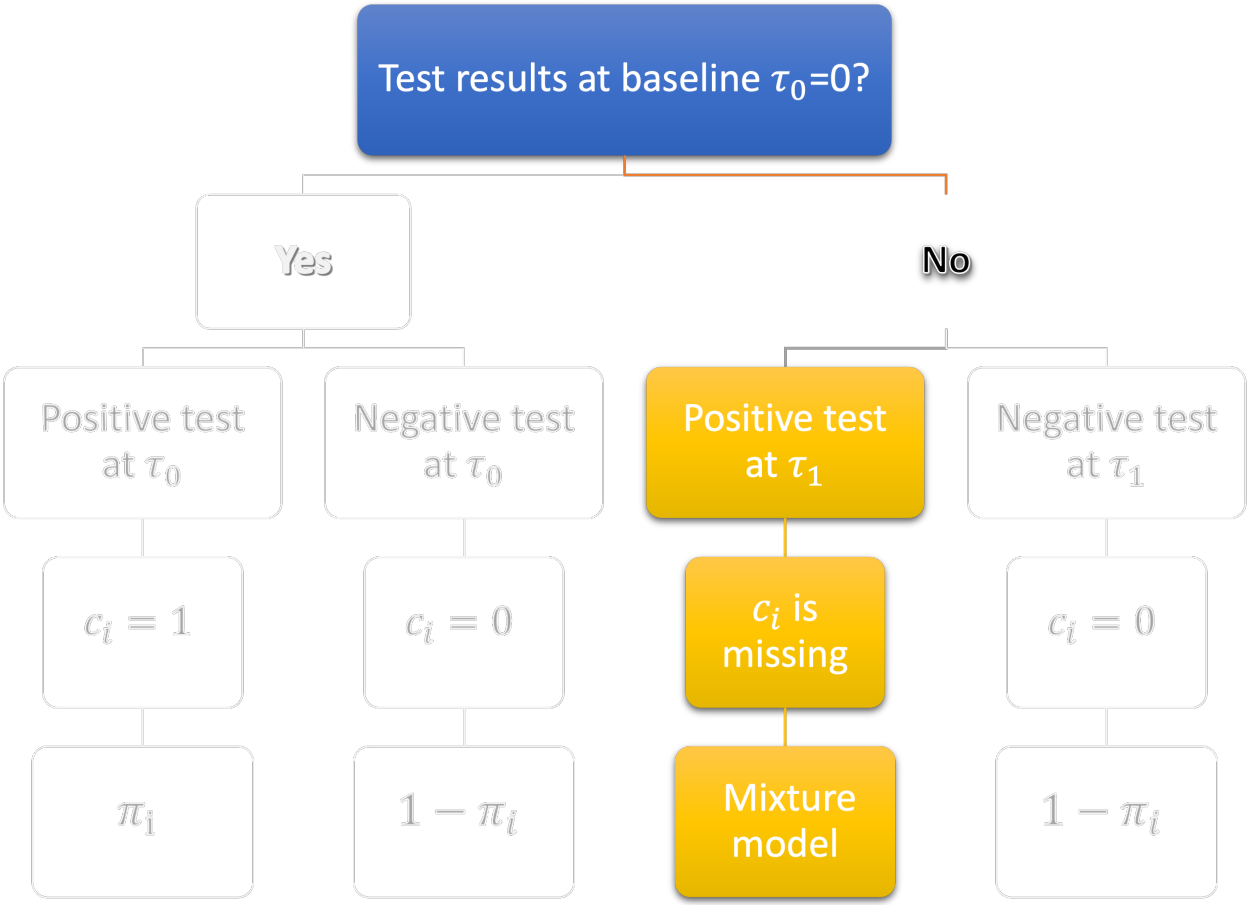
When $c_i = 1$, infant contributes π_i to the likelihood.

Diagram of Mixture Model



When $c_i = 0$, infant contributes $(1 - \pi_i)\{S(L_i) - S(R_i)\}$ to the likelihood.

Diagram of Mixture Model



When c_i is missing and assume missing at random, subjects contribute $\pi_i + (1 - \pi_i)\{1 - S(R_i)\}$ to the likelihood.

