TREATING INFANTS EARLY STUDY: TIES

Sponsored by:

The Eunice Kennedy Shriver
National Institute of Child Health and Human Development (NICHD)
and
The National Institute of Allergy and Infectious Diseases (NIAID)

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KEY DEFINITIONS

In utero HIV infection is defined as at least one positive nucleic acid test from a blood specimen collected within 48 hours of birth, confirmed with a second positive nucleic acid test from a separate blood specimen.

Intra-partum HIV infection is defined as having a negative nucleic acid test from a blood specimen collected within 48 hours of birth, but two positive nucleic acid tests from separate blood specimens in an infant born to a mother with HIV-infection after 48 hours of birth.

Perinatal HIV infection is defined as either in-utero or intra-partum HIV infection.
SCHEMA

TREATING INFANTS EARLY STUDY
“TIES”

DESIGN: This is an opportunistic observational study of infants with perinatal HIV-infection who initiate combination antiretroviral therapy (ART) very early in life, under the direction of their primary providers.

SAMPLE SIZE: At least 15 children, enrolled over 3 years by convenience sampling

POPULATION: Infants who were perinatally infected with HIV and initiated antiretroviral therapy (ART) very early in the course of their infection, even within the first hours and days of life. Infants can be up to 12 months of age at enrollment, as long as ART regimens with 3 agents were received continuously since < 6 weeks of age. Mothers of all infants are briefly enrolled for clinical data and specimen collection at one time point.

STUDY DURATION: 5 years

PRIMARY OBJECTIVES:
1) To assess the safety of initiating combination ART at < 6 weeks of age for the treatment of perinatally HIV-infected infants.
2) To characterize the plasma HIV RNA decline in perinatally HIV-infected infants who initiate combination ART at < 6 weeks of age

Secondary Objectives:
1) To describe the choice of regimen and timing utilized by HIV providers in the USA treating HIV-infected infants < 6 weeks of age
2) To collect and store samples from early-treated perinatally HIV-infected infants for future studies of HIV reservoirs and immunological response to HIV.
3) To establish a cohort of early-treated HIV-infected infants who would be potential candidates for future studies of HIV remission and eradication.
2.0 INTRODUCTION
There is currently intense interest among researchers and clinicians in the USA in the potential benefits of initiating antiretroviral therapy (ART) in HIV-infected infants in first days or weeks of life.\textsuperscript{1-3} In 2013, an infant in Mississippi was thought to have been “cured” of HIV after initiation of ART within 30 hours of birth.\textsuperscript{4} Unfortunately, viremia eventually recurred, but the prolonged “remission” for more than 27 months off ART continues to suggest potential benefit from very early ART initiation\textsuperscript{5}. Clinical benefits from initiating ART prior to CD4 decline have been demonstrated in many trials of HIV-infected adults\textsuperscript{6,7} and children\textsuperscript{8,9}. But the situation for infants is distinct, in that one knows the precise timing of exposure and initial infection. There is thus an exceptional opportunity to initiate therapy during the early stages of infection when reservoirs are seeded throughout the body\textsuperscript{10}.

To investigate the impact of very early ART in infants, the NIH-funded International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network has launched a proof-of-concept trial (“P1115”) that is enrolling in utero HIV-infected infants and treating them immediately with investigational dosing and combinations of ART (NCT02140255, www.clinicaltrials.gov/ct2/show/NCT02140255?term=NCT02140255&rank=1). This trial will yield important data about outcomes of early treated infants. But with restrictive eligibility criteria and limited study sites in the USA, many HIV-infected infants in the USA will not be able to participate.

