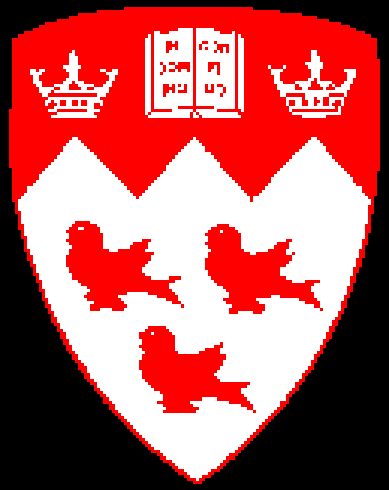
Antiretroviral based microbicides:
an overview



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Mark Wainberg, Ph.D.

What are antiretroviral (ARV)- based microbicides?

Antiretrovirals (ARVs) are chemical compounds that disrupt the molecular interactions essential and specific to HIV-1 replication at the cellular level.

Microbicides are vaginally and/or rectally applied gels, creams, films, rings, and/or suppositories that prevent the sexual transmission of HIV-1.

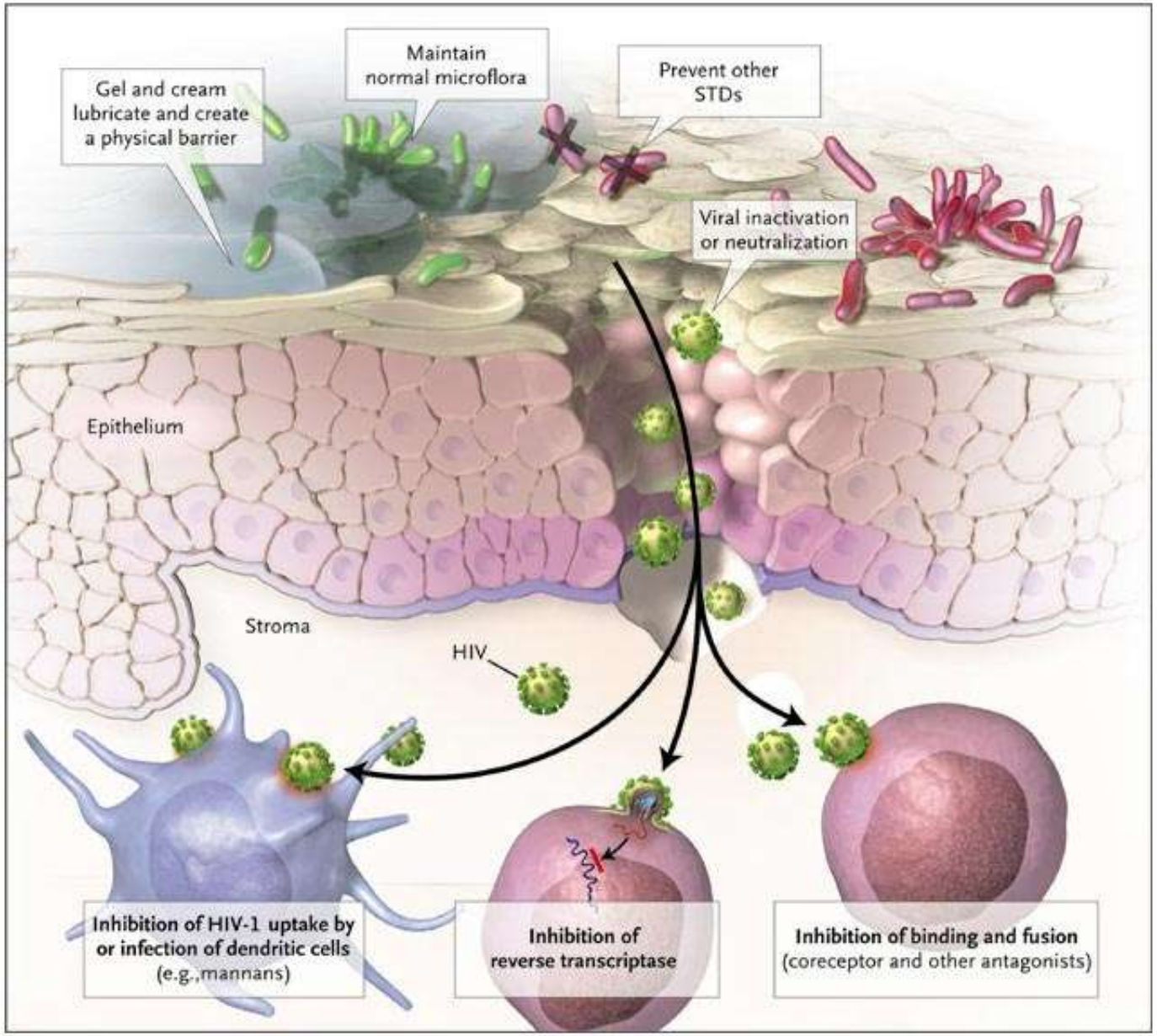
ARV- based microbicides contain a chemical compound(s) that disrupt molecular interactions specific to HIV-1 *infection* at the cellular level and are formulated as vaginally applied gels, creams, films, rings and/or suppositories to prevent the sexual transmission of HIV-1