Mixture Model Likelihood

- Let $\boldsymbol{K}_1$ and $\boldsymbol{K}_0$ be partitions of subjects into observed and missing c_i, respectively. We assume that c_i is missing at random (MAR). The observed likelihood[5] is given as

$$L(\boldsymbol{y}^{obs}) = \prod_{i \in \boldsymbol{K}_1} \pi_i^{c_i} \left[(1-\pi_i) \times \left\{ S(L_i) - S(R_i) \right\} \right]^{1-c_i} \times \prod_{i \in \boldsymbol{K}_0} \left[\pi_i + (1-\pi_i) \times \left\{ 1 - S(R_i) \right\} \right] \quad (1)$$

[5] cheung2017mixture.

Parametric assumptions, covariates

- We assume $T \mid T > 0$ follows a Weibull distribution.
- We allowed maternal ARV and other covariates to affect T through logistic and proportional hazards (PH) models.

Other approaches

- Weibull PH model to model the effect of maternal ARV on $T \mid T > 0$.
- Turnbull's nonparametric estimates of $S(t \mid T > 0)$ for each maternal ARV group.

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Mixture Model Result

- PH assumption not violated (p = 0.60)
- Analysis: Unadjusted Logistic-Weibull PH mixture model
- OR>1 means higher odds of positive test at birth
- HR>1 means Earlier Detection of HIV

Maternal ARV[1]	**Odds Ratio (OR)**	**95% CI**	**Hazard Ratio (HR)**	**95% CI**
	Association with positive test at birth		*Association with positive test after birth*	
No ARV[1]	4.29	(1.57, 11.71)	34.57	(11.72, 101.99)
Single NRTI[2]	5.35	(2.02, 14.16)	12.71	(2.63, 61.51)
cART[3](Reference)	1	N/A	1	N/A

[1] ARV: Antiretroviral
[2] NRTI: Nucleoside Reverse Transcriptase Inhibitors
[3] cART: combined Antiretroviral Therapy

