Continuing Review Submission Form (Version 12.0)

1.0

Continuing Review Form

May 2021

1.1 Principal Investigator:

[redacted]

1.2 Study Title:

HIV, EBV and HPV interaction with mucosal epithelium

1.3 Study Number:

10-03277

1.4 * Preferred Contact Information: Please provide the best contact information (phone, pager or email) for both the PI and primary Study Contact in case the IRB needs to contact you directly:

PI/study contact: [redacted] email: [redacted] phone: [redacted]

1.5 Lay Summary:

The main purpose of this study during last 15 years was to investigate the interaction of mucosal epithelial viral microbiota including herpes simplex virus (HSV), human cytomegalovirus (HCMV), Epstein Barr Virus (EBV) and Human papillomavirus (HPV) with human immunodeficiency virus (HIV). Such interaction may play a critical role in the increase of HIV mucosal transmission and HIV-associated neoplasia. Currently, we are continuing these projects under new NIDCR R 01DE023315 grant

Mother-to-child transmission (MTCT) is an important pathway for the spread of human immunodeficiency virus (HIV) from mother to fetus, neonate, and infant via oral/tonsil mucosal epithelium. The precise molecular mechanisms of HIV MTCT remain unclear, and the role of the oral microbiome in the context of HIV transmission is one of the most important questions in the field. HSV, HCMV, and EBV are common components of the oral infant microbiota, and their interaction with infant tonsil epithelial cells containing HIV may lead to the release and spread of HIV into CD4+ T lymphocytes, macrophages, and Langerhans/dendritic cells (LCs/DCs) and thus to HIV MTCT. Virtually nothing is known about the role of herpesvirus oral microbiota in HIV MTCT. Therefore, investigation of the molecular mechanisms underlying HSV-, HCMV-, and EBV-associated HIV spread from neonatal/infant oral epithelia into HIV-susceptible cells will undoubtedly lead to a better understanding of the oral microbiota-associated pathogenesis of HIV MTCT and the development of a new preventive therapeutic strategy against perinatal viral infection

The goal of this study is to investigate the role of oral mucosal microbiota HSV, HCMV, and EBV in the HIV MTCT.

1.6 * NEW - Biospecimen Banks, Research Databases, and Recruitment Registries - Does this IRB approval ONLY cover activities such as biospecimen collection/banking, and/or collection of data in a research registry or recruitment database: (REQUIRED)

1.7 * This is a: (REQUIRED)

- ○ Continuing Review Only—no changes from last approval
- ◉ Continuing Review and Minor Modification
- ○ Continuing Review and Major Modification

If your study is set to expire within 30 days, DO NOT include any modifications. Get approval of the Continuing Review first and then submit a Modification Form to make the changes.

For studies with changes (studies that do not expire within 30 days), please see our online guidance (updated May 2021) for the difference between 'Major' and 'Minor' modifications.

1.9 * Types of changes being made (check all that apply): (REQUIRED)

- ☑ Making changes to PI or personnel
- ☐ Adding a new funding source
- ☐ Adding new sites
- ☐ Increasing enrollment numbers
- ☐ Adding radiation exposure for the first time (imaging, radioactive contrast agent or ionizing radiation)
- ☐ Other changes including changes to recruitment, procedures, risks, etc.

Changes to the application are required. Please incorporate these changes in a revised application form.

1.10 * Describe each modification and provide a justification/rationale for each one: (REQUIRED)

NOTE: A scientific rationale MUST be provided for each proposed change. Submissions will be returned if they are not provided.

[redacted] left the lab, and therefore thier names were removed from the application.

1.11 * Are any of these changes being made as a result of an adverse event report (AER), protocol violation or incident report, or publication of a new Investigator's Brochure (IB) or other safety data: (REQUIRED)

○ Yes ◉ No

1.13 * The modifications require changes to: (REQUIRED)

- ☑ Study Application
- ☐ Consent Documents
- ☐ Other Study Documents
- ☐ None

1.14 Check here if this is modification includes adding the use of CTSI Clinical Research Services or Centers for the first time:

1.15 * **Are there any changes in financial interests/conflicts related to this study for the PI or any other study personnel: (REQUIRED)**

○ Yes ◉ No

1.16 **Expiration Date: Hint: Click 'Refresh Constant Fields' to update the expiration date if this is a copied form.**

02/01/2022

* **Has your study expired: (REQUIRED)**

○ Yes ◉ No

1.17 **Outstanding Stipulations:**

No Stipulation is outstanding.

2.0 Study Status for Research Involving Subject Contact and Repositories

2.1 * **Enrollment Status: (REQUIRED)**

- ○ No subjects have EVER been enrolled here (or at any other sites if UCSF is the Coordinating Center)
- ◉ We are continuing to enroll subjects
- ○ Some subjects have been enrolled but we are not actively recruiting
- ○ All subjects have been enrolled and study is now closed to accrual

2.2 * **Study Activity Status: (REQUIRED)**

- ○ Study activities have not yet commenced
- ◉ Study in progress and subjects are currently participating in study procedures, interventions, and/or research activities (some subjects may be in follow up)
- ○ Study intervention is complete for all subjects but there is ongoing research-related follow-up contact with participants via questionnaires, phones calls, interviews, or mailings.
- ○ Study procedures are complete for all subjects but ongoing medical record review/biological specimen analysis continues (no subject contact)
- ○ Data analysis only - study is complete and the only activities are data analysis and/or manuscript preparation

2.3 * **Planned Number of Participants (from the Study Application): (REQUIRED) This is the number from the Sample Size and Eligibility Section of the application.**

Number of subjects that will be enrolled at UCSF and affiliated institutions:

292

* **Are you requesting an increase to enrollment targets at this time: (REQUIRED)**

○ Yes ◉ No

2.4 * **Have you exceeded your approved enrollment number: (REQUIRED) This is the number from the Sample Size and Eligibility Section of the last approved version of the application.**

○ Yes ◉ No

2.5 * **Enrollment Activity: (REQUIRED) Note: These numbers DO NOT have to add up but please make sure you have completed these sections correctly. Mistakes in the accrual section are the most common reason why a Continuing Review Form is returned for corrections!**

Activity *IN THE LAST YEAR* (or since the last renewal) Under This IRB Approval

Provide information about all of the subject accrual and withdrawal activities carried out at UCSF locations, or under this approval if the study activities take place in another city, county, state, or country.

	If None, Enter 0
Number Enrolled Under This IRB Approval (people who signed consent forms)	3
Number of Subjects Determined to be Ineligible After Signing the Consent	0
Number of Subjects Who Withdrew or Dropped Out (changed their mind about participating)	0
Number of Subjects Withdrawn by the PI Due to Toxicity or Adverse Events	0
Number of Subjects Withdrawn Due to Other Reasons (e.g., lack of compliance, response failure or worsening of disease, death due to disease progression, etc. - provide details below)	0

Activity *OVERALL* (since the study was first approved) Under This IRB Approval

Provide numbers for total accrual, completed participants, current enrollees, and persons lost to follow-up **TO DATE** at UCSF locations, or under this approval if the study activities take place in another city, county, state, or country.

	If None, Enter 0
Number of Subjects Enrolled To Date (people who signed consent forms)	285
Number of Subjects Who Have Completed the Study	0
Number of Subjects Currently Active on Study or in Follow-Up	0
Number of Subjects Lost to Follow-Up	0

2.7 * Progress to date, including interim results, if available. (REQUIRED)

Mother-to-child transmission (MTCT) of HIV-1 may occur during pregnancy, labor, and breastfeeding; however, the molecular mechanism of MTCT of virus remains poorly understood. Infant tonsil mucosal epithelium may sequester HIV-1, serving as a transient reservoir, and may play a critical role in MTCT. Innate immune proteins human beta-defensins 2 (hBD-2) and -3 inactivate intravesicular virions. To establish delivery of hBD-2 and -3 into vesicles containing HIV-1, we tagged hBDs with the protein transduction domain (PTD) of HIV-1 Tat, which facilitates an efficient translocation of proteins across cell membranes. Our new findings showed that hBD-2 and -3 proteins tagged with PTD efficiently penetrated polarized tonsil epithelial cells by endocytosis and direct penetration. PTD-initiated internalization of hBD-2 and -3 proteins into epithelial cells led to their subsequent penetration of multivesicular bodies (MVB) and vacuoles containing HIV-1. Furthermore, PTD played a role in the fusion of vesicles containing HIV-1 with lysosomes, where virus was inactivated. PTD-initiated internalization of hBD-2 and -3 proteins into ex vivo tonsil tissue explants reduced the spread of virus from epithelial cells to CD4+ T lymphocytes, CD68+ macrophages, and CD1c+ dendritic cells, suggesting that this approach may serve as an antiviral strategy for inactivating intraepithelial HIV-1 and reducing viral MTCT.

2.8 * Brief summary of plans for the coming year: (REQUIRED)

In the coming year, we will continue to study the mechanism of HIV mother-to-child transmission (MTCT) using our polarized cell model and ex vivo tonsil tissue sample model.

3.0 Significant Findings & Other Reportable Events

3.1 * Has this IRB determined that this is a 'greater than minimal risk' study: (REQUIRED) Hint: 'Risk Level' can be found in your approval letter.

(•) Yes ( ) No

3.2 * Have any NEW *significant* risks been identified since the last continuing review (or since approval if

this is the first continuing review): (REQUIRED)

○ Yes ◉ No

3.5 * Are there any new or preliminary findings, pertinent scientific publications, therapeutic developments, or results of similar or related studies that could have an impact on safety or subjects' willingness to participate: (REQUIRED)

○ Yes ◉ No

3.6 * Did you report any **5- or 10-day reportable events** (e.g., adverse events, medication or laboratory errors, privacy or confidentiality breaches, etc.) since the last continuing review (or since initial approval if this is the first continuing review): (REQUIRED)

○ Yes ◉ No

Note: Non-reportable events should no longer be submitted at the time of Continuing Review on the AE Summary Log.

