

Design of Phase 1 Rectal Microbicide Studies

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Guidance: Previous Rectal Phase 1 trials

- Usually in ***disease setting*** such as ulcerative proctitis/colitis
- Safety indices: clinical, endoscopic, histologic
- Clinical: clinical exam, bowel pattern, disease-specific staging criteria, standard blood assessments, UA
- Endoscopic: to ensure that already friable, ulcerated/erosive mucosa not worsened
- Histologic: also not worsening
- No guidelines for safety monitoring in healthy
- *Setting the stage, with PSRC and FDA support*

Distinct 'rectal-compartment' issues

- fragile epithelia – single cell
- increased absorptive potential/resistance profiles
- minimal benefit of endoscopic appearance in healthy subjects
- tube with constant cleansing flow
- untested, still developing safety indices
- suspected but not proven gender differences
- sequence of rectal fluid, tissue sampling critical to avoid confounders
- 'preparatory enema' injurious itself?
- rectal-specific applicator-avoid trauma/AE

**A Phase I Randomized, Blinded, Placebo-Controlled
Safety and Acceptability Study
of the UC-781 Vaginal Microbicide Gel Formulation
Applied Rectally
in HIV-1 Seronegative Adults**

- Sponsored by Biosyn, Inc with NIAID's U19 IP/CP
- Single site: UCLA

- NNRTI evaluated in seronegatives
- 2 concentrations/placebo with single and 7d exposures
- UC-781 gel: Carbomer 974P, methycellulose, glycerin, methyl- propylparaben...*interacts with many lubricants*)
- Universal Placebo: (not excipient; same as vaginal trials)
- Acceptability
- pilot PK

Trial Objectives and Indices

- **Primary Objective:**

To evaluate the safety and acceptability of 0.1% and 0.25% UC-781 vaginal microbicide gel versus placebo when applied rectally.

Indices:

- Frequency of \geq Grade 2 adverse events
- Acceptability assessments

Trial Objectives and Indices

- **Secondary Objectives:** To determine whether use is associated with rectal mucosal damage:
 - Epithelial sloughing*
 - Histopathology
 - Mucosal mononuclear cell phenotype (flow)
 - Mucosal cytokine mRNA (tissue)
 - Mucosal immunoglobulins
 - Fecal calprotectin*
 - Explants* - susceptibility to HIV infection

* not in HPTN 056

Trial Objectives and Indices

- **Tertiary Objective**: To determine the pharmacokinetics of UC-781 vaginal gel administered rectally (subset).

UC-781 blood levels to determine absorption from the GI tract

Will help guide future HIV+ trials/resistance

Acceptability Measurements

Prevention tools effective only if used. **Acceptability** critical from first efforts. Qualitative and quantitative..of product, applicator, technique as well as in-depth contextual eval.

