

**METHODOLOGICAL
CHALLENGES IN THE
EVALUATION OF RECTAL
MICROBICIDES**

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**CREATING A RESEARCH AND
DEVELOPMENT AGENDA FOR
RECTAL MICROBICIDES THAT
PROTECT AGAINST HIV INFECTION**

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RATIONALE FOR WORKSHOP

- **HIV TRANSMISSION MORE EFFICIENT VIA RECTAL THAN VAGINAL EXPOSURE.**
- **COMMON RISK FACTOR IN MSM; HIGH RISK HETEROSEXUALS.**
- **MICROBICIDES DEVELOPED FOR VAGINAL USE WILL BE USED FOR ANAL INTERCOURSE.**
- **VAGINAL AND RECTAL MUCOSA AND MICROENVIRONMENTS ARE DIFFERENT. PRODUCTS SAFE AND EFFECTIVE FOR VAGINAL USE MAY NOT ACT SIMILARLY IN THE RECTUM.**

RATIONALE FOR WORKSHOP

- **TO DEVELOP EFFECTIVE MICROBICIDES, KNOWLEDGE ABOUT HOW TO EVALUATE RECTAL SAFETY AND EFFICACY IS NEEDED.**
- **NEW KNOWLEDGE ABOUT RECTAL MICROBICIDES COULD BENEFIT THE DEVELOPMENT OF VAGINAL MICROBICIDES.**

PREVALENCE OF ANAL SEX IN NATIONAL HEALTH AND SOCIAL LIFE SURVEY

	<u>PREVALENCE</u>	
	<u>MEN (1511)</u>	<u>WOMEN (1921)</u>
LIFETIME ANAL SEX	26%	21%
ANAL SEX IN LAST 6 MONTHS	8%	8%
ANAL SEX IN LAST ENCOUNTER	2%	1%

E.O. LAUMANN, ET AL, 1992

RECTAL MICROBICIDE WORKSHOP CONCLUSIONS: MOLECULAR AND CELLULAR RESEARCH QUESTIONS

- **WHICH RECTAL CELLS ARE THE INITIAL AND/OR MAJOR TARGETS OF HIV?**
 - **WHAT ARE THE MOST IMPORTANT PATHS FOR SUBSEQUENT DISSEMINATION?**
- **WHAT IS THE LOCAL HOST IMMUNE RESPONSE?**
- **CAN SURROGATE MARKERS BE USED TO EVALUATE SAFETY AND/OR PROTECTION? IF YES, WHICH ONES?**
 - **BIOPSIES? CYTOKINES? HIV EXPRESSION IN INFECTED PTS? STANDARDIZATION IS NEEDED.**

RECTAL MICROBICIDE WORKSHOP CONCLUSIONS: CLINICAL QUESTIONS

- **WHAT ARE THE EFFECTS OF SEXUAL TRAUMA? DOUCHING?**
- **HOW LONG DO THEY PERSIST?**
- **HOW EXTENSIVE DOES PROTECTION NEED TO BE? COULD THIS VARY BY POSITION?**
- **WHAT ARE THE EFFECTS OF LOCAL FACTORS; e.g., HEMORRHOIDS, DEFECATION, ON SUSCEPTIBILITY AND PRODUCT ACTIVITY?**
- **ARE THERE SIGNIFICANT GENDER DIFFERENCES IN SUSCEPTIBILITY TO TRAUMA, HIV SHEDDING, RESPONSE TO INFLAMMATION?**

RECTAL MICROBICIDE WORKSHOP CONCLUSIONS: BIOLOGICAL QUESTIONS

- **ARE CERTAIN PHYSICAL AREAS MORE VULNERABLE TO TRAUMA OR INFECTION AND NEED GREATER PROTECTION?**
- **WHAT IS THE RELEVANCE OF pH IN RELATION TO EJACULATE?**
- **DO SPECIFIC MICROFLORA IMPEDE OR FACILITATE HIV TRANSMISSION IN THE RECTUM?**
- **COULD MICROBICIDES AFFECT CCR5 EXPRESSION?**
- **WHAT ARE THE BEST ANIMAL MODELS?**