3.7 * Are there any new or missed 5- or 10-day reportable events that haven't yet been submitted: (REQUIRED)

○ Yes ◉ No

3.8 * Have there been any concerns or complaints by subjects or others: (REQUIRED)

○ Yes ◉ No

3.9 * Does this study undergo formal on-site monitoring: (REQUIRED)

○ Yes ◉ No

3.10 * Has this study been audited by any external group or entity (e.g., sponsor, CRO, FDA) since its last renewal: (REQUIRED)

○ Yes ◉ No

3.12 * Does this study have a local and/or external Data and Safety Monitoring Board (DSMB) or other Data Monitoring Committee (DMC) providing oversight of this study: (REQUIRED)

○ Yes ◉ No

4.0 Revisions to the Application Form

4.1 * Click the bar below to make revisions to the application form: (REQUIRED)

(Note: you are seeing this section because you either indicated that there are changes that affect the application or there are personnel changes that need to be made in the application.)

Edit/	Version	Title

	1.16	Study Application (Version 1.16) - Attached

5.0 Consent Forms

5.1 * Indicate which type(s) of consent documents are attached: (REQUIRED)

If your study is closed to accrual but you have a previously approved version of the consent form that is being used to reconsent ongoing participants, check the "Addendum consent" option and describe the plans to reconsent patients in the "plans for the upcoming year" question (2.8).

- [ ] New consent documents
- [x] Active consent documents with NO changes
- [ ] Active consent documents with revisions
- [ ] Addendum consent with new risk and/or procedures
- [ ] No consent documents attached

5.2 Attach all active consent forms as Word documents: Please note: All already approved consent forms should be attached as "Revisions" of the previous version, even if they have no changes. Your approval may be delayed if they are uploaded as "New" documents.

Attach your consent forms following these instructions:

Approved Consent Documents with No Changes: All approved consent documents that you will continue to use must be attached. Click Select or Revise Existing. *If you have the currently approved consent form saved on your computer,* click Upload the Revised Consent. *If you need to download the approved consent form first,* click Download Document for Editing and then Upload the Revised Consent. Save your work. DO NOT SELECT THE CURRENTLY APPROVED VERSION OF THE CONSENT FORM. The IRB cannot stamp over last year's approval stamp and the submission will be returned to you.

Approved Consent Documents with Revisions: Click the Select or Revise Existing button. Click Upload the Revised Consent form and select the revised document from your computer. *If you need to download the current version of the consent form from iRIS first,* click Download Document for Editing and then Upload the Revised Consent after you've updated the document. Save your work.

For more information, click on the Help icon and read the "Revising Documents and Forms" quick guide.

New Consent Documents: Click on the Add a New Consent button and upload your new consent form.

NOTE: Please make sure that any tracked changes have been accepted for both consent forms and study documents. If tracked changes are submitted, they will show in the stamped PDF and you will have to submit a modification to get clean documents stamped.

Version	Sponsor Version	Title	Category	Language	Expiration Date	Consent Outcome	View Document
1.3.12		tonsil tissues		English	01/17	Void	167.65

						KB
1.15		Consent-oral biopsy-HIV+	English	01/17 /2023	Void	151.08 KB
1.16		Consent-oral biopsy-HIV-	English	01/17 /2023	Void	151.27 KB
1.11		Consent-blood-HIV+	English	01/17 /2023	Void	151.16 KB
1.11		Consent-blood-HIV-	English	01/17 /2023	Void	151.31 KB
1.12		Consent breast milk-	English	01/17 /2023	Void	161.55 KB

Study Application (Version 1.16)

1.0 General Information

***Enter the full title of your study:**

HIV, EBV and HPV interaction with mucosal epithelium

***Enter the study alias:**

H8597-30664-04
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
○	UCSF - [redacted]

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

[redacted]

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

[redacted]

Other Investigator

B) Research Support Staff

[redacted]

3.3 *Please add a Study Contact

[redacted]

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

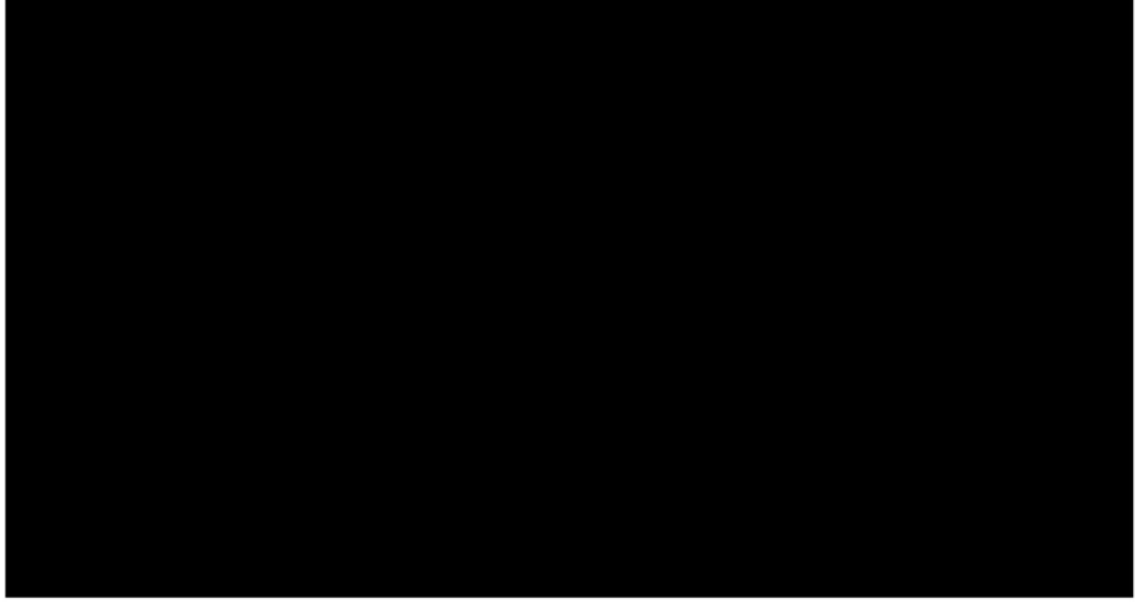
3.5 If applicable, please select the Designated Department Approval(s)

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Qualifications of Key Study Personnel

4.1 List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button: NOTE: This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
[redacted]		



5.0 Initial Screening Questions

5.1 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

- (•) No
- ( ) Yes, and requires CHR and GESCR review
- ( ) Yes, and requires GESCR review, but NOT CHR review

5.2 * This application involves a Humanitarian Use Device:

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

5.3 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

( ) Yes (•) No

5.4 * This application includes a request to rely on another UC IRB to be the IRB of record:

( ) Yes (•) No

Note: If this request is approved, the CHR will **NOT** review and approve this study. Another UC campus will be the IRB of record.

6.0 Application Type

6.1 * This research involves:

- (•) Minimal risk
- ( ) Greater than minimal risk

6.2 * This application is:

- (•) Full Committee
- ( ) Expedited

6.3 If you think this study qualifies for expedited review, select the regulatory category(ies) that the research falls under:

- ☐ Category 1: A very limited number of studies of approved drugs and devices
- ☐ Category 2: Blood sampling
- ☐ Category 3: Noninvasive specimen collection (e.g. buccal swabs, urine, hair and nail clippings, etc.)
- ☐ Category 4: Noninvasive clinical procedures (e.g. physical sensors such as pulse oximeters, MRI, EKG, EEG, ultrasound, moderate exercise testing, etc.)
- ☐ Category 5: Research involving materials (data, documents, records, or specimens) that were previously collected for either nonresearch or research purposes
- ☐ Category 6: Use of recordings (voice, video, digital or image)
- ☐ Category 7: Low risk behavioral research or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies
- ☐ Category 8: Continuing review of previously approved full committee research that is essentially complete
- ☑ Category 9: Continuing review of research NOT involving an IND or IDE where the IRB has determined that the research poses no greater than minimal risk

6.4 * This study involves:

- ◉ Subject contact (including phone, email or web contact)
- ○ No subject contact (limited to medical records review, biological specimen analysis, and/or data analysis)

7.0 Funding

7.1 Identify all sponsors and provide the funding details:

External Sponsor:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	California HIV /AIDS Research Program	14	UCSF	Grant	P0037598	

Sponsor Name:	California HIV/AIDS Research Program
Sponsor Type:	14
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	P0037598
UCSF RAS System Award	

Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	HIV tat- and gp120-facilitated HPV epithelial entry
PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

⊟	NIH Natl Cancer Institute	01	UCSF		P0531161	

Sponsor Name:	NIH Natl Cancer Institute
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	1R01CA232887
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	
Project Number:	P0531161
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Role of HIV in acceleration of HPV malignancy
PI Name: (If PI is not the same as identified on the study.)	[redacted]
Explain Any Significant Discrepancy:	

⊟	NIH Natl Inst Dental & Craniofacial Res.	01	UCSF	Grant		A121266

Sponsor Name:	NIH Natl Inst Dental & Craniofacial Res.
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	
UCSF RAS System Award Number ("A" + 6 digits):	A121266
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	HIV TRANSCELLULAR AND TRANSSYNAPTIC PENETRATION OF MUCOSAL EPITHELIUM

PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

⊟	NIH Natl Inst Dental & Craniofacial Res.	01	UCSF	Grant		A121266

Sponsor Name:	NIH Natl Inst Dental & Craniofacial Res.
Sponsor Type:	01
Sponsor Role:	
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	No
If No, then who is the Primary Grantee?	
Contract Type:	Grant
Project Number:	
UCSF RAS System Award Number ("A" + 6 digits):	A121266
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	HIV transcellular and transcynaptic penetration of mucosal epithelium
PI Name: (If PI is not the same as identified on the study.)	[redacted]
Explain Any Significant Discrepancy:	

⊟	NIH Natl Inst Dental & Craniofacial Res.	01	UCSF	Grant	P0538448	A131939

Sponsor Name:	NIH Natl Inst Dental & Craniofacial Res.
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	R01DE028129
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	P0538448
UCSF RAS System Award Number ("A" + 6 digits):	A131939
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Role of oral herpesvirus microbiota in pathogenesis of HIV mother to child transmission
PI Name: (If PI is not the same as identified on the study.)	