In the community, physicians and families always seek to give HIV-infants the best outcome possible. Historically, physicians have not rushed to start therapy in HIV-infected infants, generally waiting for confirm HIV infection with testing at 2 or 4 weeks while working on adherence counselling and preparing the family for starting what is likely life-long treatment. But in light of the new attention on early treatment, physicians are more often testing infants at birth and starting ART rapidly, some even treating high risk infants “presumptively” while test results are pending. For infants < 2 weeks of age, this means using ART dosing that has not yet been endorsed by the FDA or DHHS (https://aidsinfo.nih.gov/guidelines). This shift in practice to rapid treatment is within the normal standard of care in pediatrics in which off-label dosing is often necessary due to limited data. But when it occurs outside of a research setting, it means that critical data about the safety and efficacy of a new treatment strategy is lost.

The Treating Infants Early Study (TIES) aims to address the gap in information about the safety and efficacy of ART initiated within first weeks of life in perinatally infected infants. TIES is an opportunistic observational study of infants with documented perinatal HIV-infection who have initiated combination ART at < 6 weeks of age. The primary objectives are to assess the safety and efficacy of early ART in this population. With a streamlined protocol we aim to recruit and follow infants who live in community settings, providing them a chance to participate in research and generating important data on this topic. The trial does not direct any intervention, but collects clinical data obtained in standard clinical care and banks specimens for future analysis.
2.0 HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypotheses:
2.1.1 The initiation of combination ART at < 6 weeks of age among perinatally HIV-infected infants will be safe.
2.1.2 The initiation of combination ART at < 6 weeks of age among perinatally HIV-infected infants will lead to rapid suppression of HIV plasma RNA.

2.2 Primary Objectives:
2.2.1 To assess the safety of initiating combination ART at < 6 weeks of age for the treatment of perinatally HIV-infected infants.
2.2.2 To characterize the plasma HIV RNA decline in perinatally HIV-infected infants who initiate combination ART at < 6 weeks of age.

2.3 Secondary Objectives:
2.3.1 To describe the choice of regimen and timing for treatment utilized by HIV providers in the USA treating HIV-infected infants < 6 weeks of age.
2.3.2 To collect and store samples from early-treated perinatally HIV-infected infants for future studies of HIV reservoirs and immunological response to HIV.
2.3.3 To establish a cohort of infants with well-characterized decay of plasma viral RNA and banked specimens to serve as potential candidates for future trials of HIV remission and eradication.

3.0 STUDY DESIGN
This is an opportunistic observational study of infants who become HIV-infected perinatally and are initiated on combination ART at less than 6 weeks of age. The primary objectives are to assess the safety and plasma HIV RNA response of HIV-infected infants who initiate ART early. The secondary objective is to establish a cohort of infants who, with well characterized clinical histories and banked specimens, will be candidates for future studies of HIV reservoirs and remission. We aim to enroll infants at hospitals and clinics throughout the United States and possibly Canada who initiated ART early, at the discretion of their local providers. Once enrolled, infants continue to receive care directed by their local physician, but provide clinical data and specimens to the study team. Infants will be enrolled over 3 years, and followed until the end of the 5 year study period, guaranteeing at least 2 years of follow up per child. Infants may be up to 12 months of age at enrollment, as long as treatment with three agents since < 6 weeks of life can be documented. Mothers are briefly enrolled for clinical data and specimen collection at one time point.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Infant Inclusion Criteria
4.1.1 HIV-infected: Documentation of perinatal HIV infection with 2 positive HIV nucleic acid tests (“NAT,” can be RNA or DNA) from two separate specimens obtained within the first 4 weeks of life. Infants can enroll with one positive HIV NAT result, but second test should be sent immediately or be pending upon enrollment; subject will be withdrawn if 2nd test is negative.
4.1.2 Early ART initiation: Initiated a regimen of ≥ 3 ART drugs with daily dosing at age < 6 weeks.
4.1.3 Age < 12 months.

4.2 Infant Exclusion Criteria

4.2.1 Any clinically significant condition that, in the investigator’s opinion, would interfere with study participation or interpretation.

4.2.2 Mother or legal guardian unable or unwilling to provide informed consent for infant participation per the laws of that state.