Early Generation Microbicides

- Gel products that non-specifically block HIV from interacting with target cells or are directly virucidal
  - Surfactants
  - Multiple poly-anions
- Short-acting (used just prior to or just after sex)
- Efficacy trials complete
  - Partial, low or no effectiveness

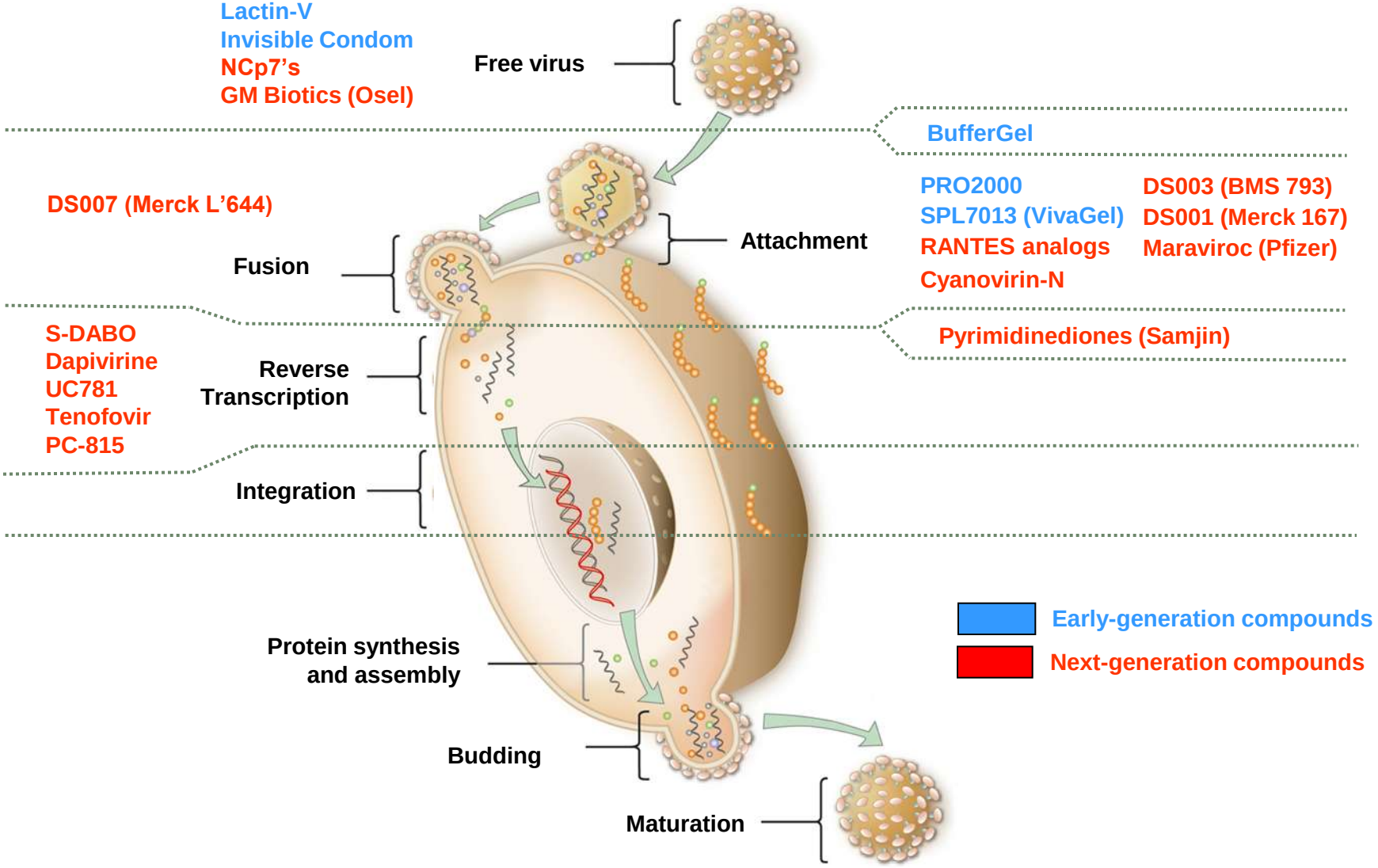
Next Generation Microbicides

- Based on successful HIV treatment drugs (IPM's microbicide candidates fall in this category)
- Once a day or monthly use offering longer term protection
- Trial of tenofovir gel initiated May 2007
  The CAPRISA trial demonstarated 45% protection against HIV transmission



J P Moore. 2005. N Engl J Med 352, 298-300.

