THE SPRING 2019 PHARMACY EDUCATIONAL MEETING:
THEME: NEW HORIZONS IN CONTEMPORARY PHARMACY PRACTICE

HIV Prevention and Drug Development: Past, Present, Future

May 4, 2019

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DHHS/NIH Disclaimer

- The views expressed are those of the presenter and do not necessarily reflect the official policies of the Department of Health and Human Services (HHS), nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Conflicts of Interest

- None to report

Investigational Products for HIV Prevention

- In this presentation, the following candidate HIV prevention products will be described:

Nonoxynol-9 gel	**PRO2000 gel**	**Tenofovir gel**
Dapivirine intravaginal ring	**Long-acting Cabotegravir injection**	

- None of these products are licensed for HIV prevention, but all have been studied for the prevention of HIV in uninfected individuals at high risk of HIV infection.

- Studies supporting the licensure of Truvada (emtricitabine/tenofovir disoproxil fumarate; FTC/TDF) for pre-exposure prophylaxis (PrEP) will also be described.

Outline of Presentation

- **Introduction**
  - Current HIV statistics
  - Sexual HIV transmission
  - Drug delivery in HIV prevention
  - HIV targets in HIV prevention
  - Timeline for HIV prevention products
- **Past:** Lessons Learned from 1st Generation HIV Prevention Products
- **Present:** Approval of Truvada for Pre-Exposure Prophylaxis and Current Products in Development
- **Future:** Multipurpose Prevention Products and Long-Acting Injectables
- **Conclusions**

Learning Objectives

- As a result of this activity, participants will be able to:
  - Describe factors that impeded further development of first generation HIV prevention products
  - Discuss clinical trial results that supported licensure of Truvada for Pre-Exposure Prophylaxis (PrEP) to prevent HIV infection
  - Explain how pharmacokinetic differences between men and women impact dosing of Truvada for PrEP
  - Recognize drug-drug interactions between Dapivirine and topical miconazole nitrate

Snapshot of HIV Infections (2016)

In the United States, there were new HIV diagnoses in every state in 2016. According to the Centers for Disease Control and Prevention (CDC):[1]

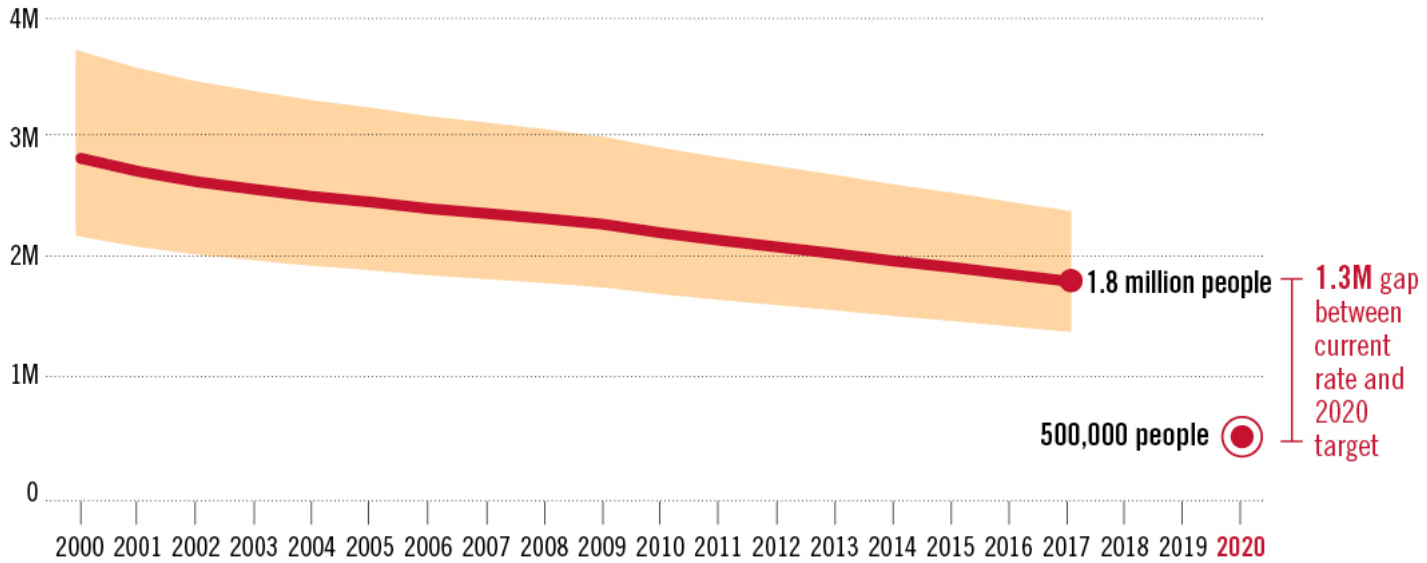
- **Approximately 1.2 million people** in the United States are living with HIV.
- **More than 39,000 people** in the United States were diagnosed with HIV in 2016.
- **Some populations have higher rates** of HIV infection:
  - **Although 37 percent of the U.S. population lives in the South**, more than half of new diagnoses (52%) and deaths (49%) among persons diagnosed occur in the South.
  - **African Americans comprise** 12 percent of the total U.S. population, yet were 44 percent of new HIV diagnoses.
  - **Latino men and women**, comprising 18 percent of the population, were 25 percent of all new HIV diagnoses.
  - **Youth ages 13 to 24 accounted for 22 percent** of all new HIV diagnoses.
- **45 percent of PWH** are over the age of 55 and are more likely to face comorbidities of HIV, aging, and/or complications of treatment.