Explain Any Significant Discrepancy:

Gift, Program, or Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below, if applicable)
- ☐ Unfunded (miscellaneous departmental funding)
- ☐ Unfunded student project

List the gift, program, or departmental funding source:

7.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps:

- **If funding has already been awarded or the contract is being processed by the Contracts and Grants or Industry Contracts unit, your sponsor is already in the system and the project has a UCSF RAS System Proposal or Award number. Check with your department's Research Services Analyst (RSA) to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is.**
- **If you need additional assistance, contact the Contracts and Grants Award Team at CGAwardTeam@ucsf.edu and list the sponsor in the box below.**

○ Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

7.3 * This study is supported in whole or in part by Federal funding:

◉ Yes ○ No

If **yes**, indicate which portion of your grant you will be attaching:

- ☑ The Research Plan, including the Human Subjects Section of your NIH grant or subcontract
- ☐ For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- ☐ The section of your progress report if it provides the most current information about your human subjects work
- ☐ The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards)

8.0 Statement of Financial Interest

8.1 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

○ Yes ◉ No

If **Yes**, attach the **Disclosure of Investigators' Financial Interests Supplement** to this

9.0 Sites

9.1 Institutions (check all that apply):

- [x] UCSF
- [ ] Mt. Zion
- [x] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Helen Diller Family Comprehensive Cancer Center
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno (Community Medical Center)
- [ ] Gallo
- [ ] Gladstone
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)

9.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project:

- [ ] Other UC Campus
- [x] Other institution
- [ ] Other community-based site
- [ ] Foreign Country

List the foreign country/ies:

9.3 * This is a multicenter study:

- ( ) Yes
- (•) No

9.4 Check any research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Osher Center
- [ ] Positive Health Program

10.0 Studies Involving Other Sites

10.1 UCSF is the coordinating center:

- ( ) Yes
- (•) No

If **Yes**, describe the plan for communicating safety updates, interim results, and other information that may impact risks to the subject or others among sites:

If **Yes**, describe the plan for sharing modification(s) to the protocol or consent document(s) among sites:

10.2 Check any other UC campuses with which you are collaborating on this research study:

- ☐ UC Berkeley
- ☐ UC Davis
- ☐ Lawrence Berkeley National Laboratory (LBNL)
- ☐ UC Irvine
- ☐ UC Los Angeles
- ☐ UC Merced
- ☐ UC Riverside
- ☐ UC San Diego
- ☐ UC Santa Barbara
- ☐ UC Santa Cruz

10.3 Are the above UC campuses requesting to rely on UCSF's IRB (check all that apply)?

- ☐ Yes (Attach the Notice of Intent to Rely on One UC IRB form in the Other Study Documents section)
- ☐ No (Complete IRB Approval Certification section)

11.0 IRB Approval Certification

(Note: This section replaces the old IRB Approval Certification Supplement form. Please do not attach the old form(s) to this application.)

11.1 IRB Approval Certification Sub-Form

Click "Add a new row" to enter information for a site. Click it again to add a second site and againand again for a third, a fourth, etc.

12.0 Study Design

12.1 * Study design:

HIV mucosal transmission is a potentially important, poorly understood route of HIV infection that has global consequences. The oropharyngeal mucosal epithelium of the fetus/neonate/infant and adult genital mucosa may serve as an efficient portal of entry for HIV, yet oral transmission of HIV among adults is rare (2, 10, 14, 15). The reasons for this difference are not well understood. The goal of our study is to investigate molecular mechanisms of resistance of adult oral epithelial cells and the susceptibility of fetal/infant oral and adult genital epithelial cells for HIV infection. We hypothesize that resistance of adult oral epithelial cells for HIV infection is due to the expression of multiple anti-HIV innate molecules, including calprotectin, defensins, lactoferrin, secretory leukocyte protease inhibitor, thrombospondin, polyanionic albumins, acidic proline-rich proteins, and salivary agglutinins (12). These proteins may not be expressed or may not have anti-HIV function in fetal/neonatal oral and adult genital epithelial cells. These molecules are present in breast milk, however, their role in HIV infection with fetal/neonatal mucosal epithelium in not clear. Therefore we will investigate role of fetal/infant mucosal epithelium in HIV

epithelium. We have shown that HIV infection may disrupt mucosal epithelium leading paracellular penetration of Epstein-Barr virus (EBV) and human paplillomavirus (HPV). Uisng biopsy tissues from HIV-infected donors we will study the paracellular penetration of EBV and HPV.

It is well known that during the systemic HIV infection the innate immune and barrier functions of mucosal epithelium may be impaired (8, 13). This could be due to reactivation and dissemination of common oral pathogens such as EBV and HPV within the oral epithelium, which may lead to disruption of oral epithelium and lead to HIV transmission (1, 3-5, 7, 9). Therefore, our research will focus to investigate the molecular mechanisms of HIV, EBV and HPV interactions with mucosal epithelium.

12.2 Check all that apply:

- ☐ Phase I
- ☐ Phase II
- ☐ Phase III
- ☐ Phase IV

13.0 Scientific Considerations

13.1 Hypothesis:

This study has a hypothesis:

◉ Yes ○ No

If yes, state the hypothesis or hypotheses:

Hypothesis: The HIV envelope contains PS, and interaction of virus-associated PS with the PS receptor TIM-1 at the fetal/infant oral and intestinal mucosal surfaces induces viral macropinocytosis. Interaction of HIV with heparan sulfate proteoglycan (HSPG) and galactosylceramide initiates endocytosis of HIV into fetal/infant oral and intestinal epithelium. Both macropinocytosis and endocytosis of HIV facilitate transport of virions into intracellular vesicular/endosomal compartments, which subsequently deliver virus to basolateral membranes by transcytosis.

Hypothesis: HIV-infected monocytes/macrophages attach to the mucosal surfaces of fetal/infant oral and intestinal epithelia by binding of LFA-1 of monocytes/macrophages to ICAM-1 of oral epithelial cells. Secretion of TNF-a from HIV-infected monocytes/macrophages activates MCP-1 in oral/intestinal epithelium, facilitating migration of HIV-infected monocytes/macrophages into the epithelium.

Hypothesis: HBD-2 and/or -3 binds to HSPG, which mediates HBD binding to HIV gp120, leading to inactivation of HIV within the vesicular/endosomal compartments of fetal/infant oral and intestinal epithelial cells. Recombinant HBD-2 and -3 containing protein trunsduction signals are efficiently taken up into infant oral and intestinal epithelia, and spread of HBDs within mucosal epithelial tissues inhibits or substatially reduces HIV MTCT.

Hypothesis: In HIV infected individulas the tight junctions of mucosal epithelium disrupted, leading to paracellular penetration of EBV and HPV into epithelium.

13.2 * List the specific aims:

Aim 1. Establish and characterize an ex vivo organ culture model from the oral of the adult, and oropharyngeal, and intestinal mucosal epithelium of the fetus, and tonsil epithelium of infants.
Aim 2. Analyze expression of HBD1, HBD2, HBD3 and SLPI in adult, fetal and infant epithelia.
Aim 3. Study mechanisms of HIV spread via the oral of the adult, and oropharyngeal and intestinal mucosal epithelium of the fetus and tonsil epithelium of infant.

Aim 4. Determine the role of breast milk in the interaction of HIV with the mucosal epithelium of the fetus and infant.
Aim 5. Study the mechanisms of HIV-mediated tigh junction disruption and its role in HPV and EBV paracellular penetration.

13.3 Statistical analysis:

Data will be analyzed by a study steering committee, which will be composed by [redacted] and [redacted] It is estimated that 30 adult, 50 fetal and 50 infant tissues will be investigated for this study. Fifteen breast milk from HIV-negative woman will be analyzed. A five years cumulative enrollment is planned.
HIV-1 infection of the mucosal epithelium and breast milk will be evaluated in the presence of HIV by immunostaining and ELISA assays, respectively. At least five samples will be used for each experiment. The statistical analysis will account for the paired nature of the data. Quantitative data for statistical analysis of the number of cells containing HIV infection will be obtained by screening 30-50 fields per tissue section. We will test the null (no difference) hypothesis against the alternative hypothesis that there is a difference. With five tissue samples, using a paired *t* test with a 5% false-positive rate, we will have 80% power to detect a difference between treated and untreated samples.

13.4 * This is an investigator-initiated study:

(•) Yes ( ) No

13.5 This study has received scientific or scholarly review from (check all that apply):

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval or contingent PRC approval is required prior to final CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Center (CRC) advisory committee
- [ ] Departmental scientific review
- [x] Other:

Specify **Other**:

Committee on human research

If applicable, attach the **Departmental Scientific Review Form** at the end of the application.