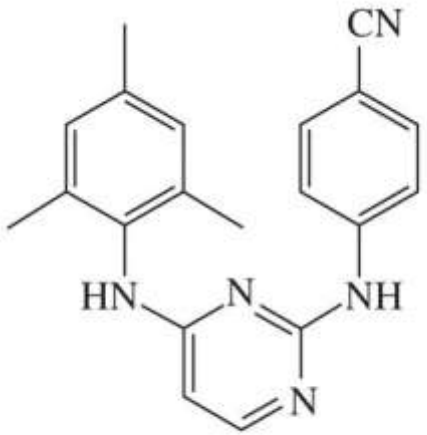
Microbicides in product development



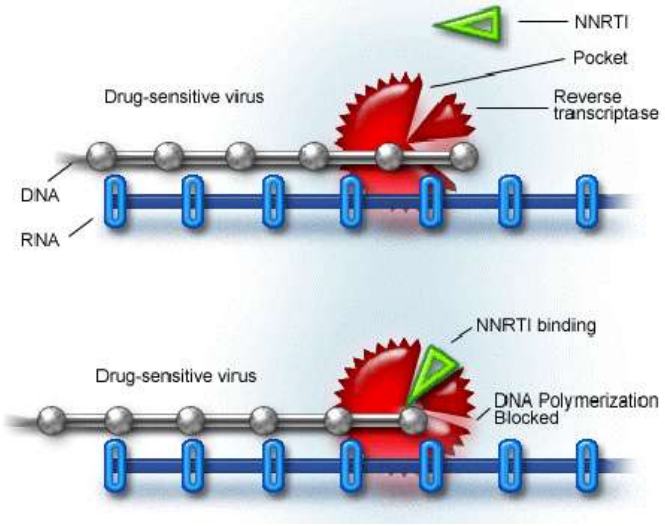
ARV-Based Microbicides

- Advantages
  - Highly potent and HIV-specific
  - Established safety & efficacy in AIDS treatment
  - Developed as single drugs and in combination
  - Multiple mechanisms of action against HIV
  - Can be formulated for sustained protection
    - Once a day / once a month (or less frequent)
    - Gels / rings / tablets / films (increased options)
- Disadvantages
  - Potential to select for resistant virus in HIV+ persons is unknown
  - Lack of activity against other STDs
  - Likely to be prescription only