FACTORS THAT WILL NEED TO BE ASSESSED IN RECTAL MICROBICIDE DEVELOPMENT

- **ACTIVITY IN RELATION TO DIFFERENT CONCENTRATIONS OF RECTAL HIV, ROLE IN INHIBITING SHEDDING VS. PROTECTING UNINFECTED MUCOSA**
- **EFFECT ON MUCUS PRODUCTION**
- **PRODUCT VOLUME AND DISTRIBUTION**
- **SYSTEMIC ABSORPTION**
- **LUBRICITY, LEAKAGE, PRODUCT ELIMINATION**
 - **FLATULENCE AND DEFECATION**
- **ACCEPTABILITY**

RECTAL MICROBICIDE WORKSHOP: ISSUES FOR PHASE I/II CLINICAL TRIALS

- **SAFETY STUDIES SHOULD EVALUATE HIV+ AND HIV- MSM, HIGH RISK WOMEN.**
- **CAN SAFETY DATA FROM VAGINAL STUDIES BE USED? MAY DEPEND ON MECHANISM OF ACTION OF PRODUCT, AND pH ISSUES.**
- **NEED OBSERVATIONAL CONTROLS B/C HIGH DEGREE OF VARIABILITY
e.g., NON-INTERVENTION RUN-IN.**
- **MAJOR CLINICAL END POINTS: BLEEDING, ULCERATION, EROSION, SLOUGHING, INFLAMMATION, AND ABSORPTION. PLUS: ITCHING, FULLNESS, FECAL URGENCY, DIARRHEA, NUMBNESS.**

RECTAL MICROBICIDE WORKSHOP: ISSUES FOR PHASE I/II CLINICAL TRIALS

- **RECTAL HIV MUCUS CONCENTRATION MAY BE A USEFUL MEASUREMENT**
- **BIOPSY MAY OFFER ADDITIONAL OBJECTIVE INFORMATION. LOCATION?**
- **PERMEABILITY STUDIES MAY BE USEFUL.**
- **APPLICATOR AND DIGITAL USE OF PRODUCT SHOULD BE EXAMINED.**
- **NEED PRE-IND MEETINGS WITH FDA TO ESTABLISH CRITERIA.**

SURROGATE MARKERS FOR RECTAL INFLAMMATION

- **FECAL CALPROTECTIN**
LOW IN HIV- PTS, ↑ IN HIV AND CROHN'S.
HIV RX ↓ FECAL CALPROTECTIN.
 - LACTULOSE/PARACELLULOSE ABSORPTION MEASURES RELATIVE LEVEL OF INFLAMMATION?
- **MAY BE USEFUL MARKERS TO DECIDE IF A PRODUCT DOES NOT CAUSE RECTAL INFLAMMATION.**

(BJARNASON, RMW)

PHARMACOLOGY OF RECTAL MEDICATIONS

**ISSUES TO CONSIDER: FORMULATION/
ADHERENCE/KINETICS/DYNAMICS**

HOW WELL THE PRODUCT ADHERES

HOW IT MOVES ACROSS MEMBRANES

IS IT PUMPED OUT OF CELLS (P-GP)

PROTEIN-BINDING, CHARGE DENSITY

**HOW MUCH IS ABSORBED (IVC vs PORTAL
CIRCULATION)**

PHARMACOLOGY OF RECTAL MEDICATIONS

- LOTS OF KNOWLEDGE ABOUT PRODUCTS FROM EXPERIENCE WITH IBD, SUPPOSITORIES FOR INFANTS, ELDERLY AND INFIRM
- RECTAL AZT LESS ABSORBED THAN ORALLY
ddl: NO RECTAL ABSORPTION.