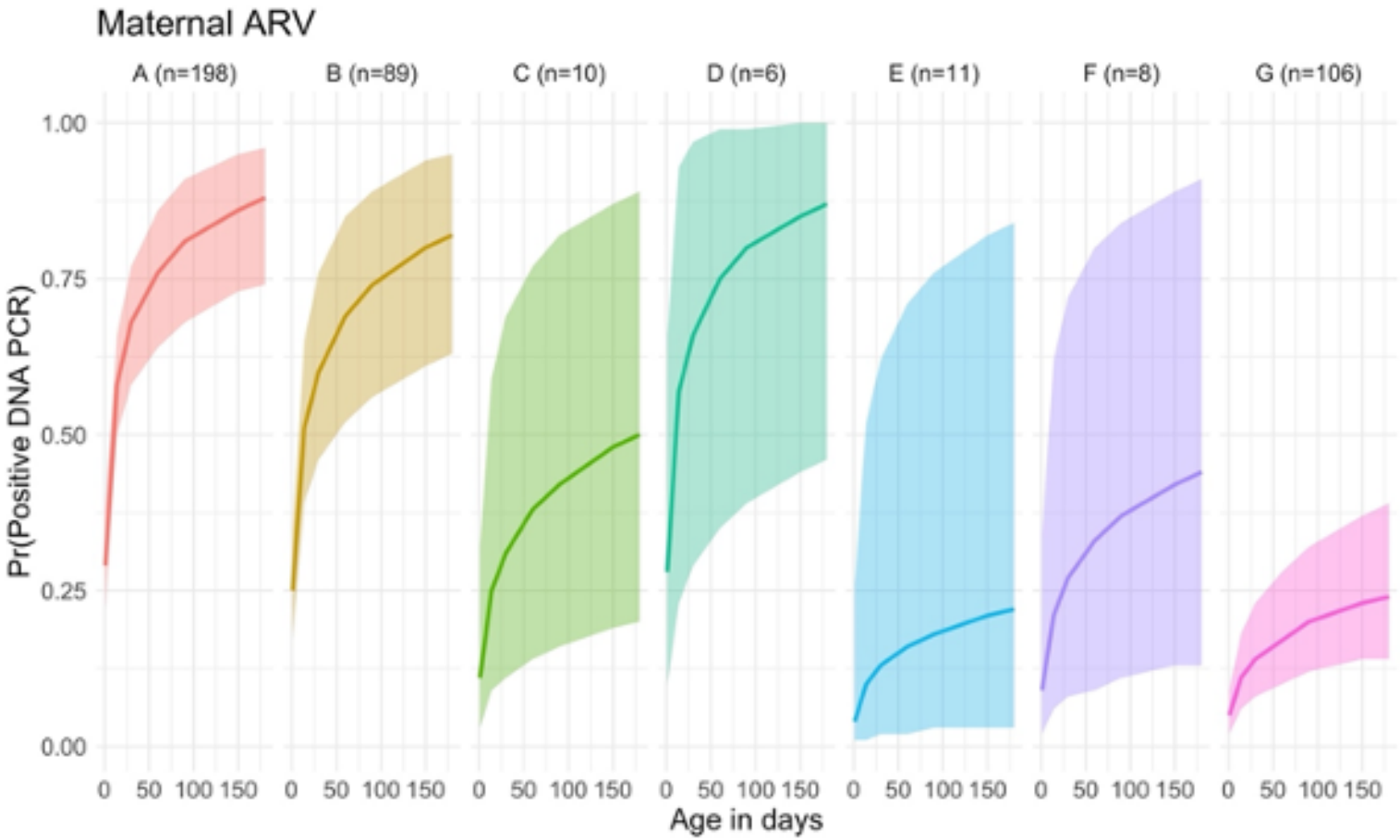
Turnbull Nonparametric Estimates

Cumulative Probability of Positive DNA-PCR Tests by Age

Maternal ARV[1]	# of Infants	Birth - 1 day	≤ 14 days	≤ 30 days	≤ 42 days	≤ 90 days
No ARV[1]	198	0.26	0.52	0.89	0.90	1.00
Single NRTI[2]	89	0.31	0.36	0.58	0.67	1.00
cART[3]	106	0.09	0.09	0.13	0.13	0.13

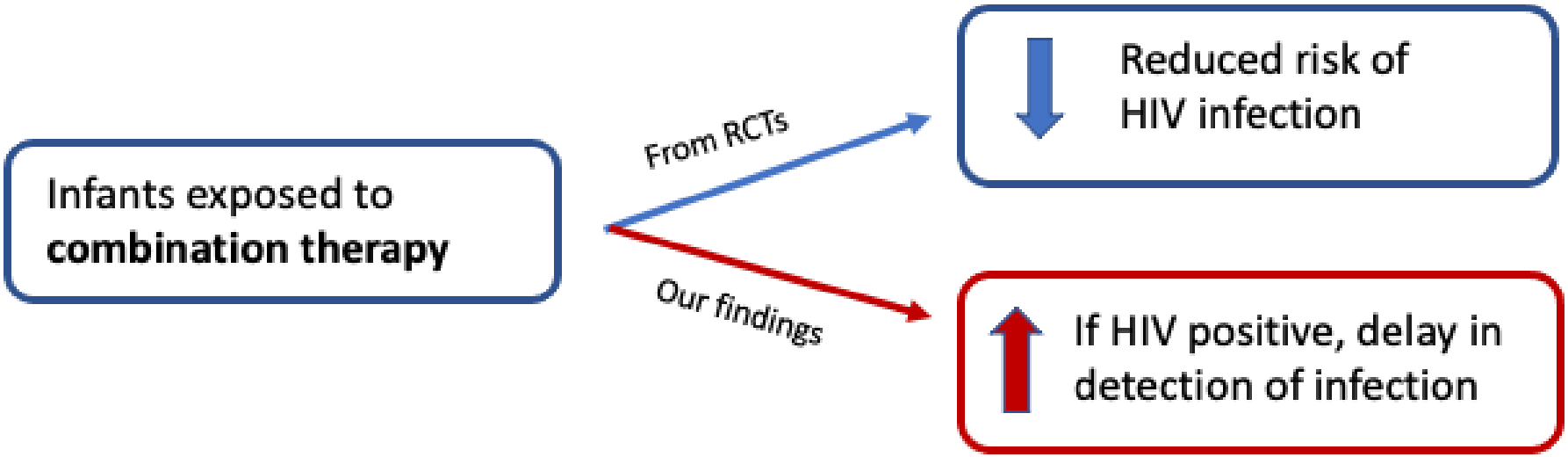
[1] ARV: Antiretroviral
[2] NRTI: Nucleoside Reverse Transcriptase Inhibitors
[3] cART: combined Antiretroviral Therapy

Weibull PH model results



A: No ARV; **B**: Single NRTI ; **G**: 3+ ARV with NNRTIs +/- PIs (cART)