ARV- based microbicide development: TMC120/Dapivirine



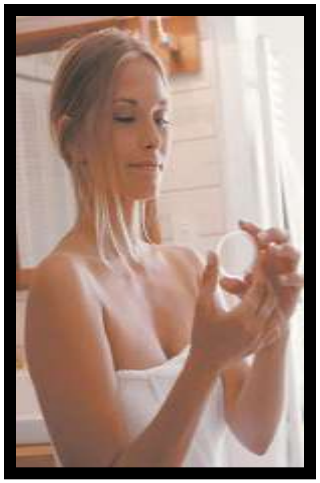
TMC-120



Tissue culture
-cervical explants
-PBMC replication assays

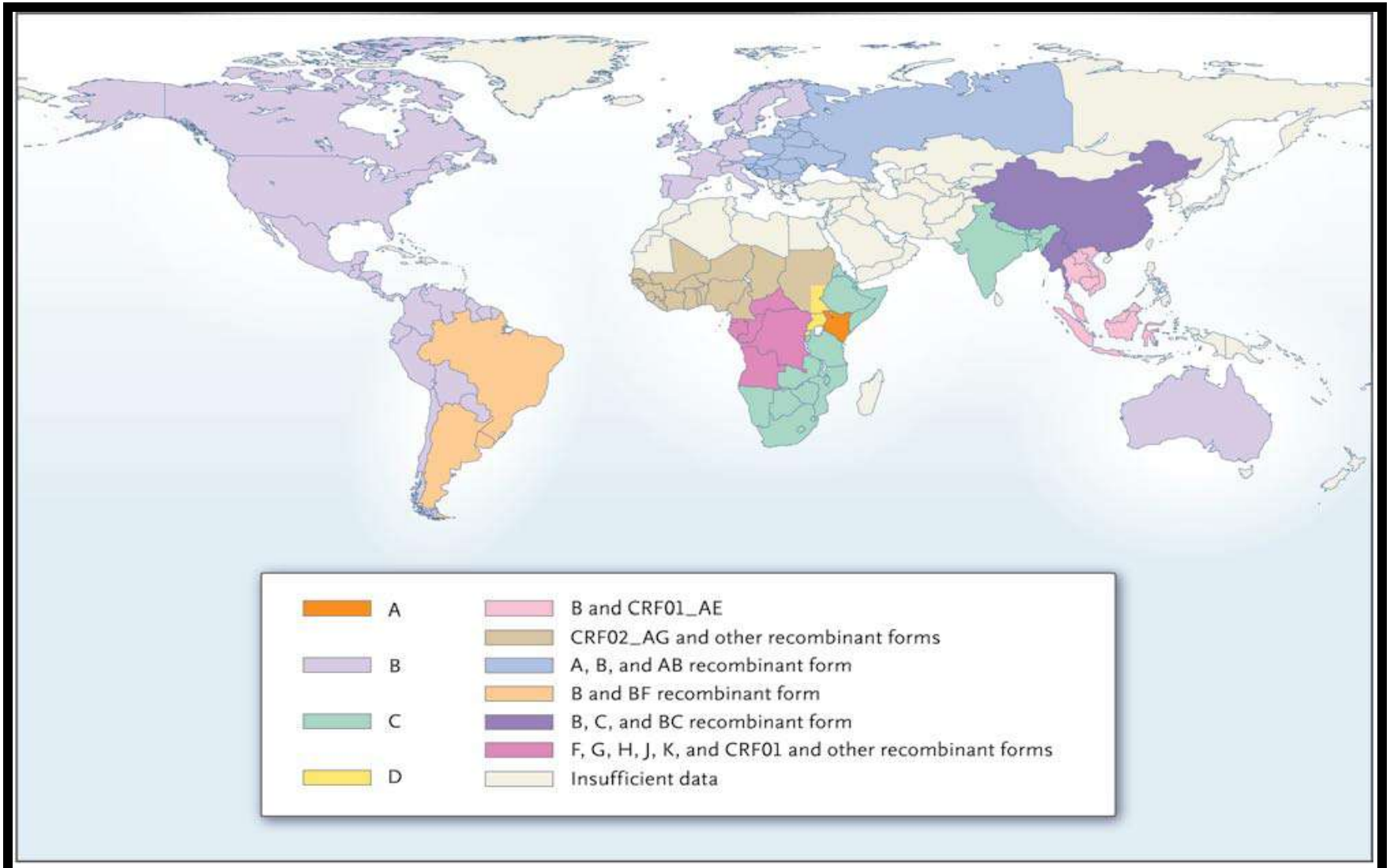
Formulation
-vaginal ring, gel, and film

Animal model
-toxicity



HIV negative women
-safety, pharmacokinetics

Global distribution of HIV-1 subtype variability



Barbara S. Taylor, M.D., Magdalena E. Sobieszczyk, M.D., M.P.H., Francine E. McCutchan, Ph.D., and Scott M. Hammer, M.D. The Challenge of HIV-1 Subtype Diversity. 2008: n engl j med 358;15

Do candidate microbicide ARVs protect against HIV-1 infection from different subtypes?

Table 1
Coreceptor usage, genetic subtype, source and p24 production in PBMC HIV-1 test isolates

Isolate	Coreceptor usage	Subtype	Source reference	HIV (ng/
KNH 1088	R5	A	Polonis, V	6.6
KNH 1144	R5	A	Polonis, V	5.0
KNH 1207	R5	A	Polonis, V	3.5
JRFL	R5	B	NIH	6.5
AK103	R5	B	Trkola, A	8.0
AK115	R5	B	Trkola, A	3.8
56313	R5	C	Polonis, V	6.2
94ZW109	R5	C	JPM (Trkola 97)	24
PBL288(411)	R5	C	Polonis, V	19
DJ259	R5	C	JPM (Trkola 97)	15
TZBD 9/11	R5	C	Polonis, V	10
A08083M1	R5	D	Polonis, V	11
J32228M4	R5	D	Polonis, V	2.7
NKU 3006	R5	D	Polonis, V	6.7
A07412M1	R5	D	Polonis V	2.4
BZ162	R5	F	JPM (Trkola 97)	12
MSD28019	R5	F	Trkola A	12
R1	R5	F	JPM (Trkola 97)	5.7
G3	R5	G	Abimiku, A (via NIH)	12
AK112	R5	G	Trkola, A	23
MSD28017	R5	G	Trkola A	16
RU570	R5	G	Bobkov, A and Weber, J (via NIH)	17
AK104	R5	CRF01_AE	Trkola, A	9.6
002(PIS2 CD4)	R5	CRF01_AE	Trkola, A	3.0
CM235	R5	CRF01_AE	JPM (Trkola 97)	16
HC4	X4	B	JPM (Trkola 97)	28
2044	X4	B	JPM (Simmons 96)	36
MN	X4	B	NIH	14
ZAM-20	X4	C	JPM (Trkola 97)	21
SW7	X4	C	Morris	25
UG270	X4	D	JPM (Trkola 97)	26
92UG046	X4	D	NIH	24
92UG024	X4	D	NIH	26
93UG070	X4	D	NIH	22
94TH304	X4	CRF01_AE	JPM (Zhang 96)	38
93TH053	X4	CRF01_AE	NIH	12
E4002 (90CF402)	X4	CRF01_AE	Gao, F	16
92RW009	R5X4	A	NIH	62
92US076	R5X4	B	Sullivan, J (via NIH)	68
2076 C13	R5X4	B	JPM (Trkola 97)	46
CC 2/86	R5X4	B	Connor, R	18
DH123	R5X4	B	JPM (Trkola 97)	27
SP116	R5X4	B	Trkola, A	23
S2206	R5X4	B	Trkola, A	19