The United Nations General Assembly declared the AIDS pandemic "a global emergency and one of the most formidable challenges to human life and dignity…which undermines social and economic development throughout the world and affects all levels of society—national, community, family, and the individual." According to the joint United Nations Programme on HIV/AIDS (UNAIDS), in 2016:[4]

- **36.7 million people globally** were living with HIV.
- **1.8 million people** were newly infected with HIV.
- **Approximately 1 million people** died from AIDS-related illnesses.
- **Only 19.5 million people**, slightly more than half (53%) of those living with HIV, were using ART.
- **In 2015, 1.8 million children under 15** years of age were living with HIV worldwide.
- **An estimated 160,000 children** acquired HIV globally in 2016.[5]

(from CDC & UNAIDS)

Global HIV Infections and 2020 Target



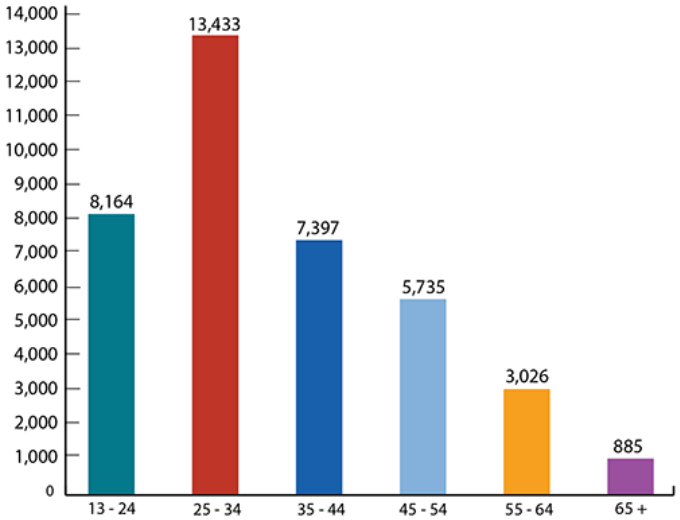
Source: UNAIDS. *Miles to Go—Closing gaps, breaking barriers, righting injustices.* July 2018. Accessible at: *www.unaids.org/en/resources/documents/2018/global-aids-update.*

AVAC Report 2018: No Prevention, No End
www.avac.org/report2018

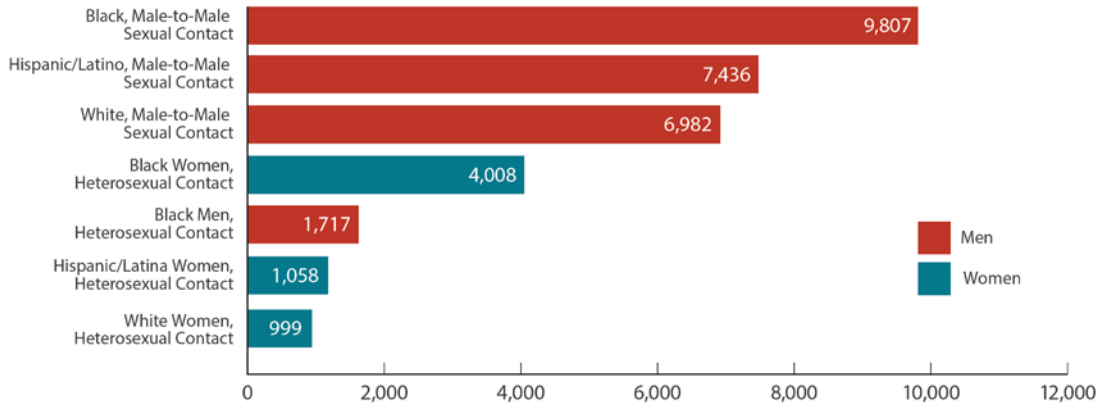
New HIV Diagnoses in the U.S. (2017)

- 38,739 people received an HIV diagnosis in the U.S.
- The annual number of new HIV infections remained stable between 2012 and 2016.

Age Distribution



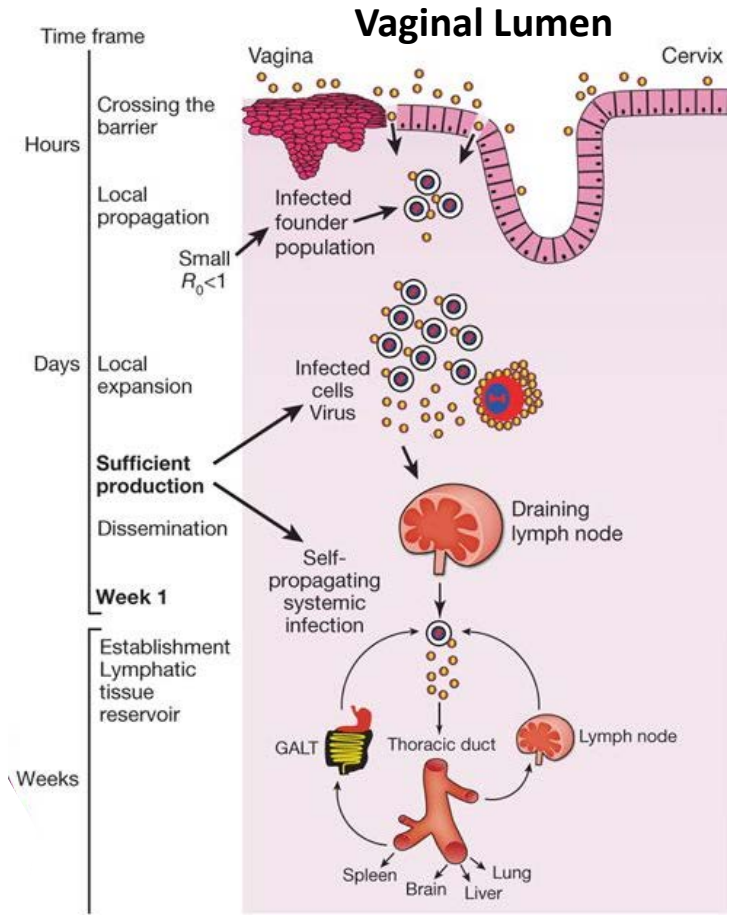
Most-Affected Subpopulations

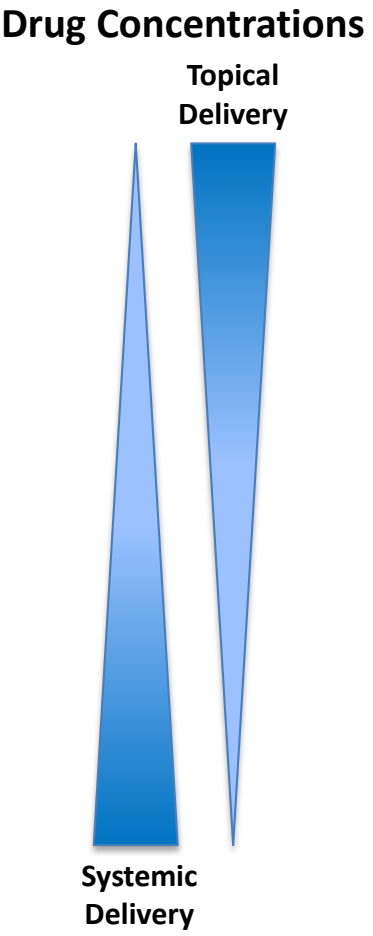


(from CDC *HIV Surveillance Report* 2018:29)

Sexual HIV Transmission

- After sexual exposure, HIV must be blocked within the mucosa to prevent dissemination and establishment of a lymphatic tissue reservoir.
- To prevent sexual transmission, drug concentrations that block HIV infection must be maintained within the mucosa.