14.0 Background

14.1 Background:

It is well documented that HIV oral transmission in adult population is rare, and oral mucosal epithelium is resistant for HIV infection (4, 6, 8). However, the oropharyngeal mucosal epithelium of the fetus/neonate may serve as an efficient portal of entry for perinatal and postnatal mother-to-child transmission (MTCT) of HIV (6). It was also well documented that HIV transmission via genital epithelium is substantially higher than the oral epithelium. MTCT of HIV may occur in utero before birth (prenatal), during labor and delivery (perinatal) or after birth (postnatal) (6). In prenatal MTCT, RNA/DNA and proteins were detected in placental trophoblasts, endothelial cells, and villous Hofbauer cells from 8 weeks of gestation, suggesting HIV transmission by the transplacental route (6). An alternative prenatal route could be transamniotic, where cell-free HIV virus and/or HIV-infected cells may penetrate into the amniotic sac and infect the fetus via the oropharyngeal cavity or gastrointestinal (GI) tract. A case report showed that HIV was detected in the amniotic fluid of HIV-positive women at 32 weeks gestation (6). Another showed that HIV-1 was detected in gastric aspirates of a 15-week-old fetus (6). Enzyme-linked immunosorbent assay (ELISA) analysis of HIV-1 p24 in samples of amniotic fluid from 10 HIV-positive women showed that 8 women were positive for p24 (6). Maiques et al. examined HIV in the amniotic fluid of 366 pregnant women, and HIV was detected in 17% of the amniotic fluid before HAART and in 3% of the fluid under HAART (6). Mohlala et al. showed that

normal pregnancy, and these data indicate that HAART treatment substantially reduces MTCT of HIV in utero (11). The solid evidences indicate that postnatal MTCT of HIV via breastfeeding, and HAART treatment does not efficiently inhibit postnatal MTCT (6). All above evidence clearly indicate that fetal/neonatal mucosal epithelium play critical role in HIV MTCT. The higher rate of genital HIV transmission also indicate that genital epithelium may play critical role in HIV spread. Therefore our research focuses on HIV interaction with adult oral and genital, and fetal oral and GI mucosal epithelium. An adult oral mucosal epithelium is resistant for HIV infection. However, during the HIV/AIDS disease HIV may disrupt epithelial tight junctions leading to facilitate EBV and HIV paracellular penetration. Therefore we will study mechanisms of HIV, EBV and HPV dissemination within the adult oral mucosal epithelium.

14.2 Preliminary studies:

Our preliminary results show the following: (ii) HIV via mucosal epithelium is initiated by macropinocytosis and clathrin- and caveolin-mediated endocytosis. (iii) The HIV envelope contains PS, and infant oral epithelium expresses the PS receptor TIM-1, which may play a critical role in viral macropinocytosis. (iv) Infant oral epithelium expresses ICAM-1, which may bind macrophage LFA-1, facilitating binding of HIV-infected macrophages to mucosal surfaces. TNF-a induces MCP-1 expression in infant tonsil keratinocytes, which may initiate migration of HIV-infected monocytes/macrophages into epithelium. (v) Infant oral epithelial cells do not express the anti-HIV innate proteins HBD-2 and -3. Recombinant HBD-2 and/or -3 internalized into polarized infant oral cells bind indirectly to HIV gp120 and inactivate virus during its transcytosis. HIV tat containing a PTD signal rapidly penetrates into oral epithelium, suggesting that generation of HBDs containing a PTD signal could facilitate their penetration into epithelium. (vi) Infant tonsil epithelium contains M cells, which may play an important role in HIV transcytosis and MTCT.

14.3 References:

1. **Boulter, A. W., N. Soltanpoor, A. V. Swan, W. Birnbaum, N. W. Johnson, and C. G. Teo.** 1996. Risk factors associated with Epstein-Barr virus replication in oral epithelial cells of HIV-infected individuals. Aids **10:**935-40.
2. **Casper, C., and E. M. Fenyo.** 2001. Mother-to-child transmission of HIV-1: the role of HIV-1 variability and the placental barrier. Acta Microbiol Immunol Hung **48:**545-73.
3. **Chou, L. L., F. Boustany, and D. Nathanson.** 1996. G to A hypermutation in env loop V2 region of HIV-1 in oral hairy leukoplakia. J Dental Res **75:**115.
4. **Greenspan, D., and J. S. Greenspan.** 1997. Oral manifestations of HIV infection. AIDS Clin Care **9:**29-33.
5. **Greenspan, D., J. S. Greenspan, N. G. Hearst, L. Z. Pan, M. A. Conant, D. I. Abrams, H. Hollander, and J. A. Levy.** 1987. Relation of oral hairy leukoplakia to infection with the human immunodeficiency virus and the risk of developing AIDS. J Infect Dis **155:**475-81.
6. **Hille, J. J., J. Webster-Cyriaque, J. M. Palefski, and N. Raab-Traub.** 2002. Mechanisms of expression of HHV8, EBV and HPV in selected HIV-associated oral lesions. Oral Dis **8 Suppl 2:**161-8.
7. **Lau, R., J. Middeldorp, and P. J. Farrell.** 1993. Epstein-Barr virus gene expression in oral hairy leukoplakia. Virology **195:**463-74.
8. **Leigh, J. E., K. Shetty, and P. L. Fidel, Jr.** 2004. Oral opportunistic infections in HIV-positive individuals: review and role of mucosal immunity. AIDS Patient Care STDS **18:**443-56.
9. **Lucht, E., P. Biberfeld, and A. Linde.** 1995. Epstein-Barr virus (EBV) DNA in saliva and EBV serology of HIV-1-infected persons with and without hairy leukoplakia. J Infect **31:**189-94.
10. **Minkoff, H.** 2003. Human immunodeficiency virus infection in pregnancy. Obstet Gynecol **101:**797-810.
11. **Mohlala, B. K., T. J. Tucker, M. J. Besser, C. Williamson, J. Yeats, L. Smit, J. Anthony, and A. Puren.** 2005. Investigation of HIV in amniotic fluid from HIV-infected pregnant women at full term. J Infect Dis **192:**488-91.
12. **Moutsopoulos, N. M., T. Greenwell-Wild, and S. M. Wahl.** 2006. Differential mucosal susceptibility in HIV-1 transmission and infection. Adv Dent Res **19:**52-6.
13. **Patton, L. L., and C. van der Horst.** 1999. Oral infections and other manifestations of HIV disease. Infect Dis Clin North Am **13:**879-900.
14. **UNAIDS.** 2004. UNAIDS, AIDS epidemic update. Geneva:UNAIDS/WHO.
15. **UNAIDS.** 2006. UNAIDS, AIDS epidemic update. Geneva:UNAIDS/WHO.

If you have a separate bibliography, attach it to the submission with your other study documents.

15.0 Sample Size and Eligibility

15.1 Number of subjects that will be enrolled at UCSF and affiliated institutions (locally):

292

15.2 Total number of subjects that will be enrolled at all sites (for study overall):

292

15.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

235

15.4 Sample size calculation:

This is an ongoing project and the first CHR application was submitted in 2007 for NIH R01 and UCSF intramural grants with the initial sample size of 586. However, the NIH R01 was not funded and we were not able to perform some studues. Therefore, so far we have colleced 162 samples, we are currently analyzing data from these samples.

We are continuing this project under new NIH R01 grant. For this study will be used 50 tonsil tissues from young children (between 0.5 to 5 years old). We also will use 50 fetal tissue explants (25 oropharyngeal and 25 intestinal), which will be collected from aborted (discarded) fetuses between 18 and 24 weeks of gestation. Next, we will use 15 oral (buccal) biopsies from adult donors (18+ years old). Finally, we will collect breast milk from 15 donors. Will be propagated small tissues explants from each tissue, and each experiment will be performed using a set of explants from the same biopsy and will be repeated at least 3 times with biopsies obtained from independent donors. HIV transmission through mucosal epithelium will be examined by applying of virus with and without breast milk from the surface of epithelium and detection of virus in the lamina propria.

Total sample size = 292, estimated sample szie= 335
162 samples are already collected and currently under investigation

Anticipated sample size for next 5 years:
Tonsil tissues from tonsillectomy/surjical material= 50
Fetal tissues from discarded fetuses= 50
Oral (buccal) biopsy =15
Breasr milk= 15

We will use total of 50 tonsil tissues from children, 50 tissues from fetus (25 oropharyngeal and 25 intestinal), 15 oral tissues and 15 breast milk samples from adults. These numbers have chosen based on nature of treatment and controls.

15.5 * Eligible age range(s):

- [x] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years

15.6 Inclusion criteria:

The only inclusion criterion will be willingness to donate oral tissues, and breast milk samples.

15.7 Exclusion criteria:

The only exclusion criteria would be inability to provide informed consent and having a contraindication for a biopsy procedure, e.g., bleeding diathesis or infection and inflammation.

15.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

○ Yes ◉ No

If **yes**, please explain the nature and rationale for the restrictions:

16.0 Drugs and Devices

16.1 * Drugs or biologics will be studied under this application:

○ Yes ◉ No

16.2 * Investigational medical devices or in vitro diagnostics will be used OR approved medical devices or in vitro diagnostics will be studied under this application:

○ Yes ◉ No

16.3 * A Non-Significant Risk (NSR) determination is being requested for an investigational device:

○ Yes ◉ No

16.4 Verification of IND/IDE numbers: If the sponsor's protocol does not list the IND/IDE number, you must submit documentation from the sponsor or FDA identifying the IND/IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.