4.3 Maternal Inclusion Criteria

4.3.1 Able to provide informed consent per the laws of that state.

4.3.2 Birth mother of an infant eligible for study.

4.4 Maternal Exclusion Criteria

4.4.1 Unable or unwilling to provide informed consent.

4.5 Recruitment and Enrollment Procedures

4.5.1 Recruitment:

4.5.1.1 Provider contacts study team by email or phone; devoted email account and phone voice mail are checked at least every 24 hours. Physician and Patient Information.

4.5.1.2 Study staff contacts provider to review eligibility, without involving any protected health information.

4.5.2 Enrollment:

4.5.2.1 If subject is eligible by screening, the mother or legal guardian will be referred to a website to review the study information and electronic consent and Authorization for Release of Health Information forms; if internet is not available, a written form will be mailed to her by overnight mail (with return pre-paid).

4.5.2.2 If the mother or legal guardian has questions, she/he can speak with a member of the study team. Contact information is listed on the website and could occur by phone, Skype or other mechanism. If the PI (Dr. Ruel) has served as clinical consultant to the provider, he will not be the person to counsel the patient about informed consent.

4.5.2.3 If mother or legal guardian of infant desires for her infant to participate, she/he provides consent by: 1) electronic signature of the online consent form, or 2) printing the consent, and signing it, and returning it by pre-paid express mail. An “Authorization for Release of Health Information” (sample in Appendix III) must also be printed, signed, copied (with copy kept by the mother or legal guardian), and sent by pre-paid express mail to the study team.

4.5.2.4 If mother of infant desires to participate herself, she provides consent and medical release forms by the same mechanisms.

4.5.2.5 A member of the study team will travel to the site to review the study with the mother or legal guardian once during the study, and ideally within first 4 weeks of enrollment.

5.0 STUDY PROCEDURES

5.1 Treatment

The study aims to characterize the safety and virologic efficacy of combination ART initiated early in life to treat HIV-infected infants. However, all infants will have already
initiated ART prior to enrollment (see enrollment criteria) and all decisions about ongoing treatment will be made by the subject’s primary provider(s) and guardian(s).

5.2 Toxicity Management:
Management of any toxicity experienced by subjects will be directed by the primary providers of patients.

5.3 Clinical Data Collection:
Clinical data, including history and laboratory results, will be primarily collected by review of medical records and by phone or in-person conversation with the subject’s providers and parents, according to the Schedule of Evaluations (Appendix I). The study team will contact mother or legal guardian of subjects approximately monthly to inquire about medication adherence and any interval clinical events. The study team will contact subject’s providers approximately quarterly to request updated documents and data. Local providers, as per the applicable medical release form, will send copies of source documents to the study team who will complete case report forms at the study coordination center. The subject’s mother will have clinical data collected at the time of enrollment only. No case forms or other study documents will be located at the sites where subjects receive primary care.

5.4 Specimen Collection:
5.4.1 Blood specimens: Blood is requested according to the Schedule of Evaluations (Appendix I), with sampling specifically aligned to times that the subject would be expected to undergo blood testing for routine clinical reasons per US national guidelines. Mothers will have blood collected once at enrollment only (8ml). Fresh blood specimens will be sent overnight at room temperature to the study coordinating center, where it will have plasma separated, peripheral blood mononuclear cells isolated, and all be cryopreserved. Shipping of all blood specimens will be paid for by the study. If the state where the infant was born obtained dried blood spots for newborn testing, the study team will attempt to obtain any extra specimen.

5.4.2 Non-blood specimens: If any biopsy or lumbar puncture is performed as part of clinical care for the subject for any clinical reason, the study team requests any excess tissue/fluid, including, but not limited to: cerebrospinal fluid, gastrointestinal tract, or lymph node. Specimens should be cryopreserved and sent to the study coordinating center for storage, with transport costs paid for by the study.

5.4.3 Specimen storage. On arrival to the study laboratory, specimens will be processed (if applicable), labeled with a unique study ID and date, and stored for future use, as per the consent form.