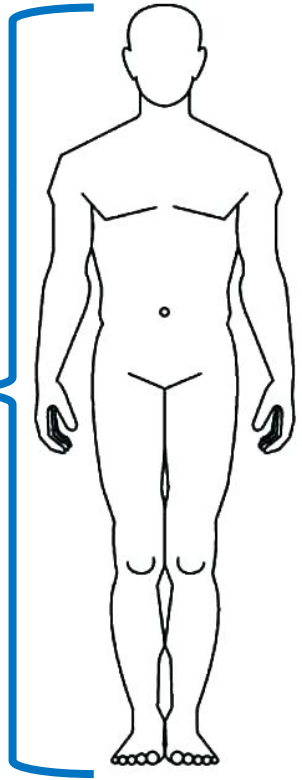


(from *Nature* 2010; 464: 217-23)

Drug Delivery in HIV Prevention

Systemic Delivery

Protects against all potential routes of exposure



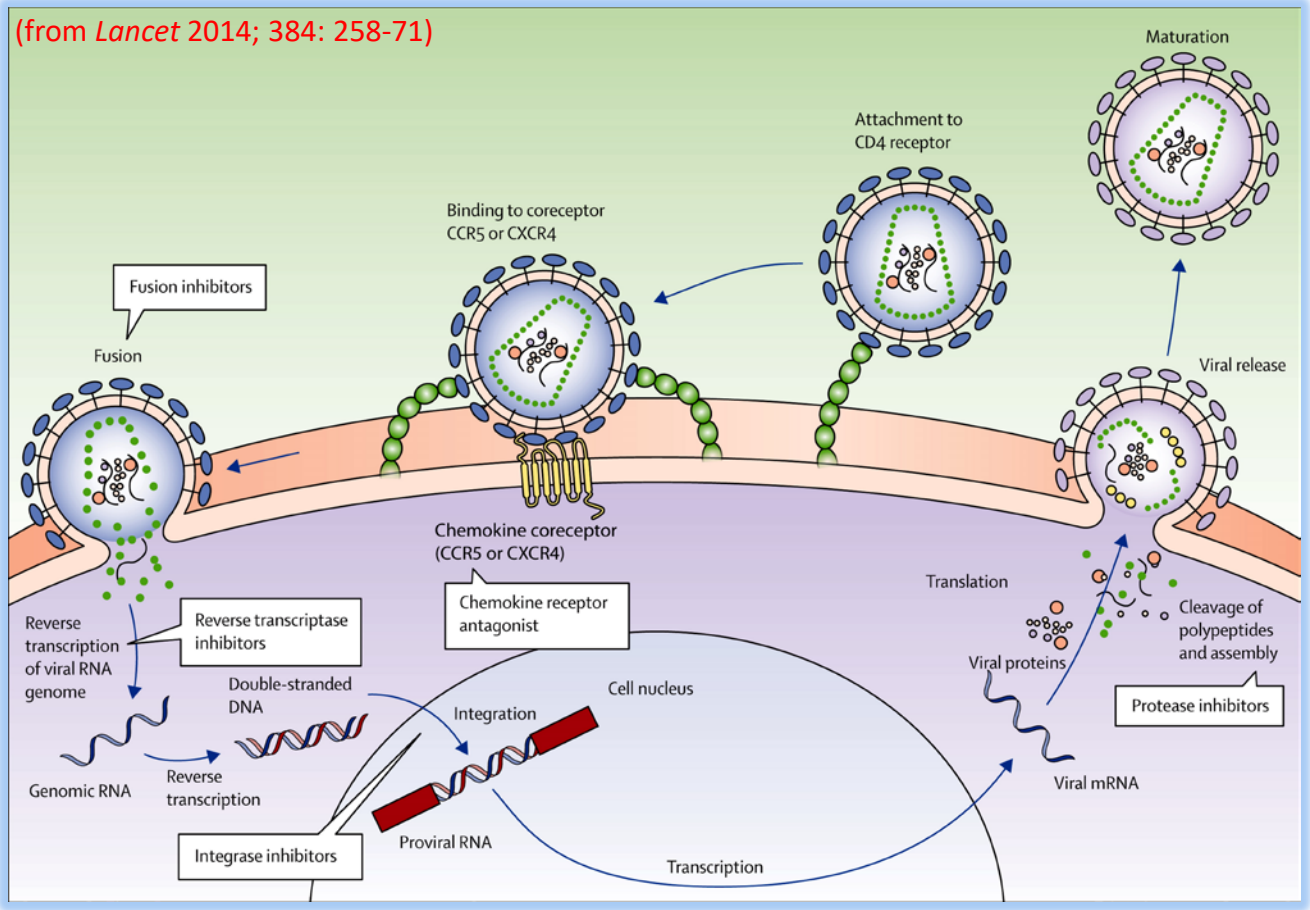
Topical Delivery

Protects against mucosal exposure

- **Right Drug**
- **Right Amount**
- **Right Place**
- **Right Time**

HIV Drug Targets in HIV Prevention

- **Virus itself**
  - Nonoxynol-9
- **Virus attachment**
  - PRO2000
- **Reverse Transcription**
  - Tenofovir
  - Dapivirine
  - Truvada
- **Integration**
  - Cabotegravir



Timeline for HIV Prevention Products

Systemic Products

Concept for Topical Microbicide (1990)