(Hendrix, RMW)

FORMULATION CHARACTERISTICS OF RECTAL MICROBICIDES

- **HAVE TO AVOID IRRITATION → FECAL INCONTINENCE**
 - DEBATE ABOUT HOW MUCH PRODUCT IS TOLERATED.
- **ISSUES TO CONSIDER:**
 - VEHICLE: VISCOSITY, FORMULATION, pH
- **COLON-RECTUM: LACK SOME ENZYMATIC PATHWAYS COMPARED TO UPPER GI, BUT ↑ ORGANISMS → COULD METABOLIZE PRODUCTS**

FORMULATION CHARACTERISTICS OF RECTAL MICROBICIDES

- **HAVE TO CONSIDER ROLE OF SEMEN**
 - **DILUENT**
 - **BIOACTIVE SUBSTANCES--FREE AND INTRACELLULAR**
 - **MAY ALTER MUCOSAL PERMEABILITY OR AFFECT RECEPTOR EXPRESSION**
EG: PROINFLAMMATORY CYTOKINES

(ROGERS, RMW)

WHERE DOES PRODUCT END UP?

- **NEW IMAGING STUDIES**
 - MRI - CAN TAG COMPOUND AND OBSERVE HOW FAR AND EXTENSIVE PRODUCT IS DISTRIBUTED.
 - FIBEROPTIC ENDOSCOPY - FLUORESCINE LABEL.
- **USEFUL TO ASSESS: WHERE ARE BARE SPOTS, WHERE THE BULK OF A COMPOUND IS DISTRIBUTED.**
- **NOT YET OPTIMIZED FOR HUMAN STUDIES. COULD PRODUCT INSERTION AND OBSERVATION → LESIONS?**

(Katz, RMW)

RECTAL MICROBICIDE WORKSHOP: ISSUES FOR PHASE III CLINICAL TRIALS

- **INITIAL PHASE III LIKELY TO FOCUS ON HIGH RISK MSM BECAUSE OF ↑ FREQUENCY OF ANAL INTERCOURSE AND HIV INCIDENCE, BUT TRIALS SHOULD ALSO INCLUDE AT RISK WOMEN (CONCOMITANT VAGINAL USE?)**
- **PRIMARY ENDPOINT: HIV INCIDENCE**
- **SECONDARY ENDPOINT: LOWER HIV SET POINT IN PTS. WHO BECOME INFECTED**
- **↓ OTHER STD? PRODUCT DEPENDENT.**

RECTAL MICROBICIDE WORKSHOP: ISSUES FOR PHASE III CLINICAL TRIALS

- **EFFECT SIZE: AT LEAST 30%, LIKE VAGINAL MICROBICIDES.**
- **RISK REDUCTION COUNSELING AND SELECTION BIAS MEANS THAT THOUSANDS OF PTS. WILL BE NEEDED**
- **IDEALLY WILL WORK IN RECTUM AND VAGINA**
RECTAL-ONLY PRODUCTS SHOULD NOT BE PRECLUDED.
- **NEED TO TRACK ↑ RISK TAKING.**

RECTAL MICROBICIDE WORKSHOP: PREFERRED EFFICACY OF MICROBICIDE BY HIV SEROSTATUS

MEN	PREFERRED EFFICACY*	% WHO WANT 95% EFFICACY
HIV(+)	71%	26%
HIV(-)	83%	55%
HIV STATUS UNKNOWN	91%	65%

GROSS ET AL, 1998

***TO USE INSTEAD OF CONDOM**

WAS THE MEETING SUCCESSFUL?

- NEW INTEREST
- NEW INFORMATION
- NEW COLLABORATIONS
- NEW COMMITMENT
- INCREASED PRODUCTIVITY

- THANKS TO ALL THE PRESENTERS

WORKSHOP ORGANIZING COMMITTEE

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**ALLIANCE FOR MICROBICIDE
DEVELOPMENT**

U PITTSBURGH

CDC

NICHHD

FHI

OAR