* The concentrations represent the total p24 (intracellular and extracellular) content per culture volume on Day 7 (or 10 or 14) of cultures of PBMC from 3 to 4 different donors. The values are means of 3 intra-experimental replicates and are rounded off to two significant digits.

Entry inhibitor-based microbicides are active *in vitro* against HIV-1 isolates from multiple genetic subtypes

Thomas J. Ketas [a], Susan M. Schader [a,1], Juan Zurita [a], Esther Teo [a], Victoria Polonis [b], Min Lu [c], Per Johan Klasse [a], John P. Moore [a,*]

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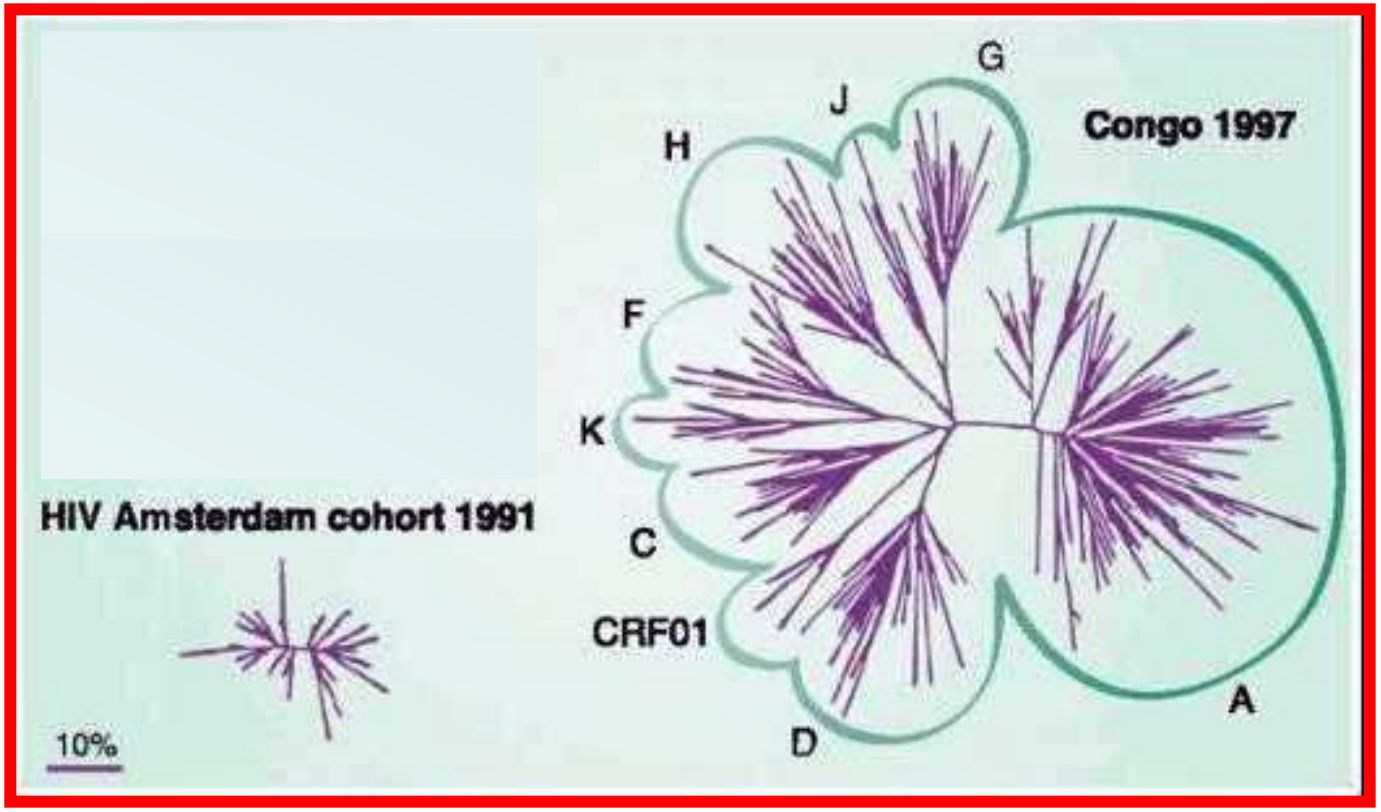
Received 18 January 2007; returned to author for revision 26 February 2007; accepted 2 March 2007
Available online 10 April 2007