5.5 Compensation:
Mothers or legal guardians of infants who participate will be compensated up to $585 per year (paid $195 every 4 months) for completing study activities in that time period. This will be reduced by $15 per missed phone call and $75 per missed blood draw. Birth mothers who participate themselves will receive a one-time payment of $115 ($15 for phone call, $100 for blood draw). Subjects will receive additional reimbursement for travel costs as necessary. Providers’ offices will be reimbursed for exceptional costs related to the provision of medical documents (up to $300 a year.)
5.6 Co-enrollment:
Co-enrollment in other studies is generally permitted but permission must be granted by
the study team.

5.7 Study Discontinuation
5.7.1 The subject or parent/legal representative/guardian refuses further study
participation
5.7.2 Death
5.7.3 The investigator determines that further participation would be detrimental to the
subject’s health or well-being.
5.7.4 The study is discontinued (See Section 9.3).

7.0 ADVERSE EVENT REPORTING
As this study directs no intervention for subjects, there will be no adverse event reporting to
DAIDS or the UCSF IRB.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues.
The primary objectives of this study are to define the safety and the dynamics of HIV
RNA suppression associated with early initiation of ART For secondary objectives, additional analyses using clinical data and banked specimens will also be performed.

8.2 Outcome Measures
8.2.1 Primary
8.2.1.1 Adverse events of Grade 3, 4 using signs/symptoms, laboratory values or diagnoses per 2014 DAIDS adverse grading system, or death at least possibly, probably or definitely related to ART. Relatedness of event to ART will be based on reports from the site with adjudication by the study team. (http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf)
8.2.1.2 Plasma HIV RNA < 50 c/ml at 12 weeks.

8.2.2 Secondary
8.2.2.1 Plasma HIV RNA levels of < 20, < 50, < 400 at other times in the follow-up period
8.2.2.2 Grade I/II adverse events
8.2.2.3 Age at ART initiation, ART regimen

8.3 Stratification
Enrollment will not be stratified. However, analyses of the primary outcome measures will be performed using all data overall, and stratified by the timing of infection: in utero (first positive NAT at < 48 hours of life), intrapartum (negative NAT at < 48 hours of life, then positive); unknown (no NAT testing at < 48 hours of life).

8.4 Sample Size and Accrual
No formal sample size calculations have been performed for this study. In the team's opinion, a sample size of at least 15 would provide sufficient data to inform the studies objectives. It is recognized with such a small number of subjects, this study will only
provide exploratory data about safety and not reliably capture any rare events. We aim to enroll any eligible HIV-infected infant born in the United States, and therefore hope to exceed that minimal target size of 15 infants.

8.5 Monitoring
Since no treatment or intervention will be given as part of the study, no formal safety monitoring will take place.

8.6 Analyses
As this is an opportunistic observational study, analyses for primary objectives will consist of descriptive statistics. Data summaries will provide point estimates with corresponding 95% confidence intervals for parameters of interest. For example, the proportion of infants with plasma HIV RNA suppression at 12 weeks will be provided, along with a 95% confidence interval on this probability. Secondary analysis will include additional descriptive analyses of maternal and infant characteristics, as well as multivariate analysis of maternal and infant predictors of adverse events and HIV RNA < 50 c/ml throughout the follow up period.

9.0 HUMAN SUBJECTS

9.1 Institutional Review Board
This study will be conducted in accordance with the Declaration of Helsinki, Belmont Report, and Good Clinical Practice guidelines recommended by the International conference on Harmonization. This protocol, the informed consent (Appendix II), a sample medical information release form (Appendix III), and any subsequent modifications will be reviewed and approved by the Institutional Review Board (IRB) at the University of California, San Francisco.

All research activities will be performed by the UCSF-based study team and are limited to data collection by chart review, data collection by phone interview and specimen collection. The local providers are not considered investigators and do not participate in any study activities; sharing of clinical data and specimens by medical providers is legally and ethically permitted as per the release of medical information forms signed by the mother or legal guardian. It is thus believed that local IRB approval at sites outside of UCSF will not be required for this study.