Truvada (FTC/TDF) pill

2007-2014

Cabotegravir injection

2016-2022

Virucide | Entry Inhibitors | Antiretroviral Drugs

Nonoxynol-9 gel

1996 - 2000

PRO2000 gel

2005-2009

Dapivirine IVR

2012-2016

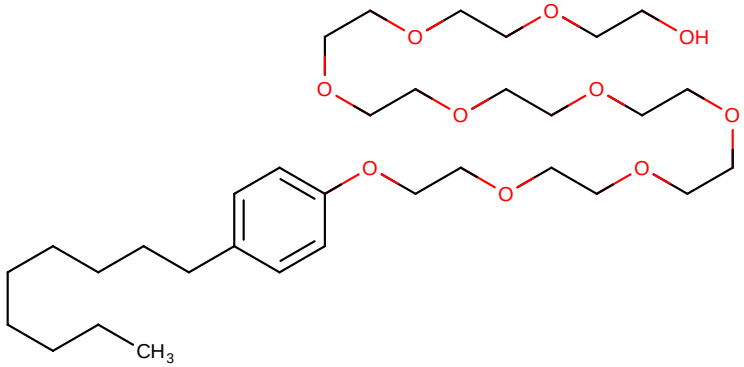
Tenofovir gel

2007-2014

Topical Products

Nonoxynol-9 Gel

- **Drug Class**: Surfactant used as a vaginal spermicide (available in OTC formulations)
- **Mechanism of Action**
  - Interacts with the lipids in the membranes of HIV virions – inhibits HIV *in vitro*
- **Formulation/Dosing**
  - Topical gel (3.5% w/w) applied vaginally with each sex act
- **Clinical Studies**
  - **COL-1492:** Phase 2/3 study in 892 female sex workers (≥16 years of age) in Africa and Thailand (1996-2000)
- **Sponsors**: UNAIDS & Columbia Laboratories



Molecular Weight: 616.8

$C_{33}H_{60}O_{10}$

Nonoxynol-9 Gel: Clinical Trial Results

COL-1492 Trial: HIV Incidence per treatment group & frequency of use

Nonoxynol-9			Placebo				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Hazard Ratio (95% CI)	p
376	59	14.7	389	45	10.3	1.5 (1.0-2.2)	0.047

	Nonoxynol-9		Placebo			
Gel Use (#/day)	Seroconversions	HIV incidence per 100 woman-years	Seroconversions	HIV incidence per 100 woman-years	Hazard Ratio (95% CI)	p
Low (<1.5)	13	10.9	13	10.2	1.1 (0.54-2.4)	0.87
Medium (1.5-3.5)	13	7.4	11	6.5	1.3 (0.6-2.9)	0.56
High (>3.5)	33	30.6	20	14.5	1.8 (1.0-3.2)	0.03

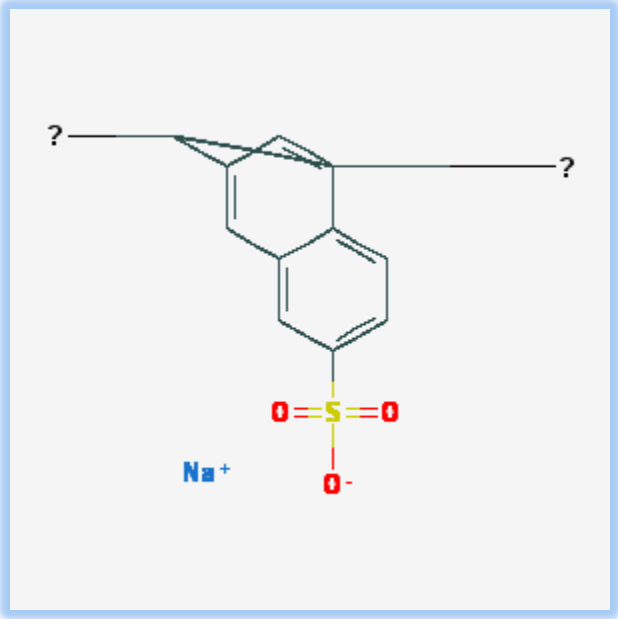
(from *Lancet* 2002; 360: 971-77)

Nonoxynol-9 Gel: Conclusions

- The COL-1492 study did not show a protective effect of Nonoxynol-9 gel on HIV transmission in high-risk women.
  - Frequent use of Nonoxynol-9 gel was associated with an increased risk of HIV transmission.
  - Frequent use of Nonoxynol-9 gel was associated with epithelial lesions (cervix, vagina, and vulva).
- Development of Nonoxynol-9 gel as an HIV prevention method was discontinued.

PRO2000 Gel

- **Drug Class**: Napthalene sulfonate polymer
- **Mechanism of Action**
  - Inhibits binding of HIV to target cell receptors (gp120 binding to CD4)
- **Formulation/Dosing**
  - Topical gel (0.5% or 2.0% w/w) applied vaginally 1 hr before each sex act
- **Clinical Studies**
  - **HPTN-035:** Phase 2/2b study in 3101 women (≥18 years of age) in Africa and USA (2005-2009)
  - **MDP-301:** Phase 3 study in 9385 women (≥16 years of age) in Africa (2005-2009)
- **Sponsors**: NIH & Endo Pharmaceuticals



Molecular Weight: 5 kDa

PRO2000 Gel: Clinical Trial Results

HPTN-035 Trial: HIV Incidence per treatment group

PRO2000			Placebo				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Hazard Ratio (95% CI)	p
764	36	2.7	760	51	3.9	0.70 (0.46-1.08)	0.10

(from *AIDS* 2011; 25: 957-66)

MDP-301 Trial: HIV Incidence per treatment group

PRO2000			Placebo				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Hazard Ratio (95% CI)	p
3156	130	4.5	3112	123	4.3	1.05 (0.82-1.34)	0.71

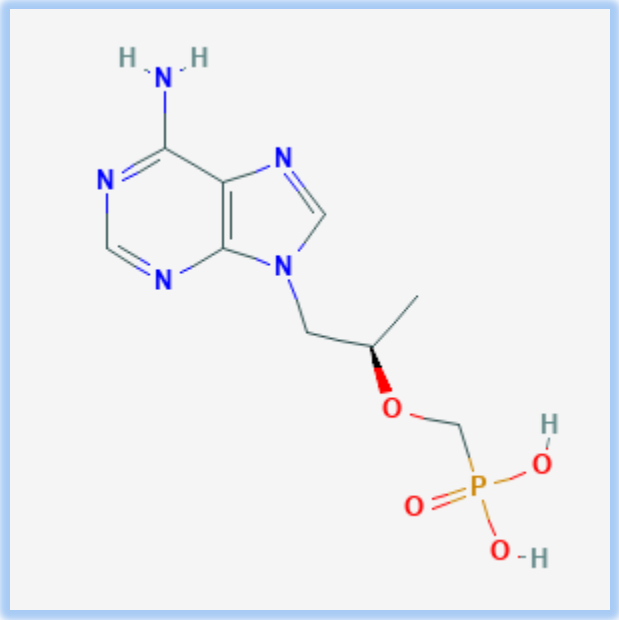
(from *Lancet* 2010; 376: 1329-37)

PRO2000 Gel: Conclusions

- Although the HPTN-035 study showed a modest protective effect of PRO2000 gel on HIV transmission (~30%) in high-risk women, the results were not statistically significant.
- The MDP-310 study did not show a protective effect of PRO2000 gel on HIV transmission in high-risk women.
- Development of PRO2000 gel as an HIV prevention method was discontinued.