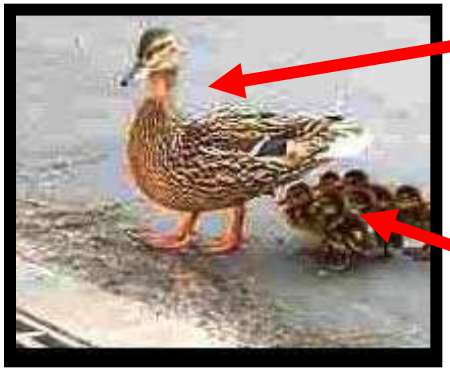
Entry inhibitors protected against HIV-1 infection better in combination over single compound treatment.

The scale of HIV-1 variation



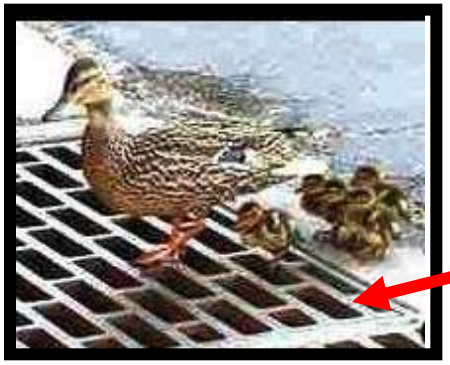
Weiss, R.A. 20 Years of HIV Science. Nature Medicine 9: 887-891 (2003)
Original analysis from Bette Korber, Los Alamos National Labs

Is ARV resistance a concern in microbicide development?



dominant variant
example-'wild type'

sub-dominant variants
example- drug resistant



selective pressure
example- drug pressure (TMC120)