17.0 Other Approvals and Registrations

17.1 * This is a clinical trial:

○ Yes ◉ No

Clinical Trial Registration
"NCT" number for this trial:

17.2 * Data from this study will be submitted to NIH for Genome-Wide Association Studies (GWAS):

○ Yes ◉ No

○ Yes ◉ No

17.4 * This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to CHR approval):

○ Yes ◉ No

17.5 * The study protocol requires radiological procedures (e.g. CT scans, x-rays) or exposes subjects to radiation:

○ Yes ◉ No

17.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

8597-BU-01-INC

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Radiation Safety Committee

Specify RUA #:

☐ Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

☐ Controlled Substances

18.0 Procedures

18.1 * List all study procedures, test and treatments required for this study:

1. Collection of adult oral tissue and establishment of tissue explants ex vivo.
The buccal explants will be obtained from HIV-positive and –negative adult volunteers. First, donor from oral biopsies will be treated with local anesthetic agent lidocaine (4.5 mg/kg) for 5-10 min. After confirmation of numbness the biopsy procedure will be performed. Biopsies of the oral mucosa containing epithelium and connective tissue will be obtained using 4-mm-diameter biopsy punches in the [redacted]
Immediately after biopsy the tissue will be placed into a tube with 2 ml of RPMI medium (explant medium) containing 10% heat-inactivated fetal bovine serum, 20 mM HEPES, 100 mM glutamine, 20 µg/ml gentamicin, 100 U/ml penicillin, 100 µg/ml streptomycin, and 50 ng/ml amphotericin-B. Before use the explants will be washed three times with 0.5 ml cold explant medium.

For verification of HIV-negative status 20 ml of blood sample will be taken from arm vein of each donor. HIV test will be performed by HIV diagnostic lab at [redacted]. If HIV test shows positive results, [redacted] will contact donor by phone to discuss this issue and will refer for treatment and care. [redacted] will inform HIV positive result by name of donor to the Department of Public Health and tissue of HIV-positive donor will be removed from the experiments.

2. Collection of fetal oropharyngeal and intestinal tissue explants
Fetal ropharyngeal gastric and intestinal tissue explants will be collected from discarded fetal tissues obtained following an elective termination of pregnancy at [redacted] We will not have access the any identifying documents associated with fetal materials. The tissues will be obtained from discarded fetuses at 18 to 22 weeks of gestation, because, in most cases, abortion later than 23 weeks of gestation is generally not be permitted or performed. The 5-mm pieces of tissue will be dissected from oropharyngeal area by surgical instrument. Similarly sized pieces will be dissected from the small intestine. All mucosal samples will include the epithelium and lamina propria with connective tissues. Immediately after biopsy isolation, the tissues will be placed into a tube with 2 ml of RPMI medium (explant medium) containing 10% heat-inactivated fetal bovine serum (FBS), 20 mM HEPES, 100 mM glutamine, 20 µg/ml gentamicin, 100 U/ml penicillin, 100 µg/ml streptomycin and 50 ng/ml amphotericin-B. Before use, the explants will be washed three times with 0.5 ml cold explant medium. To establish a polarized organ culture system, the explants, with the epithelial layer oriented on top, will be placed in the top chamber on a Transwell-clear filter insert with a pore size of 0.4 µm and a diameter of 6.5 mm (#3472, Costar Corp., Cambridge, Mass). Filter inserts with explant will be incubated at 37 C in a humidified atmosphere containing 5% CO_2, and one third of the medium from each chamber will be changed every other day.

3. Collection of tonsil tissue samples from 0.5-5 years old children.
Collection of discarded tonsil tissue samples from HIV-negative children under 5 years old after routine tonsillectomy. A small tissue samples with about 5 -5 cm will be collected from surgical materials after routine tonsillectomy. Immediately after biopsy isolation, the tissues will be placed into a tube with 2 ml of RPMI medium (explant medium) containing 10% heat-inactivated fetal bovine serum (FBS), 20 mM HEPES, 100 mM glutamine, 20 µg/ml gentamicin, 100 U/ml penicillin, 100 µg/ml streptomycin and 50 ng/ml amphotericin-B. Before use, the explants will be washed three times with 0.5 ml cold explant medium.

4. Collection of breast milk.
To examine the role of breast milk in HIV infection of fetal/infant mucosal epithelium we will collect breast milk. Fifty ml of breast milk from 15 healthy HIV-seronegative women will be collected during the first 2-3 month of breast-feeding. Prior to sample collection, 2-3 ml of milk will be removed from the breast, and the nipple and surrounding areas of the breast that will have contact with the pump (Lactation Care Inc., Newton MA) will be cleaned with an ethanol-infused sterilizing pad and completely dried. The bottle and tubes will be sterilized by boiling them, according to manufacturer instruction. After collection breast milk samples will be filtered through 0.8-µm pore filters and aliquoted in 500 µl and stored at –80 C for further use in our research. It is expected that the donors will be between the ages of 18 and 40 years.

5. Infection of tissue explants with HIV, HPV and/or EBV.
Tissue explants mounted in filter inserts will be infected from their mucosal surface. For HIV infection HIV-1 X4 tropic SF33 and R5 tropic SF162 viruses will be used. For each explant 10^5 TCID50 virions will be used. For HPV infection will be used HPV 16 pseudovirions (1 ng/per biopsy). For EBV B95-8 strain will be used and each explant will be infected with 10^5 virions. HIV and EBV co-infection will be performed by simultaneous infection of HIV and EBV viruses. Also, the tissue explants will be infected with HPV-16 pseudovirions.

If you have a procedure table, attach it to the submission with your other study documents.

18.2 Interviews, questionnaires, and/or surveys will be administered or focus groups will be conducted:

○ Yes ◉ No

List any standard instruments used for this study:

Attach any non-standard instruments at the end of the application.

18.3 Conduct of study procedures or tests off-site by non-UCSF personnel:

○ Yes ◉ No

If yes, explain:

18.4 Sharing of experimental research test results with subjects or their care providers:

○ Yes ◉ No

If yes, explain:

18.5 * Specimen collection for future research and/or specimen repository/bank administration:

◉ Yes ○ No

18.6 Time commitment (per visit and in total):

1. For obtaining one oral biopsy sample per visit will be required about 30 min.
2. For obtaining one tonsil sample per visit will be required about 1 h.
3.The time to obtaining one breast milk sample will be about 10 min.

18.7 Locations:

1.The oral biopsy tissues from the adult buccal mucosa from normal healthy individuals and HIV-positive patients will be collected in [redacted] Contact person: [redacted]
2. The discarded fetal oropharyngeal and intestinal tissue samples from discarded fetus will be collected in [redacted]
3. The discarded infant tonsil tissues will be collected in [redacted] Contact person, [redacted]
4. The breast milk samples will be collected in breastfeeding healthy HIV-negative women at [redacted] Contact person: [redacted]
5. All HIV and/or EBV and/or HPV infection procedures with tissue samples in presence or absence of breast milk will be performed in [redacted] Contact person, [redacted]

18.8 Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

All specimens will be de-identified and designated by study numbers. The researchers and tissue bank staff will not have access to this information, rather they will have only study numbers. This numbers will be destroyed as soon as the study in completed. All data required by the protocol will be recorded and entered into electronic database using the unique study number. The study team will review the electronic data for accuracy. Data clarification or corrections will be made electronically and the databases will be password secured.

To minimize the discomfort of the tissue biopsy procedures, a local anesthetic is provided, followed by as-needed pain medications after the procedure. Sterile technique is used to avoid infection, and bleeding is stopped using standard clinical procedures

19.0 Specimen Collection for Future Research and/or Specimen Repository/Bank Administration

(Note: This section replaces the old "Human Biologic Specimen Collecting and/or Banking for Future Research" supplement form. Please do not attach the old form to this application.)

19.1 Specimens are (check all that apply):

- [x] Surplus clinical specimens from a diagnostic or therapeutic procedure
- [x] Specimens collected for research purposes only
- [ ] Other

If Other, explain:

19.2 Types of specimens:

- [ ] Blood
- [x] Tissue (describe below):
- [ ] Existing/archival materials (name source below): --
- [x] Other (describe below):

Describe and/or name source:

Oral biopsy tissues and breast milk will be collected

19.3 Consent will be obtained via:

- [ ] Separate specimen banking consent form
- [x] Specimen banking section within a main research study consent form
- [ ] Surgical consent form with tissue donation brochure

19.4 Specimens will ultimately be stored (check all that apply):

UCSF

- [x] UCSF repository/bank being established under this protocol
- [ ] Existing UCSF specimen repository/bank with CHR approval

Provide the name of the bank and CHR approval number (if not being banked at UCSF under this protocol):

Outside Entity

- [ ] Cooperative group bank
- [ ] NIH
- [ ] Other university
- [ ] Industry sponsor
- [ ] Other

Specify to what institution, cooperative group or company specimens will be transferred:

19.5 Direct identifiers will be sent with specimens or shared with other researchers and/or outside entities:

- ○ Yes
- ◉ No
- ○ N/A - Specimens will not be shared with others

If **Yes**, which identifiers will be sent with specimens:

- ☐ Name
- ☐ Date of birth
- ☐ Social Security number
- ☐ Medical record number
- ☐ Address
- ☐ Phone number
- ☐ Email address
- ☐ Other dates (surgery date, clinic visit dates, etc.)

If **Yes**, provide a justification for sending direct identifiers with the specimens:

20.0 Establishing a Specimen Repository/Bank at UCSF

(Note: This section replaces the old "Human Biologic Specimen Collecting and/or Banking for Future Research" supplement form. Please do not attach the old form to this application.)

20.1 The repository/bank is physically located at (list the address and room number for all locations):

[redacted]

20.2 Methods for maintaining confidentiality:

- ☑ Samples are completely de-identified before being added to the bank/repository. There is no way to link the specimens back to the subjects.
- ☐ Samples are coded and researchers are able to link the specimens to specific subjects. However, future recipients will not receive direct identifiers with the specimens.
- ☐ Samples are stored with direct identifiers in the repository. However, future recipients will not receive direct identifiers with the specimens.
- ☐ Samples are coded and/or kept with direct identifiers in the repository. The bank/repository may release identifiers with specimens to researchers under special circumstances with prior IRB approval.