Tenofovir Gel

- **Drug Class**: Nucleoside Reverse Transcriptase Inhibitor (NRTI)
- **Mechanism of Action**
  - Inhibits the activity of reverse transcriptase, a viral DNA polymerase required for HIV replication
- **Formulation/Dosing**
  - Topical gel (1% w/w) applied vaginally before & after sex (within 12 hr) or applied daily
- **Clinical Studies**
  - **CAPRISA-004:** Phase 2b study in 889 women (18-40 years of age) in Africa (2007-2010)
  - **MTN-003/VOICE:** Phase 2b study in 5029 women (18-45 years of age) in Africa (2009-2012)
  - **FACTS-001:** Phase 3 study in 2059 women (18-30 years of age) in Africa (2011-2014)
- **Sponsors**: CAPRISA, NIH, & CONRAD



Molecular Weight: 287.2
$C_9H_{14}N_5O_4P$

Tenofovir Gel: Clinical Trial Results

CAPRISA 004 Trial: HIV Incidence per treatment group

Tenofovir Gel			Placebo Gel				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Incident Rate Ratio	p
422	38	5.6	421	60	9.1	0.61	0.017

(from *Science* 2010; 329: 1168-74)

MTN-03/VOICE Trial: HIV Incidence per treatment group

Tenofovir Gel			Placebo Gel				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Hazard Ratio (95% CI)	p
996	61	6.0	996	70	6.8	0.85 (0.61-1.21)	0.37

(from *N Eng J Med* 2015; 372: 509-18)

Tenofovir Gel: Clinical Trial Results (continued)

FACTS-001 Trial: HIV Incidence per treatment group

Tenofovir Gel			Placebo Gel				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Incidence Rate Ratio (95% CI)	p
935	61	4.0	934	62	4.0	0.98 (0.7-1.4)	0.95

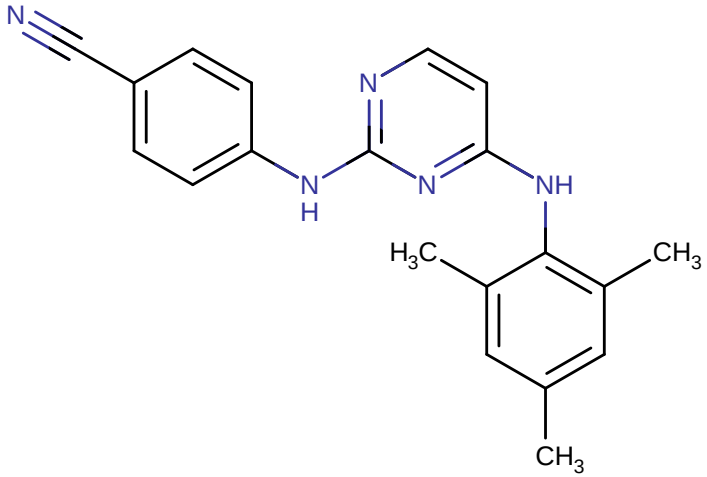
(from *Lancet* 2018; 18: 1241-50)

Tenofovir Gel: Conclusions

- The CAPRISA-004 study showed a modest protective effect of Tenofovir gel on HIV transmission (~39%) in high-risk women.
- The MTN-03/VOICE* and FACTS-001 studies did not show a protective effect of Tenofovir gel on HIV transmission in high-risk women.
  - *Major issue was product adherence: Tenofovir was only detected in 25% of available plasma samples from women using the gel (vs. 83-90% adherence based on product counts and interviews).
- Development of Tenofovir gel as an HIV prevention method was discontinued.

Dapivirine Intravaginal Ring (IVR)

- **Drug Class**: Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
- **Mechanism of Action**
  - Inhibits the activity of reverse transcriptase, a viral DNA polymerase required for HIV replication
- **Formulation/Dosing**
  - Intravaginal ring (25 mg) worn 28 days
- **Clinical Studies**
  - **MTN-020/ASPIRE:** Phase 3 study in 2629 women (18-45 years of age) in Africa (2012-2015)
  - **IPM-027/The Ring Study:** Phase 3 study in 1959 women (18-45 years of age) in Africa (2012-2016)
- **Sponsor**: International Partnership for Microbicides, Inc.



Molecular Weight: 329.4

$C_{20}H_{19}N_5$

Dapivirine IVR: Clinical Trial Results

MTN-020/ASPIRE Trial: HIV Incidence per treatment group

Dapivirine IVR			Placebo IVR				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Effectiveness (95% CI)	p
1308	71	3.3	1306	97	4.5	27% (1-46)	0.05

(from *N Eng J Med* 2016; 375: 2121-32)

IPM-027/The Ring Trial: HIV Incidence per treatment group

Dapivirine IVR			Placebo IVR				
n	Seroconversions	HIV incidence per 100 woman-years	n	Seroconversions	HIV incidence per 100 woman-years	Hazard Ratio (95% CI)	p
1307	77	4.1	652	56	6.1	0.69 (0.49-0.99)	0.04

(from *N Eng J Med* 2016; 375: 2133-43)

Dapivirine IVR: Conclusions

- The MTN-020/ASPIRE study showed a modest protective effect of Dapivirine IVR on HIV transmission (~27%) in high-risk women.
  - In post hoc analysis, a higher rate of HIV protection (~56%) was observed in women over 21 years of age (CI 31-71; $p<0.001$) with a higher rate of product adherence (~70%) vs. women <21 years of age.
- The IPM-027/The Ring Study showed a modest protective effect of Dapivirine IVR on HIV transmission (~31%) in high-risk women.
- The Dapivirine IVR is the first topical microbicide submitted for regulatory approval by the European Medicines Agency under Article 58. An opinion is expected by mid-2019.