9.2 Informed Consent
The process of obtaining informed consent for participation in the study and release of medical information is outline in section 4.5.2.

9.2 Subject Confidentiality
Patient clinical information will be collected by receipt of medical records or by phone interview of providers or mothers/legal guardians. Clinical Research Forms will be only be completed by the study team at UCSF. All documents containing patient identifying information will be stored in files organized by assigned study ID and kept in a secured area. The majority of data will be stored electronically on a secure university database. All data entry will be done with coded numbers only. Clinical information will not be released without written permission of the participant or the participant’s parent or legal guardian, except as necessary for monitoring by the Office for Human Research Protections (OHRP), the NIH and the UCSF Institutional Review Board (IRB).
Study-specific blood draws will happen at community laboratories that will send the specimen to the UCSF Center for AIDS Research Laboratory. On arrival, the specimens will be assigned a study ID number, date of collection; any patient identifying information will be removed and destroyed.

All study records will be stored in secure locations, databases will be on password protected and encrypted devices. Because of the sensitive nature of HIV, the study will obtain a Certificate of Confidentiality in order to further protect participant confidentiality (http://grants.nih.gov/grants/policy/coc/index.htm).

9.3 Study Discontinuation
The study may be discontinued at any time by the NICHD, NIAID, the OHRP, NIH, or UCSF IRB, or other governmental agencies as part of their duties to ensure that research subjects are protected.

10.0 REFERENCES

8. Violari A, CM, Gibb D., Babiker A., Steyn J., Jean-Phillip P., McIntyre J., on behalf of the CHER Study Team. Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study. 1Perinatal HIV Research Unit, University of Witwatersrand, Witwatersrand, South Africa, 2Children's Infectious Diseases Clinical Research Unit, Faculty of Health Sciences, Stellenbosch University, Stellenbosch, South Africa, 3MRC-Clinical Trials Unit, London, United Kingdom, 4Division of AIDS, NIAID, NIH, Bethesda, United States; 2007.
## APPENDIX I

### INFANT SCHEDULE OF EVALUATIONS (SOE)\(^1\)

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<th>2-3 weeks of life</th>
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<th>After 1-2 weeks of ART</th>
<th>After 2-4 weeks of ART</th>
<th>3-4 times a year</th>
<th>2-4 weeks after ART Change</th>
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NOTES ON SCHEDULE OF EVALUATIONS:

1. This study is observational and the timing of evaluations is decided by the subject’s primary physician. This Schedule of Evaluations was therefore based on the data anticipated from the routine care recommended by the Department of Health and Human Service (DHHS) Guidelines for Use of ARV in Pediatric HIV infections, available at http://aidsinfo.nih.gov/guidelines. However, it is recognized that complete data may not be available at these exact time points.

2. Current DHHS guidelines suggest testing of HIV-exposed infants 14 to 21 days and 1 to 2 months; we anticipate that infants who must enter this study on ART will have had HIV diagnosis based on testing at birth and/or 14-21 days of life. But we will collect data on HIV NAT testing done at any date.

3. ART initiation can occur at any age < 6 weeks for this protocol; therefore, there may or may not be additional assessments at this time point if they had been recently acquired.

4. Because the study aims to capture toxicity, that could of course occur at routine or non-routine points, the study will collect information about any clinical events that occur between routine visits.

5. Enrollment can occur at any age up to 12 months, and thus at any point in the series of visits considered standard care represented elsewhere in the table.

6. The study will contact the participant monthly to inquire about adherence and any clinically significant interim events that may be related to HIV or ART.

7. History at birth includes sex; race/ethnicity; Apgar scores, weight, length, head circumference and gestational age at birth; and clinical history (diagnoses, signs, and symptoms), ART and other concomitant medications, and method of feeding since birth. Patient History at future intervals will include clinical history (diagnoses, signs, and symptoms), ART and other concomitant medications, and method of feeding.