At Baseline: Baseline Behavioral Questionnaire

After single-dose exposure: none

During 7-day exposure: Product Acceptability Questionnaire

Following 7-day exposure: Acceptability Interview

Study Outline

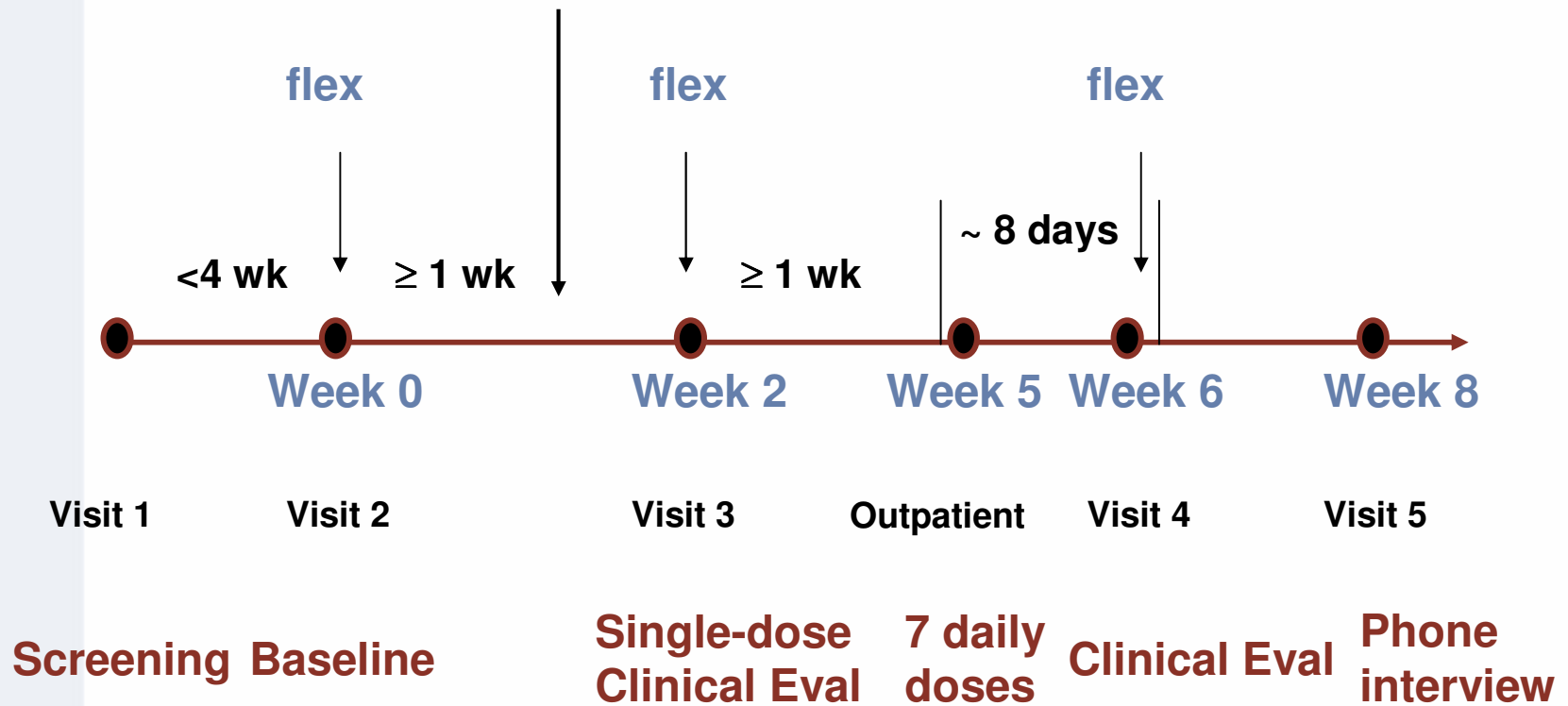
- **Study Population:** HIV negative men and women with a history of RAI *

**in order to give context to acceptability assessments.*

- **Study Size:** 36 participants (men and women) in 3 arms
Subset of 6 participants assigned to pK study.
- **Accrual:** 9-12 months.
- **Duration:** 18 months.

RM Phase 1 Trial Design

Randomization: 0.1% UC-781, 0.25% UC-781, or placebo



Study Design II

- **PK Substudy:**

Subset of 6 subjects

6 timepoints:

pre-dose, 0.25, 2, 4, 24 hr & post 7d use

- **2 stages of treatment.** Each treatment stage is independent of the other. Study examines the effects of 2 different dosing regimens, **NOT** cumulative safety over both stages.

Inclusion Criteria

Men who meet the following 10 criteria and women who meet the following 12 criteria are eligible for inclusion in the study:

- 1. \geq Age of 18
- 2. HIV-1 status antibody negative as documented at screening
- 3. Understands and agrees to local STI reporting requirements
- 4. Able and willing to communicate in English
- 5. Able and willing to provide written informed consent to take part in the study
- 6. Able and willing to provide adequate information for locator purposes
- 7. Availability to return for all study visits, barring unforeseen circumstances
- 8. A history of consensual RAI at least once in lifetime*
 - **Required to assure that subjects have a context for the acceptability assessments.*
- 9. Willing to abstain from insertion of anything per rectum other than the study gel for the 1 week prior to treatment, 1 week prior each flexible sigmoidoscopy (i.e. during week of study gel use), and 1 week after each flexible sigmoidoscopy.
- 10. Willing to use condoms for the duration of the study

In addition to the criteria listed above, female participants must meet the following criteria:

- 11. Negative pregnancy test
- 12. Post-menopausal or using an acceptable form of contraception.