Dapivirine IVR: Drug-Drug Interactions

- An open-label, randomized, cross-over trial was conducted in 36 women (18-40 years of age):
  - Participants used the Dapivirine IVR alone or together with a single dose of miconazole nitrate (1200 mg vaginal capsule).
  - A single dose of miconazole nitrate was administered alone as a third treatment.
  - Washout periods of 3 weeks were included between treatments.
- Dapivirine and miconazole concentrations were determined in plasma and vaginal secretions, and residual Dapivirine levels were assessed in used rings.

(from *AIDS Res Hum Retrovir* 2014; 30 Suppl 1(S1):A144)

Dapivirine IVR: Drug-Drug Interactions (continued)

- A single vaginal dose of miconazole nitrate:
  - Increased the systemic exposure (C_{max} and AUC) of Dapivirine by 20% at the time of Dapivirine IVR insertion
  - Decreased cervicovaginal fluid levels of Dapivirine up to 14 days post-IVR insertion (decreases of 26% in C_{max} and 69% in $AUC_{0\text{-}24h}$)
- No significant difference was observed between residual levels of Dapivirine in used IVRs with and without concomitant miconazole use, suggesting similar Dapivirine release.
- Dapivirine cervicovaginal fluid levels remained at least 100x higher than the *in vitro* IC_{99} in cervical tissue (3.3 ng/mL).

(from *AIDS Res Hum Retrovir* 2014; 30 Suppl 1(S1):A144)

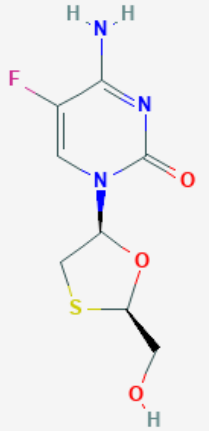
Dapivirine IVR: Drug-Drug Interactions (continued)

- Local and systemic miconazole exposure was increased after co-administration with the Dapivirine IVR (1.4 to 6-fold higher).
- Concomitant use of the two products was safe and well-tolerated.
- Although these changes are considered unlikely to affect efficacy of either drug, studies are underway to determine the cause (e.g., role of drug transporters).

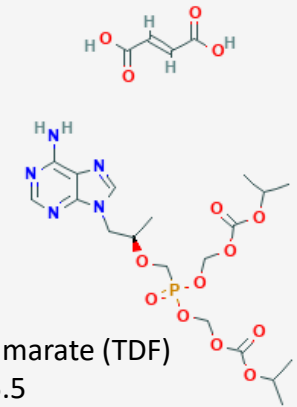
(from *AIDS Res Hum Retrovir* 2014; 30 Suppl 1(S1):A144)

Truvada Pill

- **Drug Class**: Nucleoside Reverse Transcriptase Inhibitor (NRTI)
- **Mechanism of Action**
  - Inhibits the activity of reverse transcriptase, a viral DNA polymerase required for HIV replication
- **Formulation/Dosing**
  - Oral tablet (200 mg FTC/300 mg TDF) taken daily
- **Clinical Studies**
  - **iPrEx:** Phase 3 study in 2499 MSM and transgender women (>18 years of age) in Americas, Asia, and Africa (2007-2014)
  - **Partners PrEP:** Phase 3 study in 4758 uninfected men and women (serodiscordant couples; 18-65 years of age) in Africa (2008-2013)
- **Sponsors**: NIH and University of Washington



Emtricitabine (FTC)
Molecular Weight: 247.2
$C_8H_{10}FN_3O_3S$



Tenofovir Disoproxil Fumarate (TDF)
Molecular Weight: 635.5
$C_{23}H_{34}N_5O_{14}P$

Truvada Pill: Clinical Trial Results

iPrEx Trial: HIV Incidence per treatment group, overall

Truvada Pill			Placebo Pill				
n	Seroconversions		n	Seroconversions		Effectiveness (95% CI)	p
1224	36		1217	64		44% (15-63)	0.005

(from *N Eng J Med* 2010; 363: 2587-99)

Partners PrEP Trial: HIV Incidence per treatment group, overall

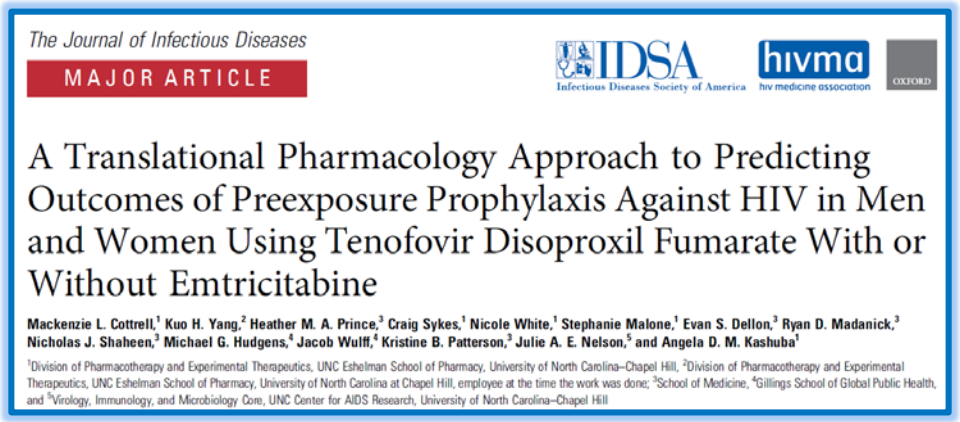
Truvada Pill			Placebo Pill				
n	Seroconversions	HIV incidence per 100 person-years	n	Seroconversions	HIV incidence per 100 person-years	Effectiveness (95% CI)	p
1576	13	0.5	1578	52	1.99	75% (55-87)	0.001

(from *N Eng J Med* 2012; 367: 399-410)

Truvada Pill: Differences in Men and Women

- Despite the efficacy observed in iPrEx and Partners PrEP, other clinical studies (FEM-PrEP) indicated that low adherence in women was linked to lack of efficacy.
  - Plasma drug concentrations in women indicated that only 24-30% of the women had recently used the product.
- Yet, in a cohort of men from iPrEx, plasma drug concentrations indicated that only 28% had recently used the product.
  - Subsequent analysis revealed drug exposure consistent with 2-3 doses/week achieved 75-90% protection in men.