8. Physical Exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.

9. Any provider documented information about adherence assessment will be abstracted from medical records; in addition we will collect our own adherence information at approximately monthly intervals.

10. Hematology: CBC (complete blood count) with white blood cell differential.

11. Chemistries: including alanine transaminase (ALT), aspartate aminotransferase (AST), and lipase.

12. HIV RNA levels (copies/ml) as per whatever assay utilized at the patient site; the assay used will also be documented.

13. Generally recommended to be obtained prior to initiation of ART, even if the results aren’t available with ART is started.

14. Specimens will be collected at these time points if possible given the age at which the subject enrolls. The study team will attempt to obtain the dried blood spots obtained for the purposes of neonatal screening for congenital disease; the mechanism and possibility of this is expected to vary state by state.

15. If a different scheduled blood draw is within 2 weeks of study enrollment, it can be used as the enrollment blood draw.
Consent to Participate in the Treating Infants Early Study (TIES)

Dr. Theodore Ruel at the University of California San Francisco is conducting a research study to better understand the effects of early treatment in HIV-infected babies. Because your baby has HIV, we are asking you to consider letting him or her participate in this study. Our goal is to better understand the risks and benefits of starting treatment early, and to help form a group of HIV-infected children who could be invited to participate in future studies. Our research is funded by the National Institutes of Health (NIH).

In addition to reading this form, the study investigator, Dr. Theodore Ruel, or the study coordinator, Kristin Hoeft, can talk to you by phone or videoconference to help explain the study and answer all of your questions.

What will happen if I let my baby participate in this study?

- The study team will talk to you once a month to ask you some questions about your baby’s health and medications. These conversations will last about 10 to 15 minutes, and you can skip any questions you don’t want to answer. (12 times per year for as long as you are in the study, a maximum of 5 years).
- If possible, we will contact the government officials in the state where your baby was born to ask about getting leftover dried blood spots from infant screening tests. You will sign a form giving your doctor permission to share medical records with the study team. We will collect details on medications, health conditions, and laboratory tests related to HIV from your baby’s medical records.
- Your baby will have about a teaspoon of blood drawn at least 3 times a year, and at most 6 times per year, to be sent to the study. The blood will be drawn by putting a needle into a vein in your baby’s arm or foot, and over a 1 year period, your baby will give between 3 and 6 teaspoons of blood.
- If your baby’s doctor collects biopsies or cerebrospinal fluid for some other purpose, we will ask them to send us any leftover specimen for research.
- Participating in this study will not affect your baby’s normal medical care. Your baby will see their regular doctor as usual.
- If you are the birth mother, we will ask you questions about your health once, ask you to go to a lab for a single blood sample (about 2 teaspoons), and you will sign a form giving your doctor permission to share your medical records (medications, health conditions and blood tests related to HIV) with the study.

How many people will take part in this study? Between 15 and 200 babies and their mothers will take part.

How long will my baby and I be in the study? Your baby will participate from whatever year they join the study until it ends in 2020, from between 2 and 5 years in total. If you are a birth mother, you would participate only briefly, to provide information and one blood specimen. The specimens will be kept indefinitely, until they are used or discarded.

What kind of research will you do with the specimens and information from me and my baby? We want to learn about how treating HIV very early benefits children. But because of rapidly changing advances in medicine, we cannot now describe all the future research studies that may use the specimens and information. We can assure you that the only purpose will be for biomedical research. We might study genes of you or your baby that are thought to be important to HIV disease. But this genetic information does not have medical or treatment importance at this time. Reports about any research will not be put in your medical record or given to you or your doctor. The specimens and information may be used to develop new drugs, tests, treatments or products.

Are there risks? This study has minimal risks. The needle stick from the blood sample may hurt. There is a small risk of bruising and fainting, and a rare risk of infection. There is a possibility of loss of privacy, however the study takes every possible precaution to protect the health information you share with the study.
**Are there benefits?** There is no direct benefit to you or your baby from participation in this study. However, the blood and information collected will be used to advance the care of other babies born with HIV.