"transmission fit" variants
example- drug resistant variants

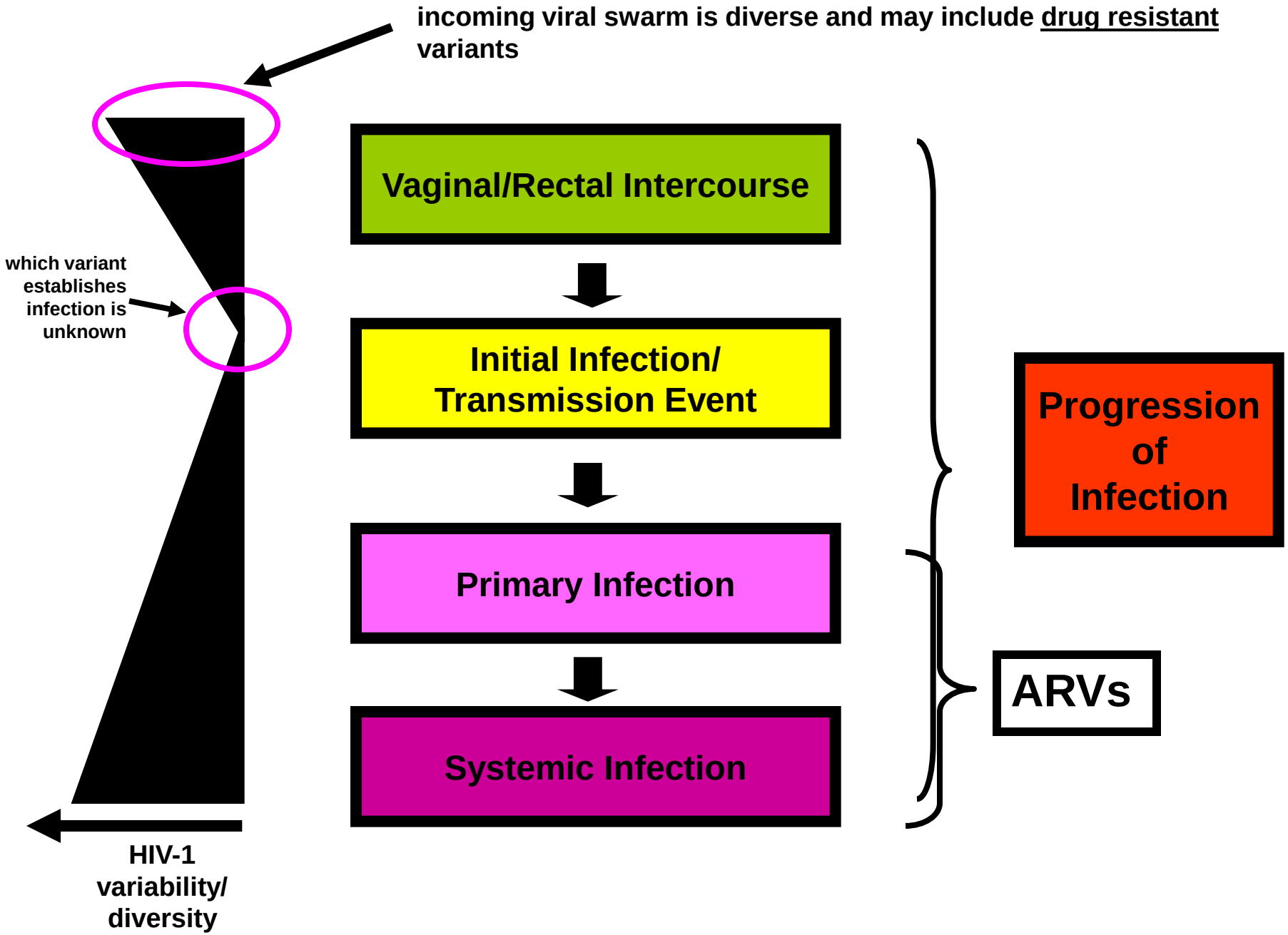
-HIV-1 mutation rate is **high**

-incidence of drug resistant virus is **increasing** worldwide

-some drug resistant HIV-1 variants are as 'fit' as drug susceptible HIV-1 variants and are transmitted <u>just as easily</u>

-ARVs that are similar to those used in treatment regimens *may* not be as efficacious against drug resistant HIV-1 in the context of microbicides

Question: Could ARV-based microbicides 'select' for drug resistant HIV-1?


incoming viral swarm is diverse and may include drug resistant variants
which variant establishes infection is unknown
Vaginal/Rectal Intercourse
Initial Infection/ Transmission Event
Primary Infection
Systemic Infection
Progression of Infection
ARVs
HIV-1 variability/ diversity

Why combine candidate microbicide ARVs?

Advantages

Different mechanisms of virus-centered inhibition

Block different steps of the replication cycle (safety net)

Better blocks a variety of subtypes

Better blocks a variety of resistant strains of HIV

Lower toxic effects

Possibility of synergy

Challenges

Possibility for antagonism

Difficult to demonstrate true/robust combination effect due to complex nature of HIV replication, lack of a standard protocol that accounts for HIV diversity, and 'tricky' data analysis

Microbicide development: pre-clinical evaluation of ARVs in combination

McGill AIDS Center

Mark A. Wainberg laboratory

ARV- based microbicide research supported by IPM

What we do

- test candidate microbicide ARVs in combination: tenofovir, dapivirine, DS001 & DS003
- test combination candidate ARVs against 'wild type' and drug resistant HIV-1 from multiple subtypes
- evaluate combined effect and the 'robustness' of this effect in increasingly more sophisticated in vitro systems

Key Question

What is the nature of the protective advantage demonstrated by combinations of candidate microbicide ARVs over single ARVs?

Key Findings

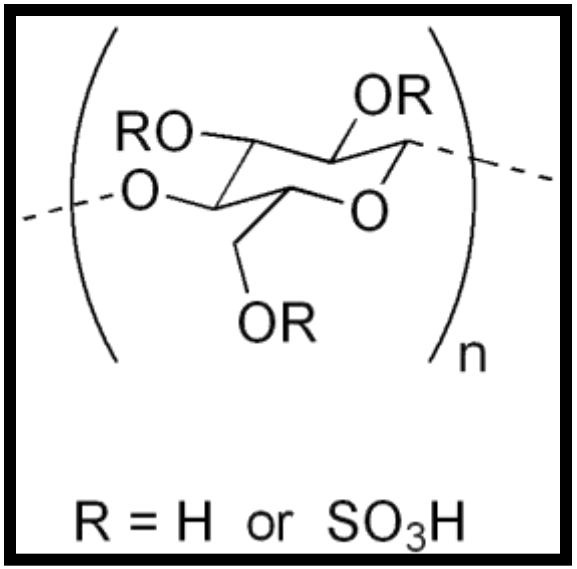
1. DS001 + DS003 is additive against HIV-1 infection
2. Tenofovir + dapivirine demonstrate synergy against wild type and drug resistant HIV-1 infection from multiple subtypes
3. Tenofovir + dapivirine synergy is stronger against dapivirine resistant 'transmission fit' HIV-1 infection (Y181C)