Explain under what circumstances identifiers may be released:

20.3 If the repository/bank maintains the identifiers, list the identifiers that will be maintained with the specimens:

- ☐ Name
- ☐ Date of birth
- ☐ Social Security number
- ☐ Medical record number
- ☐ Address
- ☐ Phone number
- ☐ Email address
- ☐ Other dates (dates of surgery, visit dates)

20.4 Clinical follow-up data will be linked to specimens:

○ Yes ◉ No

If **Yes**, provide duration of follow-up or indefinitely:

20.5 There is a formal specimen utilization review process:

○ Yes ◉ No

If **Yes**, describe the process:

20.6 Specimens banked at UCSF may be made available to (check all that apply):

☑ UCSF researchers
☐ Non-UCSF researchers
☐ Industry

21.0 Alternatives

21.1 Study drug or treatment is available off-study:

○ Yes
◉ No
○ Not applicable

21.2 * Is there a standard of care (SOC) or usual care that would be offered to prospective subjects at UCSF (or the study site) if they did not participate:

○ Yes ◉ No

If yes, describe the SOC or usual care that patients would receive if they choose not to participate:

This study does not involve any treatments and participation in the study is voluntary.

21.3 Describe other alternatives to study participation that are available to prospective subjects:

This study do not involve any treatment and do not have any significant impact on subject's concurrent or future care, the alternative may be not to participate.

22.0 Risks and Benefits

22.1 * Risks and discomforts:

A. Risks and Discomforts:

Risk and discomforts for biopsy procedures of adult oral tissue samples.The only potential risks are those associated with donating tissue biopsy material will include discomfort, bleeding, and rarely, infection. Sterile technique is used to avoid infection and bleeding is stopped using standard clinical procedures.

Risk and discomforts for collection breast milk.Collection of breast milk has minimum potential risk or discomfort, the only potential risks are those associated with un-optimized electrical pump. High suction setting of pump may cause discomfort and to minimize discomfort the setting of pump will be optimized and examined for each pumping kit and individual donor.

22.2 Steps taken to minimize risks to subjects:

To minimize the discomfort of the oral tissue biopsy a local anesthetic is provided, followed by as-needed pain medications after the procedure. Sterile technique is used to avoid infection, and bleeding is stopped using standard clinical procedures.

22.3 Benefits to subjects:

○ Yes ◉ No

If yes, describe:

22.4 Benefits to society:

Knowledge of EBV, HPV and HIV infection via the adult and fetal/infant mucosal epithelium has important biological and public health implications regarding transmission of infection from one individual to another.

22.5 Explain why the risks to subjects are reasonable:

The study risks on an individual level will be minimal (potential loss of privacy). Also, the risk of harm from oral biopsies is very low and the importance of the knowledge to be gained is very high. There are no significant risks from donating 10cc of breastmilk.

23.0 Data and Safety Monitoring Plan

23.1 Describe the plan for monitoring data and safety:

This is not an interventional trial and no data safety monitoring board is needed.

23.2 This study requires a Data and Safety Monitoring Board:

○ Yes
◉ No or not sure

If **yes**, press **SAVE and CONTINUE** to move to the next section of the application.

23.3 If No, provide rationale:

○ Social/Behavioral research
○ Phase I trial
○ Treatment IND/Compassionate Use Trial
◉ Other (explain below)

If **Other,** explain:

This project is not interventional study.

24.0 Confidentiality and Privacy

24.1 Plans for maintaining privacy in the research setting:

All specimens will be de-identified and designated by study numbers. The researchers and tissue bank staff will not have access to this information, rather they will have only study numbers. This numbers will be destroyed as soon as the study in completed. All data required by the protocol will be recorded and entered into electronic database using the unique study number. The study team will review the electronic data for accuracy. Data clarification or corrections will be made electronically and the databases will be password secured.

24.2 Possible consequences to subjects resulting from a loss of privacy:

We do not see potential risks to reputation, insurability or other social risks that would occur as a result of participation n this study that is above that received in usual medical care.

24.3 Study data are:

- ☐ Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
- ☑ Derived from a medical record (identify source below)
- ☐ Added to the hospital or clinical medical record
- ☐ Created or collected as part of health care
- ☐ Used to make health care decisions
- ☑ Obtained from the subject, including interviews, questionnaires
- ☐ Obtained from a foreign country or countries only
- ☐ Obtained from records open to the public
- ☐ Obtained from existing research records
- ☐ None of the above

If **derived from a medical record**, identify source:

[redacted]

24.4 Identifiers may be included in research records:

◉ Yes ○ No

If **yes**, check all the identifiers that may be included:

- ☑ Names
- ☐ Dates
- ☐ Postal addresses
- ☐ Phone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social Security Numbers*
- ☐ Medical record numbers
- ☐ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers

- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier

* Required for studies conducted at the VAMC

24.5 Identifiable information might be disclosed as part of study activities:

( ) Yes (•) No

If **yes**, indicate to whom identifiable information may be disclosed:

- [ ] The subject's medical record
- [ ] The study sponsor
- [ ] Collaborators
- [ ] The US Food & Drug Administration (FDA)
- [ ] Others (specify below)
- [ ] A Foreign Country or Countries (specify below)

If **Others**, specify:

24.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- [ ] Data are stored securely in My Research
- [x] Data are coded; data key is destroyed at end of study
- [ ] Data are coded; data key is kept separately and securely
- [ ] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [ ] Data are collected/stored using REDCap or REDCap Survey

24.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

All study numbers will be destroyed as soon as the needed data are transcribed.

24.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

( ) Yes (•) No

Explain:

HIV positive test results will be reported to the Department of Public Health.

24.9 This study will be issued a Certificate of Confidentiality:

○ Yes ◉ No

25.0 Subjects

25.1 Check all types of subjects that may be enrolled:

- ☐ Inpatients
- ☐ Outpatients
- ☑ Healthy volunteers
- ☐ Staff of UCSF or affiliated institutions

25.2 Additional vulnerable populations:

- ☑ Children
- ☐ Subjects unable to consent for themselves
- ☐ Subjects unable to consent for themselves (emergency setting)
- ☐ Subjects with diminished capacity to consent
- ☐ Subjects unable to read, speak or understand English
- ☐ Pregnant women
- ☑ Fetuses
- ☐ Neonates
- ☐ Prisoners
- ☐ Economically or educationally disadvantaged persons
- ☐ Investigators' staff
- ☐ Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

For this study will be collected the tonsil tissue samples from children under 10 years old, which are undergo to routine tonsilectomy procedures. The surgical tissues are discarded materials. Since,
tonsilectomy procedures do not have any interventions and do not cause risk to children.

Also, will be collected oropharyngeal and intestinal tissues from aborted fetuses that are also discarded materials. Since, above procedures do not have any interventions and do not cause risk to pregnant women or life fetus this research does not fall within the sections 45 CFR 56 subpart B.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

26.0 Inclusion of Children in Research

(Note: This section replaces the old "Inclusion of Children and Minors in Research" supplement form. Please do not attach the old form to this application.)

26.1 This study will enroll children who can legally consent for themselves:

○ Yes ◉ No

If **yes,** explain why they can consent for themselves in the research setting:

If you will **ONLY** be enrolling children who can legally consent for themselves, press **SAVE and**

26.2 Select all the regulatory categories that apply:

- [x] No greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)
- [ ] Greater than minimal risk but presenting prospect of direct benefit (45 CFR 46.405, 21 CFR 50.52)
- [ ] Greater than minimal risk (though only a minor increase over minimal risk) and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- [ ] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 21 CFR 50.54)

Explain why the research in this study falls under the above category or categories:

For this study will be collected the tonsil tissue samples from children under 10 years old, which are undergo to routine tonsilectomy procedures. The surgical tissues are discarded materials. Since,
tonsilectomy procedures do not have any interventions and do not cause risk to children.

Also, will be collected oropharyngeal and intestinal tissues from aborted fetuses that are also discarded materials. Since,
above procedures do not have any interventions and do not cause risk to pregnant women or life fetus this
research does not fall within the sections 45 CFR 56 subpart B.

26.3 Parental permission or waiver:

- [x] Parental permission will be obtained
- [ ] Waiver of parental permission is requested: Parental permission is not a reasonable requirement
- [ ] Waiver of parental permission is requested: The waiver meets the provisions for a waiver of consent set forth in 45 CFR 46.116, Subpart A

If you are requesting a **waiver of parental permission**, explain why the study meets the regulatory criteria for this waiver:

26.4 Assent of children or waiver:

- [ ] Assent of children old enough to provide assent will be obtained
- [x] Waiver of assent is requested: Children cannot be consulted or the research has prospect of direct benefit only available in the study
- [ ] Waiver of assent is requested: The waiver meets the provisions for a waiver of consent set forth in 45 CFR 46.116, Subpart A

If you are requesting a **waiver of child's assent**, explain why the study meets the regulatory criteria for this waiver:

Children under 10 years old are too young to be consulted.

26.5 Documentation of permission and assent (select all that will be used):

- [x] Permission form addressed to the parents
- [ ] Simplified assent form addressed to the child, 7-12 years old (parents get separate form)
- [ ] Assent form addressed to the child, 13 years and older (for subjects and parents)
- [ ] Assent form addressed to the child, 13 years and older (parents get separate form)

Check one:

- (•) One parent's signature will be obtained
- ( ) Two parents' signatures will be obtained

If this study is approvable under .404 or .405 and you plan to get permission from only one parent, explain why you think one parent's permission is sufficient:

26.6 This study may enroll wards of the state:

○ Yes ◉ No

27.0 Inclusion of Pregnant Women, Fetuses, and/or Neonates

27.1 Review the regulatory categories and identify all sections of 45 CFR 46 Subpart B under which you believe the research falls and provide study-specific information showing why the research falls within those sections:

Category 46.204:
For this study, will be collected the tissue samples from aborted fetuses that are also discarded materials.