**Can I say “No”?** You can say “No”. Your baby does not have to participate in this study. If you decide not to have your baby be in this study, your baby will not lose any regular medical benefits, and can still receive medical care as usual. You can also decide to have your baby stop participating any time. If you decide later that you do not want your baby’s specimens or information to be used for future research, you can notify the investigator in writing at 550 16th Street, 4th Floor, San Francisco, CA 94158 and we will destroy any remaining identifiable specimens and information. However, if any research has already been done using portions of your specimens, the data will be kept and analyzed as part of those research studies.

**Will my medical information be kept confidential?** To protect your baby’s privacy, the information we collect from you and your baby’s medical record will be stored only with a code number, and only researchers on the study team can connect your baby’s name with the code number. All information we collect will be kept secure and restricted. To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use the Certificate to legally refuse to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of suspected or documented child abuse, neglect or risk of harm. If information from this research is published or presented at scientific meetings, your baby’s name and other identifiers will not be used. We may share medical and genetic information from you and your baby with other researchers and companies not at UCSF, including limited access government health research databases, but we will not share your baby’s name and other identifiers.

**Are there any costs or payments?** There are no costs to you to participate in this study. In return for your time and effort, you and your baby will be paid up to $585 per year in check or debit card (you can choose which format you prefer) for your baby’s participation. You will be paid every 4 months (3 times a year), up to $195 each time when you complete all study activities (4 conversations with the study team and 1 or 2 blood draws). If you are unable to complete all study activities in a 4 month period, $15 will be deducted per missed conversation, and $75 will be deducted per missed blood draw. Participating birth mothers will get a one-time payment of $115 within 6 weeks after participation is completed. We will provide additional reimbursement for travel costs when necessary.

**Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California or the study sponsor (NIH), depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415-476-1814. Tell the study doctor, Dr. Theodore Ruel if you feel that you have been injured because of being in this research. You can call him at (415) 476-9197.

**Who can answer my questions about the study?** You can talk to the study doctor or study coordinator about any questions, concerns, or complaints you have about this study by emailing calling:

**Study Doctor:** Dr. Theodore Ruel   (415) 476-9197  
**Study Coordinator:** Kristin Hoeft   (415) 502-5500

The study team has no financial or proprietary interests related to this study.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at (415) 476-1814.
CONSENT

By signing this form, I give permission for my child or ward to participate in the study. I will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about my baby. Copies of these forms and the Experimental Subject's Bill of Rights will be given to me.

Date __________________ Signature for Consent for child/ward participation

By signing this form, I (the birth mother) agree to participate in the study. I will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about me. Copies of these forms and the Experimental Subject's Bill of Rights will be given to me.

Date __________________ Signature for Consent for birth mother participation

I am also interested in learning if there are other research studies for which my baby or I may be eligible.

Date __________________ Signature for future contact
APPENDIX III
SAMPLE MEDICAL RELEASE OF INFORMATION FORM

U.C.S.F. Medical Center
U.C.S.F. Benioff Children’s Hospital

AUTHORIZATION FOR RELEASE OF HEALTH INFORMATION

I authorize ____________________________
(Name of person or facility which has information - example: UCSF/Mt. Zion)
to release health information to:
Dr. Ruel at University of California, San Francisco
Name of person or facility to receive health information (full address)
Dr. Theodore Ruel
Street address:
550 18th Street, 4th Floor
City, State, Zip Code
San Francisco, CA 94158

The purpose of this release is for (check one or more):

☐ Continuity of care or discharge planning
☐ Billing and payment of bill
☐ At the request of the patient/patient representative
☐ Other (state reason) ___________

Research Study

Please specify the health information you authorize to be released:
Type(s) of health information: ________________________________
Date(s) of treatment: ________________________________

The following information will not be released unless you specifically authorize it by marking the relevant box(es) below:

☐ Information pertaining to drug and alcohol abuse, diagnosis or treatment (42 C.F.R. §§2.34 and 2.35).
☐ Information pertaining to mental health diagnosis or treatment (Welfare and Institutions Code §§5328, et seq.).
☒ Release of HIV/AIDS test results (Health and Safety Code §120980(g)).
☐ Release of genetic testing information (Health and Safety Code §124980(j)).