Truvada Pill: Differences in Men and Women (continued)



The Journal of Infectious Diseases
MAJOR ARTICLE

A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine

Mackenzie L. Cottrell,[1] Kuo H. Yang,[2] Heather M. A. Prince,[3] Craig Sykes,[1] Nicole White,[1] Stephanie Malone,[1] Evan S. Dellon,[3] Ryan D. Madanick,[3] Nicholas J. Shaheen,[3] Michael G. Hudgens,[4] Jacob Wulff,[4] Kristine B. Patterson,[3] Julie A. E. Nelson,[5] and Angela D. M. Kashuba[1]

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina–Chapel Hill, [2]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, employee at the time the work was done; [3]School of Medicine, [4]Gillings School of Global Public Health, and [5]Virology, Immunology, and Microbiology Core, UNC Center for AIDS Research, University of North Carolina–Chapel Hill

- A translational pharmacology model was used to predict PrEP outcomes in men and women.
  - Measured tissue concentrations (colorectal and female genital tract tissues) of TFV, FTC, and active metabolites (TFVdp and FTCtp)
  - Modeled the effective concentration of the active metabolites (EC_{90}) for protection against HIV

(from *J Infect Dis* 2016; 214: 55-64)

Truvada Pill: Differences in Men and Women (continued)

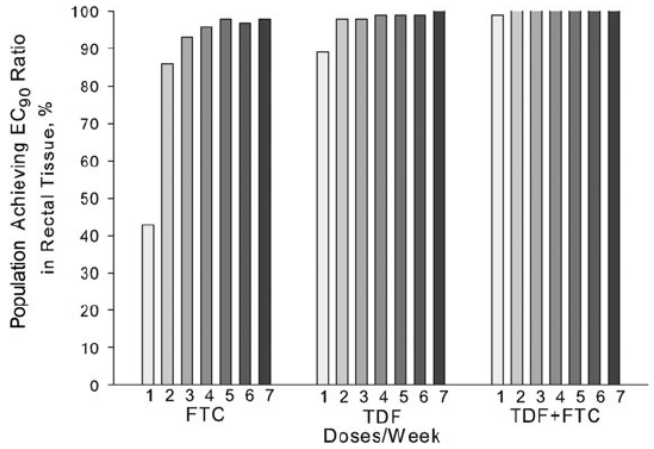
Results from Evaluating Truvada in a Translational Pharmacology Model

Factor Evaluated	Outcome
TFVdp concentration in tissues	10x higher in colorectal vs. cervicovaginal tissues
Endogenous nucleotides (that compete for active metabolites)	7-11x lower in colorectal vs. cervicovaginal tissues
Model predictions	≥98% of the population achieved protective tissue exposure by the third daily dose of FTV/TDF
Minimum adherence (i.e., # doses/ week) required to protect tissue	2 of 7 doses/week (28%) protected colorectal tissue vs. 6 of 7 doses (85%) required to protect cervicovaginal tissue

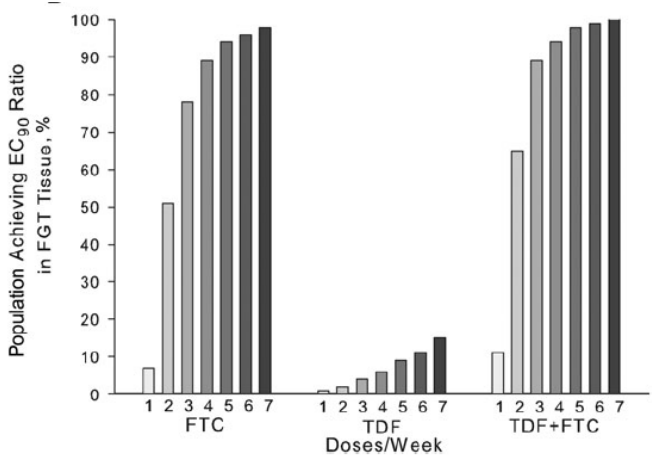
(from *J Infect Dis* 2016; 214: 55-64)

Truvada Pill: Differences in Men and Women (continued)

Time to protection as determined by pharmacokinetic/pharmacodynamic simulations for colorectal tissue and lower female genital tract tissue



Colorectal Tissue



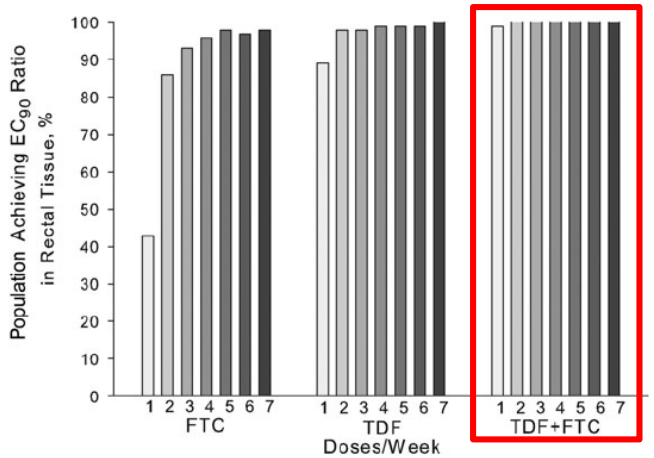
Female Genital Tract (FGT) Tissue

Percentage of the population achieving effective drug concentrations (EC_{90} ratios) with 1-7 doses/week of FTC, TDF, and TDF-FTC stratified by tissue type

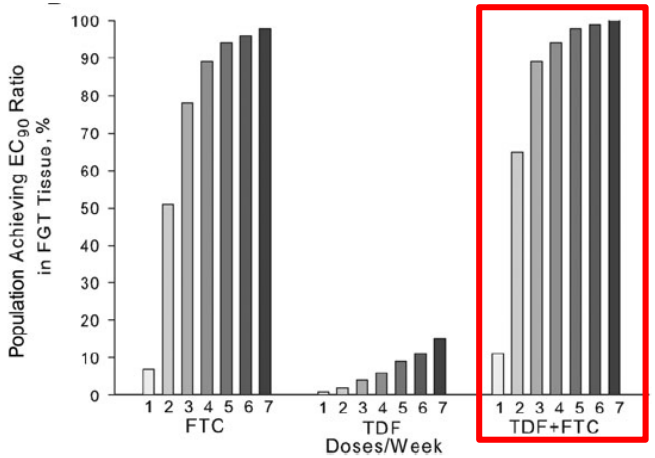
(from *J Infect Dis* 2016; 214: 55-64)