Exclusion Criteria

- 1. HIV positive at baseline
- 2. History of inflammatory bowel disease
- 3. Active inflammatory condition of the GI tract at baseline
- 4. Active rectal infection at baseline
- 5. \geq Grade 2 laboratory abnormality at baseline
- 6. Allergy to methylparaben, propylparaben, sorbic acid
- 7. History of alcoholism or IV drug abuse
- 8. Unwillingness to refrain from chronic use of aspirin and NSAIDs.
- 9. Use of warfarin or heparin
- 10. Use of systemic immunomodulatory medications within 4 weeks of Visit 2
- 11. Use of rectally administered medications, with the exception of over the counter enemas, within 4 weeks of Visit 2
- 12. Use of product containing nonoxyl-9 rectally within 4 weeks of Visit 2
- 13. Use of any investigational products within 4 weeks of Visit 2
- 14. Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the patient unsuitable for the study.

In addition to the criteria listed above, female participants will be excluded if they meet any of the following criteria:

- 15. Pregnancy
- 16. Breastfeeding
- Female of child-bearing potential unwilling to use acceptable form of contraception

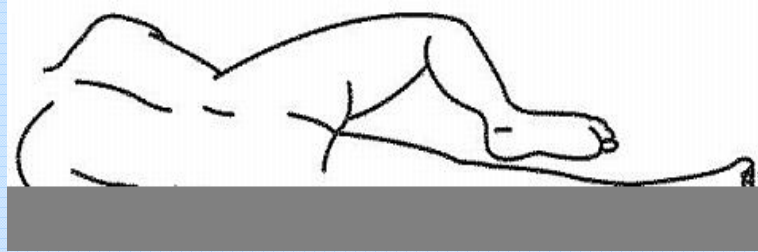
Subject education with applicators

Using the Study Gel

Find the position that feels most comfortable. Many people already have a position they prefer (kneeling, squatting, etc.). If you do not have a preferred position, we recommend one of the following 2 positions.

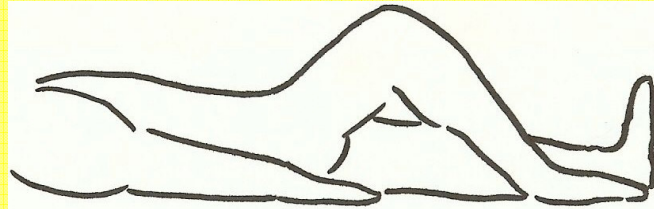
Left Side

Lie on your left side. The right leg should be bent up toward the chest.



Lying on Your Back

Lie on your back with your right knee bent. This should allow good access to your anus from below.



Applicator (vaginal form) issues



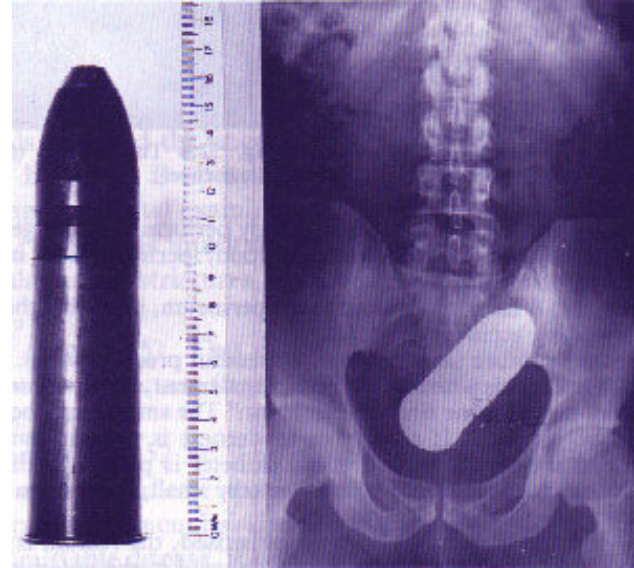
- Participants will apply small amount of lubricant to applicator for insertion.

- **Not to use OTC lubricants as they may cause toxicity and interact with the study product.**

AEs not in current tables



A screwdriver with a plastic handle.
(Dr. A.K. Sharma, Agra, India.)



A [live shell](#), which needed careful handling.

“If unsurmountable difficulty is experienced in grasping any foreign body in the rectum, a left lower laparotomy is necessary, which allows that object to be pushed from above into the assistant's fingers in the rectum. If there is considerable laceration of the mucosa a temporary colostomy is advisable”.