EXPIRATION OF AUTHORIZATION
Unless otherwise revoked, this Authorization expires November 1, 2020 (insert applicable date or event). If no date is indicated, the Authorization will expire 12 months after the date of my signing this form.

Print Name ________________________________
Signature (Patient, Parent, Guardian) ________________________________
Date ___________________________ Time ___________________________
Relationship to Patient (Parent, Guardian, Conservator, Patient Representative) ________________________________
Requested format: ☐ Paper ☐ CD
NOTICE
UCSF and many other organizations and individuals such as physicians, hospitals and health plans are required by law to keep your health information confidential. If you have authorized the disclosure of your health information to someone who is not legally required to keep it confidential, it may no longer be protected by state or federal confidentiality laws.

YOUR RIGHTS
This Authorization to release health information is voluntary. Treatment, payment, enrollment or eligibility for benefits may not be conditioned on signing this Authorization except in the following cases: (1) to conduct research-related treatment, (2) to obtain information in connection with eligibility or enrollment in a health plan, (3) to determine an entity’s obligation to pay a claim, or (4) to create health information to provide to a third party.

This Authorization may be revoked at any time. The revocation must be in writing, signed by you or your patient representative, and delivered to Health Information Management Services, UCSF Medical Center, 400 Parnassus Ave., Room A68, San Francisco, CA 94143-0308. The revocation will take effect when UCSF receives it, except to the extent UCSF or others have already relied on it.

You are entitled to receive a copy of this Authorization.
Would you and your child like to participate in a study to help understand how early treatment affects babies born with HIV?
This will help doctors better understand how to treat HIV in babies.

If you decide to participate:

- You will sign a form giving permission for your doctor to share your and your baby’s medical information with the study.
- You will talk with the study team for about 10-15 minutes once every month to tell us about your baby’s health and medicines.
- If you are the birth mother, you will answer some questions and give 2 teaspoons of blood once. You will get $115 for participating.
- Your baby will go to a lab with their regular blood draws and give 1 teaspoon of blood between 3 and 6 times per year.
- As payment for your time and participation, the study will pay you approximately $195 dollars every 4 months if you participate in the study phone calls and blood draw. This is about $585 per year.
- Nothing will change about your normal medical care. You and your baby will see your regular doctors as usual.

Please contact Kristin (415)502-5500 or ties@ucsf.edu to get more information or sign up for the study!
Treating Infants Early Study (TIES)
Provider Information Sheet

Do you treat HIV-infected infants?
They may be eligible to participate in a research study run by Dr. Theodore Ruel at the University of California San Francisco. This is an observational study of infants who start HIV treatment early to learn how the virus responds, and to track safety. We hope this research will help doctors better understand how to treat HIV in babies.

Infants are eligible if they:

- Had two positive HIV (RNA or DNA) tests within the first month of life (or 1 positive HIV test, and 2nd test in process)
- Initiated regimen of at least 3 antiretroviral drugs by 6 weeks of age
- Are less than 12 months old

If patients decide to participate:

- The parent/guardian will sign a health information release form giving permission for you to share their baby’s medical record with the study
- Birth mothers may also participate for a one-time phone call and one blood draw (they will receive $115)
- You will periodically send medical record information to the study. Compensation is available for costs associated with this task.
- Patient parent/guardians will have monthly conversations with the study team, and infants will give between 3 and 6 extra blood samples per year shipped to UCSF for research. The study will pay patients approximately $195 dollars every 4 months for participation
- Nothing will change about your patients’ normal medical care. You will continue to provide medical care as usual, no change or intervention is prescribed by the study

Please contact Kristin (415)502-5500 or ties@ucsf.edu to get more information or to refer patients for the study