Since, above procedures do not have any interventions and do not cause risk to pregnant women or life fetus this research does not fall within the sections 45 CFR 56 subpart B.

28.0 Recruitment

28.1 * Methods (check all that apply):

- ☑ Study investigators (and/or affiliated nurses or staff) recruit their own patients directly in person or by phone.
- ☐ Study investigators recruit their own patients by letter. Attach the letter for review.
- ☐ Study investigators send a "Dear Doctor" letter to colleagues asking for referrals of eligible patients. If interested, the patient will contact the PI or the PI may directly recruit the patients (with documented permission from the patient). Investigators may give the referring physicians a study information sheet for the patients.
- ☐ Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing
- ☑ Advertisements, notices, and/or media used to recruit subjects. Interested subjects initiate contact with study investigators. Attach ads, notices, or media text for review. In section below, please explain where ads will be posted.
- ☐ Study investigators identify prospective subjects through chart review. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- ☐ Large-scale epidemiological studies and/or population-based studies: Prospective subjects are identified through a registry or medical records and contacted by someone other than their personal physician. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- ☐ Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study.
- ☐ Study investigators list the study on the School of Medicine list of UCSF Clinical Trials website or a similarly managed site. Interested subjects initiate contact with investigators.
- ☐ Study investigators recruit potential subjects who are unknown to them through methods such as snowball sampling, direct approach, use of social networks, and random digit dialing.
- ☐ Other

If **Other**, explain:

28.2 * How, when, and by whom eligibility will be determined:

After obtaining of informed consent eligibility of donors for the oral biopsies will be determined by [redacted] respectively. HIV-negative donors should provide evidence of HIV negative test. Alternatevily, HIV negative status of donors will be verified by standard HIV lab testing in the [redacted] Twenty ml of blood sample will be taken from arm vein for HIV testing.

The tonsil tissues will be collected from discarded surgical materials. After obtaining of informed consent [redacted] will perform tonsilectomy from HIV-negative children and discarded tonsil tissues will be provided to [redacted] laboratory. In the lab [redacted] will verify HIV negative status of donors by tesing of tonsil lymphocytes for HIV using ELISA p24, immunofluorescence and and Western blot assays.

After obtaining of informed consent the breast milk will be collected by HIV-negative donors and provided to [redacted] will verify HIV negative status of breast milk by tesing it for using ELISA p24, immunofluorescence and and Western blot assays.and lymphocytes from tonsil tissue will be tested for HIV using ELISA p24 assay.

28.3 * How, when, where and by whom potential subjects will be approached:

Advertisements will be placed seeking volunteers to donate oral mucosal tissue, and breast milk. The advertisements will be posted around the UCSF and San Francisco General campuses, in local newspapers and on the Internet. Volunteers donating oral tissues will be financially compensated for their time. Interested individuals will be asked to contact [redacted] who will describe the study. If the individual remains interested, he or she will come to the clinic where the purpose of the study and the procedures will again be described. The individual will be enrolled after his/her questions are answered and he/she reads and signs the informed consent forms.

1.The biopsy tissues from the adult oral mucosa will be collected in [redacted]

2. The fetal oropharyngeal and intestinal tissue samples from discarded fetus will be collected [redacted]

3. The infant tonsil tissues will be collected from discarded surgical materailas in [redacted]

4. The breast milk samples will be collected in breastfeeding healthy HIV-negative women at [redacted]

28.4 * Protected health information (PHI) will be accessed prior to obtaining consent:

(•) Yes ( ) No

29.0 Waiver of Consent/Authorization for Recruitment Purposes

(Note: This section partially replaces the old "Request for Waiver of Consent/Authorization for Minimal Risk Research or for Screening for Recruitment" supplement form. Please do not attach the old form to this application.)

This section is now required when study investigators (and/or affiliated nurses or staff) recruit their own patients directly.

29.1 * Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified:

- (•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

29.2 * A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

29.3 * Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

29.4 * Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [ ] Postal addresses
- [ ] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [ ] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA requires that you collect the minimum necessary.

29.5 * Describe any health information that will be collected prior to obtaining informed consent:

HIV status of donor

Note: HIPAA requires that you collect the minimum necessary.

29.6 * Describe your plan to destroy the identifiers at the earliest opportunity consistent with the research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law:

All specimens will be de-identified and designated by study numbers. The researchers and tissue bank staff will not have access to this information, rather they will have only study numbers. This numbers will be destroyed as soon as the study in completed. All data required by the protocol will be recorded and entered into electronic database using the unique study number. The study team will review the electronic data for accuracy. Data clarification or corrections will be made electronically and the databases will be password secured.

30.0 Informed Consent

30.1 * Methods (check all that apply):

- [x] Signed consent will be obtained from subjects and/or parents (if subjects are minors)
- [ ] Verbal consent will be obtained from subjects using an information sheet or script
- [ ] Electronic consent will be obtained from subjects via the web or email
- [ ] Implied consent will be obtained via mail, the web or email
- [ ] Signed consent will be obtained from surrogates
- [ ] Emergency waiver of consent is being requested for subjects unable to provide consent
- [ ] Informed consent will not be obtained

30.2 * Process for obtaining informed consent:

After advertisements any responded subject will be invited to office of [redacted] for oral tissues.
[redacted] will meet with each of interested subject in their office and describe them he purpose of the study and the procedures and answered their questions. If the individual remains interested he/she reads and signs the informed consent forms.

The fetal samples from discarded aborted materials will be collected at the [redacted] Since, this study will use only discarded fetal materials, the mothers consent to the use of the fetal tissue in research will not be obtained by the researchers in this study. The fetal samples will be used for the research and will be banked in [redacted]

The infnat tonsil samples from discarded materials will be collected at the [redacted] She will meet with parents of child in her office and describe them the purpose of the study and the procedures and answered their questions. If the parents remains interested he/she reads and signs the informed consent forms.

30.3 * How investigators will make sure subjects understand the information provided to them:

Persons obtaining consent will ask potential participants to restate what they have understood at various steps along the informed consent procedure.

31.0 Financial Considerations

31.1 Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [ ] Subjects will not be paid
- [ ] Cash
- [x] Check
- [ ] Gift card
- [ ] Other:

Specify **Other**:

31.2 Describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.

The amount of payment for singly donation will be as follow:

$100 buccal tissue

31.3 Costs to Subjects: Will subjects or their insurance be charged for any study procedures?

- ○ Yes
- ◉ No

If **yes,** describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.

32.0 CTSI Screening Questions

32.1 * This study will be carried out at one of the UCSF Clinical Research Services (CRS) units or will utilize CRS services:

- ○ Yes
- ◉ No

32.2 This project involves community-based research:

- ○ Yes
- ◉ No

32.3 This project involves practice-based research:

- ○ Yes
- ◉ No

Continuing Review Submission Form (Version 13.0)

1.0

Continuing Review Form

April 2022, v.42

NOTE: This form features dynamic show/hide functionality. Questions will appear and disappear as you complete the form. The form hides questions that are not relevant to your study. If the question numbers skip (e.g. 2.1, 2.4, 2.5, 2.8) it's because some questions are hidden. The form is functioning normally.

1.1 Principal Investigator:

[redacted]

1.2 Study Title:

HIV, EBV and HPV interaction with mucosal epithelium

1.3 Study Number:

10-03277

1.5 * Preferred Contact Information: Please provide the best contact information (phone, pager or email) for both the PI and primary Study Contact in case the IRB needs to contact you directly:

PI: phone [redacted] email [redacted]
Study contact: [redacted]; email [redacted]

1.6 Lay Summary:

The main purpose of this study during last 15 years was to investigate the interaction of mucosal epithelial viral microbiota including herpes simplex virus (HSV), human cytomegalovirus (HCMV), Epstein Barr Virus (EBV) and Human papillomavirus (HPV) with human immunodeficiency virus (HIV). Such interaction may play a critical role in the increase of HIV mucosal transmission and HIV-associated neoplasia. Currently, we are continuing these projects under new NIDCR R01DE023315 grant

Mother-to-child transmission (MTCT) is an important pathway for the spread of human immunodeficiency virus (HIV) from mother to fetus, neonate, and infant via oral/tonsil mucosal epithelium. The precise molecular mechanisms of HIV MTCT remain unclear, and the role of the oral microbiome in the context of HIV transmission is one of the most important questions in the field. HSV, HCMV, and EBV are common components of the oral infant microbiota, and their interaction with infant tonsil epithelial cells containing HIV may lead to the release and spread of HIV into CD4+ T lymphocytes, macrophages, and Langerhans/dendritic cells (LCs/DCs) and thus to HIV MTCT. Virtually nothing is known about the role of herpesvirus oral microbiota in HIV MTCT. Therefore, investigation of the molecular mechanisms underlying HSV-, HCMV-, and EBV-associated HIV spread from neonatal/infant oral epithelia into HIV-susceptible cells will undoubtedly lead to a better understanding of the oral microbiota-associated pathogenesis of HIV MTCT and the development of a new preventive therapeutic strategy against perinatal viral infection

The goal of this study is to investigate the role of oral mucosal microbiota HSV, HCMV, and EBV in

1.7 * NEW – Biospecimen Banks, Research Databases, and Recruitment Registries – Does this IRB approval ONLY cover activities such as biospecimen collection/banking, and/or collection of data in a research registry or recruitment database: (REQUIRED)

○ Yes ◉ No

1.8 * This is a: (REQUIRED)

◉ Continuing Review Only—no changes from last approval
○ Continuing Review and Minor Modification
○ Continuing Review and Major Modification

1.9 * Does this submission include personnel changes: (REQUIRED)

○ Yes ◉ No

1.16 * Are there any changes in financial interests/conflicts related to this study for the PI or any other study personnel: (REQUIRED)

○ Yes ◉ No

1.17 Expiration Date: Hint: Click 'Refresh Constant Fields' to update the expiration date if this is a copied form.

01/17/2023

*** Has your study expired: (REQUIRED)**

○ Yes ◉ No

1.18 Outstanding Stipulations:

No Stipulation is outstanding.