Amended Toxicity Tables for AE (1^o endpoint)

- DAIDS EAE Reporting Manual and DAIDS Toxicity Tables
- **Clarifications/Additions to avoid inaccurate AE reporting:**
 - “diarrhea”
 - “hematochezia” (from NCI, not in DAIDS)
 - “bloody diarrhea”
 - “Proctitis” (stricter definition than DAIDS; used by NIDDK)
 - “bruising” (to cover AE related to applicator injury)(NCI)
- Protocol team to review q 2-4 weeks, DSMB on call
- Trial suspended if 2 or more subjects have \geq Grade 3

Tissue-based 'Safety' Indices

- **Epithelial sloughing:** main finding with N9
normal occurrence –degree is what we'll assess
choice of non-toxic bowel prep (PBS)
check 30' post exposure; microscopy and Coulter
- **Histology:** to capture significant mucosal changes
GI histopathologist, blinded (minimize variability)
Qualitative (5 grades)
(Endoscopy NOT an endpoint)
- **Immune cell changes (phenotype) using FLOW:**
check changes co-receptors and activation
intra-subject correlations

Tissue-based 'Safety' Indices

- **Mucosal cytokine changes:**

Chemokines: e.g.:RANTES/MIP-1a, MIP-1b, SDF-1
tissue mRNA by RT-PCR (baseline/post-exp)
protein in supernatants Luminex (Base/post op)

- **Mucosal immunoglobulins:**

Constant secretion of IgG, IgA
evaluate for potential non-specific hypersensitivity
secretions collected using surgical sponges; ELISA

- **Fecal Calprotectin:**

60% of secreted cytoplasmic protein in PMNs but
also mono/macrophages, eos.

indirect indicator of mucosal inflammation (96%
sensitivity to distinguish between healthy
controls and IBD)

Tissue-based 'Safety' Indices

- **Explants: 'functional assay'**

ex vivo assessment of infectivity/inhibition

in vivo microbicide exposure (2 doses)

same infectious R5 (HIV_{bal}) dose with ability to
see both increases and decreases in p24
(supernatants)

14 days, assess every 2-3 days.

controls: no microbicide (from baseline, same subject)

positive control with N9

read-outs: p24 profiles, AUC, "soft-endpoints" (MQAP)

Statistical Processes

- **Frequency of \geq Grade 2 AE primary measure of safety**
 - reported as change in grade from baseline
 - given small N, only large differences between groups detectable... i.e.: if true event rate is 1%, we have an 11% chance of observing; if 20% true rate: have a 90% chance of detection.
 - Other assays may evolve to add to safety indices.
- **Acceptability:** quantitative and qualitative; measures taken toward end of study (familiarize)

Statistical Processes

- **Mucosal damage parameters:** as per HPTN 056/CFAR Core
some parameters 3x others 4x/trial
4 of 6 parameters sensitive enough to detect differences
between group,
Analysis of covariance (ANCOVA) post-Stage 1 and
post-Stage 2, between groups
regression coefficients: low vs placebo, high vs placebo
Account for multiple hypotheses testing: informal/formal
group differences at 0.05: suggestive
group differences at 0.001: examine in detail
Longitudinal (min informative) and multivariate (more
helpful)

Next Steps; Alternative Options

- **Rectal safety testing** of all vaginal microbicides (PIII)
- **Vaginal formulation:** HIV-, sexually active and partners
- **Vaginal formulation:** HIV+, sexually abstinent (resistance)
- **Rectal formulation:** HIV-, sexually abstinent; potential second stage with sexually active
- **Rectal formulation:** HIV+, sexually abstinent with longer follow-up (resistance)
- **Exploratory INDs** (Phase 0 studies). Minimal benefit for full dose trials but microdosing for distribution, absorption etc, very useful

Next Steps; Alternative Options

- Streamline safety parameters
- Consider shift in next generation drug design plan.
- For dual-compartment use, establish rectal safety first.
- Contingent on optimal carrier formulation and concentration, may be easily adaptable for vaginal use.
- Consideration of single agent Phase 1 safety (several) followed by combination studies. Critical to assess **pace** as each Phase 1 ~2 years minimum.

UCLA
Center for
Prevention Research

CPR

Strategic Interventions Against HIV

NIH NIAID U19 IP/CP #AI060614: “Microbicide Development Program”

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