Primary findings



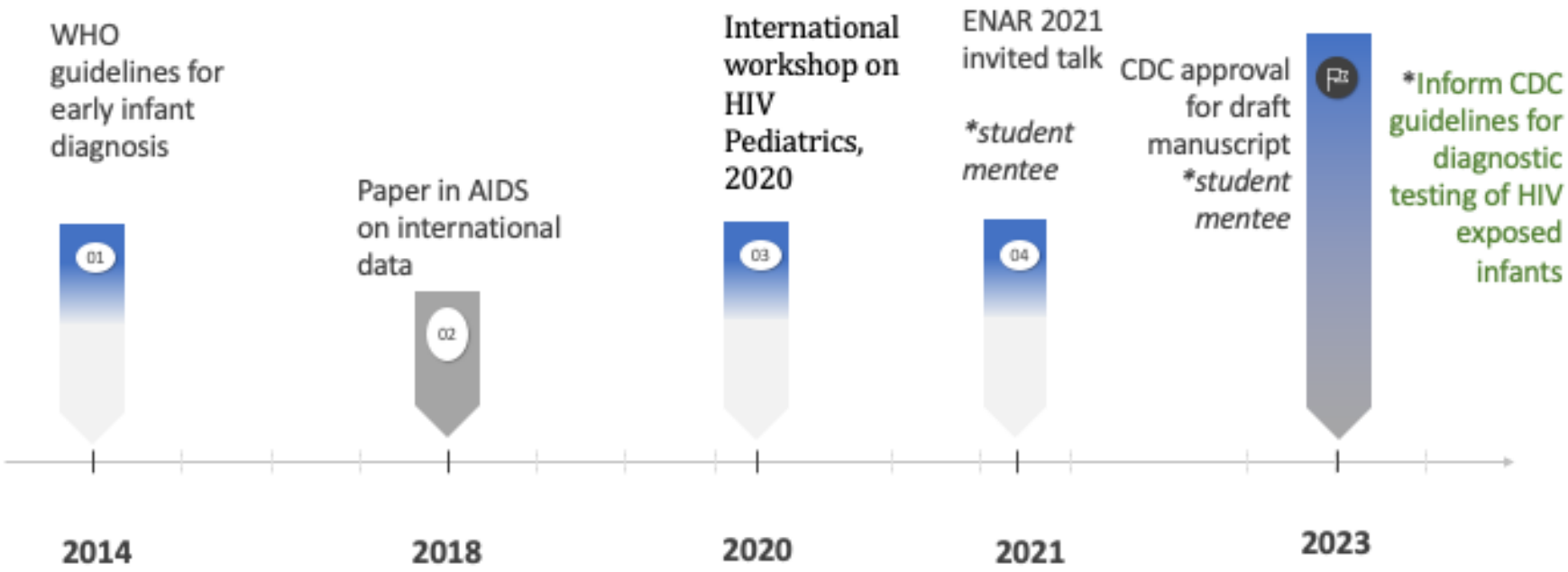
Similar trends seen in US and international cohorts, across diverse populations

Summary

- Early infant diagnosis of HIV is a critical issue in the clinical management of infants born to HIV positive mothers.
- Current guidelines for diagnostic tests from CDC[6]: definitive exclusion of HIV infection in non-breastfed infants is based on two or more negative virologic tests, with one obtained at age ≥ 1 month and one at age ≥ 4 months.
- Our research also suggests a negative test by 4 months of age is not likely to be definitive of absence of infection.
- Our research suggests these guidelines should depend on treatment exposure.

[6] https://clinicalinfo.hiv.gov/en/guidelines/perinatal/diagnosis-hiv-infection-infants-and-children

Public Health Impact



Balasubramanian R, Fowler MG, Dominguez K, et al. Time to first positive HIV-1 DNA PCR may differ with antiretroviral regimen in infants infected with non-B subtype HIV-1. *AIDS*. 2018;31(18):2465-2474.

Limitations/Future directions

- Observational data, pointing to need for causal inference approaches
- Data limitations include older cohorts, previous generation of DNA PCR assays, limited sample size.

Collaborators

- Dr. Yibai Zhao, former PhD student at UMass Amherst.
- Dr. David E. Shapiro, Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health
- Dr. Steven Nesheim (CDC), Dr. Kenneth Dominguez (CDC), Dr. Mary Glenn Fowler (Johns Hopkins University School of Medicine).