2.0 Study Status for Research Involving Subject Contact and Repositories

2.1 * Enrollment Status: (REQUIRED)

○ No subjects have EVER been enrolled here (or at any other sites if UCSF is the Coordinating Center)
◉ We are continuing to enroll subjects
○ Some subjects have been enrolled but we are not actively recruiting
○ All subjects have been enrolled and study is now closed to accrual

2.2 * Study Activity Status: (REQUIRED)

○ Study activities have not yet commenced
◉ Study in progress and subjects are currently participating in study procedures, interventions, and/or research activities (some subjects may be in follow up)
○ Study intervention is complete for all subjects but there is ongoing research-related follow-up

- ○ Study procedures are complete for all subjects but ongoing medical record review/biological specimen analysis continues (no subject contact)
- ○ Data analysis only - study is complete and the only activities are data analysis and/or manuscript preparation

2.3 * Planned Number of Participants (from the Study Application): (REQUIRED) This is the number from the Sample Size and Eligibility Section of the application.

Number of subjects that will be enrolled at UCSF and affiliated institutions:

292

*** Are you requesting an increase to enrollment targets at this time: (REQUIRED)**

○ Yes ◉ No

2.4 * Have you exceeded your approved enrollment number: (REQUIRED) This is the number from the Sample Size and Eligibility Section of the last approved version of the application.

○ Yes ◉ No

2.5 * Enrollment Activity: (REQUIRED) Note: These numbers DO NOT have to add up but please make sure you have completed these sections correctly. Mistakes in the accrual section are the most common reason why a Continuing Review Form is returned for corrections!

Activity *IN THE LAST YEAR* (or since the last renewal) Under This IRB Approval

Provide information about all of the subject accrual and withdrawal activities carried out at UCSF locations, or under this approval if the study activities take place in another city, county, state, or country.

	If None, Enter 0
Number Enrolled Under This IRB Approval (people who signed consent forms)	3
Number of Subjects Determined to be Ineligible After Signing the Consent	0
Number of Subjects Who Withdrew or Dropped Out (changed their mind about participating)	0
Number of Subjects Withdrawn by the PI Due to Toxicity or Adverse Events	0

Number of Subjects Withdrawn Due to Other Reasons (e.g., lack of compliance, response failure or worsening of disease, death due to disease progression, etc. - provide details below)	0

Activity *OVERALL* (since the study was first approved) Under This IRB Approval

Provide numbers for total accrual, completed participants, current enrollees, and persons lost to follow-up **TO DATE** at UCSF locations, or under this approval if the study activities take place in another city, county, state, or country.

	If None, Enter 0
Number of Subjects Enrolled To Date (people who signed consent forms)	288
Number of Subjects Who Have Completed the Study	0
Number of Subjects Currently Active on Study or in Follow-Up	0
Number of Subjects Lost to Follow-Up	0

2.7 * Progress to date, including interim results, if available. (REQUIRED)

Mother-to-child transmission (MTCT) of human immunodeficiency virus type 1 (HIV-1) and human cytomegalovirus (HCMV) may occur during pregnancy, labor, or breastfeeding. These viruses from amniotic fluid, cervicovaginal secretions, and breast milk may simultaneously interact with oropharyngeal and tonsil epithelia; however, the molecular mechanism of HIV-1 and HCMV cotransmission through the oral mucosa and its role in MTCT are poorly understood. To study the molecular mechanism of HIV-1 and HCMV MTCT via oral epithelium, we established polarized infant tonsil epithelial cells and polarized-oriented ex vivo tonsil tissue explants. Using these models, we showed that cell-free HIV-1 and its proteins gp120 and tat induce the disruption of tonsil epithelial tight junctions and increase paracellular permeability, which facilitates HCMV spread within the tonsil mucosa. Inhibition of HIV-1 gp120-induced upregulation of mitogen-activated protein kinase (MAPK) and NF-k B signaling in tonsil epithelial cells, reduces HCMV infection, indicating that HIV-1-activated MAPK and NF-k B signaling may play a critical role in HCMV infection of tonsil epithelium. HCMV infection of tonsil epithelial cells also leads to the disruption of tight junctions and increases paracellular permeability, facilitating HIV-1 paracellular spread into tonsil mucosa. HCMV-promoted paracellular spread of HIV-1 increases its accessibility to tonsil CD4 T lymphocytes, macrophages, and dendritic cells. HIV-1-enhanced HCMV paracellular spread and infection of epithelial cells subsequently leads to the spread of HCMV to tonsil macrophages and dendritic cells. Our findings revealed that HIV-1- and HCMV-induced disruption of infant tonsil epithelial tight

therapeutic intervention for both HIV-1 and HCMV infection may substantially reduce their MTCT.

2.8 * Brief summary of plans for the coming year: (REQUIRED)

In he coming year, we will continue to study the molecular mechanisms of HIV and HCMV interaction with infant tonsil epithelium.

3.0 Significant Findings & Other Reportable Events

3.1 * Has this IRB determined that this is a 'greater than minimal risk' study: (REQUIRED) Hint: 'Risk Level' can be found in your approval letter.

(•) Yes ( ) No

3.3 * Have any NEW *significant* risks been identified since the last continuing review (or since approval if this is the first continuing review): (REQUIRED)

( ) Yes (•) No

3.5 * Are there any new or preliminary findings, pertinent scientific publications, therapeutic developments, or results of similar or related studies that could have an impact on safety or subjects' willingness to participate: (REQUIRED)

( ) Yes (•) No

3.6 * Did you report any 5- or 10-day reportable events (e.g., adverse events, medication or laboratory errors, privacy or confidentiality breaches, etc.) since the last continuing review (or since initial approval if this is the first continuing review): (REQUIRED)

( ) Yes (•) No

Note: Non-reportable events should no longer be submitted at the time of Continuing Review on the AE Summary Log.

3.7 * Are there any new or missed 5- or 10-day reportable events that haven't yet been submitted: (REQUIRED)

( ) Yes (•) No

3.8 * Have there been any concerns or complaints by subjects or others: (REQUIRED)

( ) Yes (•) No

3.9 * Does this study undergo formal on-site monitoring: (REQUIRED)

( ) Yes (•) No

3.10 * Has this study been audited by any external group or entity (e.g., sponsor, CRO, FDA) since its last renewal: (REQUIRED)

○ Yes ◉ No

3.12 * Does this study have a local and/or external Data and Safety Monitoring Board (DSMB) or other Data Monitoring Committee (DMC) providing oversight of this study: (REQUIRED)

○ Yes ◉ No

4.0 Consent Forms

4.1 * Indicate which type(s) of consent documents are attached: (REQUIRED)

- ☐ New consent documents
- ☑ Active consent documents with NO changes
- ☐ Active consent documents with revisions
- ☐ Addendum consent with new risk and/or procedures
- ☐ No consent documents attached

4.2 Attach all active consent forms as Word documents: Please note: If you are submitting revised versions of approved consent forms, attach them as "Revisions" of the previous version, not as "New" consents. Your approval may be delayed if they are erroneously uploaded as "New" documents.

Attach your consent forms following these instructions:

Approved Consent Forms with No Changes: All approved consent forms that you will continue to use must be attached. Click "Copy Approved Consent(s)." A pop-up window will appear with a list of all currently approved consent forms (remember to allow pop-ups). Select the check box for each form you plan to use during the coming year, then click "Proceed Consent Copy." iRIS will generate and attach a copy of the selected consent form— without the previous IRB approval stamp— and will update the version number automatically.

For detailed instructions, click the **Help** icon in the upper right corner of the iRIS screen and read the quick guide titled "Attach approved consents (no changes) to the Continuing Review form."

Approved Consent Forms with Revisions: Click the "Select or Revise Existing" button. Click "Upload the Revised Consent" form and select the revised document from your computer. *If you need to download the current version of the consent form from iRIS first,* click "Download Document for Editing" and then "Upload the Revised Consent" after you've updated the document. Save your work.

New Consent Forms: Click on the "Add a New Consent" button and upload your new consent form.

NOTE: Please make sure that any tracked changes have been

changes are submitted, they will show in the stamped PDF and you will have to submit a modification to get clean documents stamped.

Version	Sponsor Version	Title	Category	Language	Expiration Date	Consent Outcome	View Document
1.3.13		tonsil tissues		English	12/05 /2023	Approved	176.14 KB
1.16		Consent-oral biopsy-HIV+		English	12/05 /2023	Approved	160.03 KB
1.17		Consent-oral biopsy-HIV-		English	12/05 /2023	Approved	160.22 KB
1.12		Consent-blood-HIV+		English	12/05 /2023	Approved	160.12 KB
1.12		Consent-blood-HIV-		English	12/05 /2023	Approved	160.27 KB
1.13		Consent breast milk-		English	12/05 /2023	Approved	168.57 KB

Version	Sponsor Version	Title	Category	Language	Expiration Date	Consent Outcome	View Document
No Consent(s) have been attached to this form.							