Microbicide development: Canadian contributions

Microbicide development: Canadian contributions

POLYDEX PHARMACEUTICALS LIMITED

Toronto, ON



Cellulose sulphate

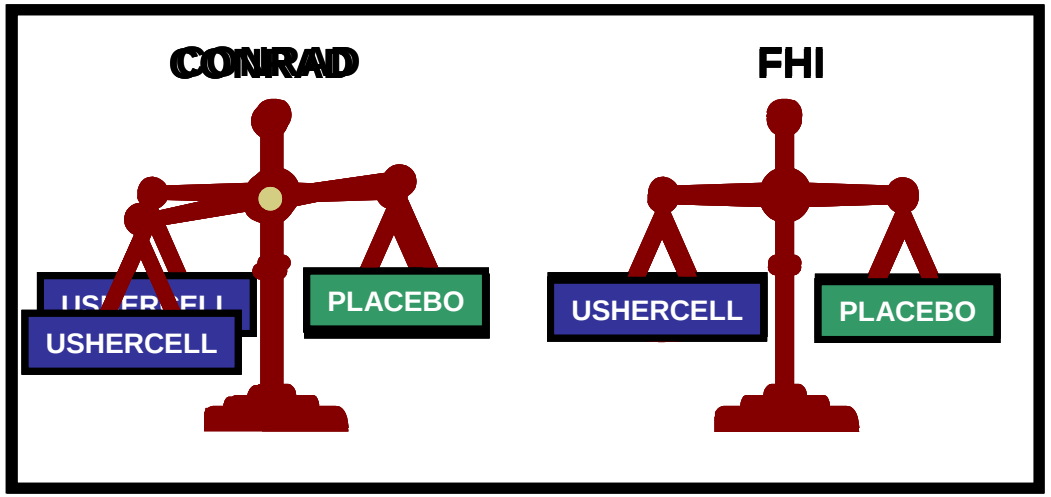
USHERCELL (6% gel)

Phase III Clinical Trials

(CONRAD study & FHI study)

Final analysis (2007)

HIV+ individuals



Conclusions

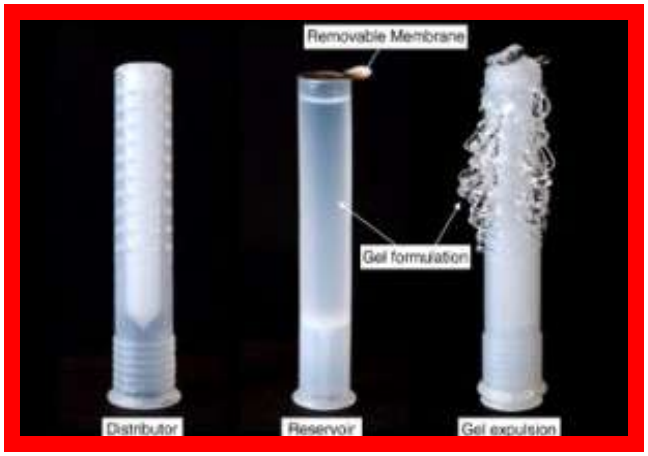
1. **increased risk of HIV seroconversion was not statistically significant**
2. **no clear benefit as an HIV microbicide**

Microbicide development: Canadian contributions

UNIVERSITÉ LAVAL

Centre de recherche en infectiologie du CHUL

Dr. Michel Bergeron and team



Invisible condom®

(sodium lauryl sulphate)

A brief history

2000

Sodium lauryl sulphate (SLS) protects non-specifically against HIV-1 and HSV infections, surfactant

SLS a potential candidate for and microbicide development

2001

SLS abrogates HIV-1 infection by interfering with viral attachment to cells

2007

Safe, tolerable and acceptable to healthy women and their male sexual partners when gel formulation applied once or twice daily for 14 days

2008

SLS in gel formulation (ethylene oxide/propylene oxide gel, 2% SLS w/w) **safe for most tissues that could be exposed under normal use** when evaluated in rats and male/female rabbits

Novel applicator design distributes Invisible condom® throughout vaginal and cervical mucosae before and after simulated intercourse

Thank you.