Truvada Pill: Differences in Men and Women (continued)

Time to protection as determined by pharmacokinetic/pharmacodynamic simulations for colorectal tissue and lower female genital tract tissue



Colorectal Tissue



Female Genital Tract (FGT) Tissue

Percentage of the population achieving effective drug concentrations (EC_{90} ratios) with 1-7 doses/week of FTC, TDF, and TDF-FTC stratified by tissue type

(from *J Infect Dis* 2016; 214: 55-64)

Truvada Pill: Differences in Men and Women (continued)

Predictions from Evaluating Truvada in a Translational Pharmacology Model

Model Predictions
The maximal percentage of the population achieved EC_{90} ratios by the third daily dose of TDF+FTC
Consistent use (7 doses/week) will achieve EC_{90} ratios in 100% of the population in both tissue types
Only 65% of the population using 2 doses/week achieved target exposure in FGT tissue but >95% using 2 doses/week achieved target exposure in colorectal tissue

(from *J Infect Dis* 2016; 214: 55-64)

Truvada Pill: Conclusions

- The iPrEx study showed a modest protective effect of Truvada pill on HIV transmission (~44%) in high-risk men and transgender women.
- The Partners PrEP showed a high protective effect of Truvada pill on HIV transmission (~75%) in high-risk men and women.
- iPrEx and Partners PrEP participants with measurable drug levels (i.e., the most adherent) had ~90% decreased chance of HIV infection.
- Based on these studies, in 2012 the U.S. FDA approved Truvada pill for PrEP to reduce the risk of sexually acquired HIV infection in adults at high risk.
- A translational pharmacology model indicates that women should adhere to the daily Truvada regimen to maintain maximum protection against HIV infection.

Future: Multipurpose Prevention Technologies

- Multipurpose Prevention Technologies (MPTs) are an innovative class of products that deliver varied combinations of HIV prevention, other sexually transmitted infection (STI) prevention, and contraception.

- MPTs in development include:

  - Longer-acting vaginal rings
  - Fast-dissolving films and tablets
  - Innovative and effective gels
  - Injectables that combine contraception and protection against infection
  - Nanofiber delivery systems

- Product adherence may be higher for products with multiple indications.

Future: Multipurpose Prevention Technologies (continued)

MPT Product Development: Many possibilities for MPT development			
Indications	**Delivery Modes**	**Mechanisms of Action**	**Dosage & Administration**
BV*	Diaphragm*	Anti-microbial*	Oral daily*
Candida	Film*	Anti-fungal	Oral on-demand Gel*
Chlamydia*		Anti-viral*	Systemic sustained*
Gonorrhea*	Implant	Barrier*	Topical daily*
HIV*	Injection*	HC *	Topical on-demand*
HPV*	Intrauterine Device	Non-HC*	Topical sustained
HSV*	Oral pill*	Probiotic	
Pregnancy*	Ring (Non-IVR)		
Syphilis	Ring (IVR)*	*Currently being tested in human clinical trials.	
Trichomoniasis	Tablet*		

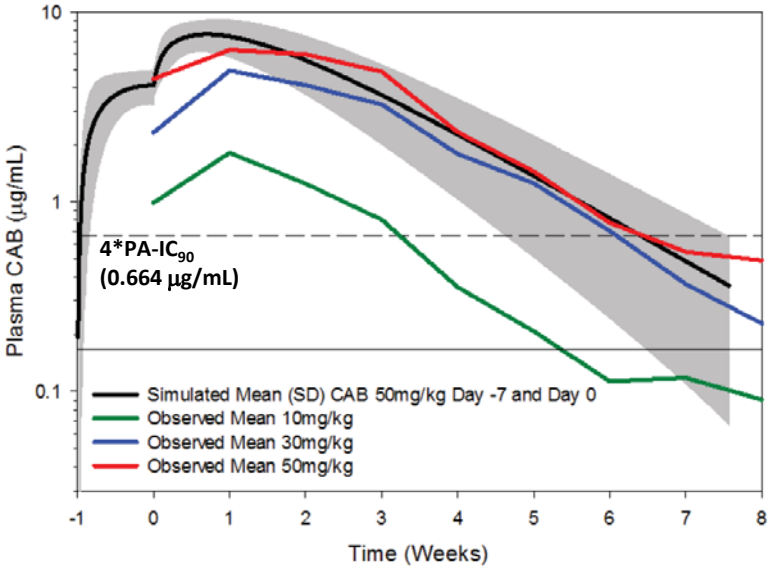
(from *MPTs: An Introductory Factsheet.* 2016. AVAC)

Future: Long-acting Injectables

- Long-acting injectables are an innovative class of products in which an antiretroviral drug (ARV) is delivered by an injection and persists within the body for an extended period of time.
- For HIV prevention, the goal is to develop an injectable-only regimen that would minimize adherence requirements.
- Ideal products should contain a potent ARV with a long half-life that allows for less frequent dosing.
- Preclinical data and studies in nonhuman primates indicated that Cabotegravir was an ideal candidate when formulated as a long-acting injectable.

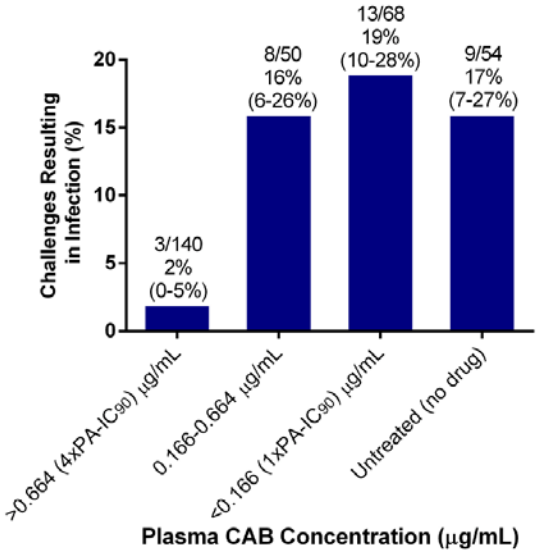
Cabotegravir Long-Acting Injection

Protective Levels of Cabotegravir in a Rhesus Macaque Model of Infection



Plasma concentrations of Cabotegravir (CAB) within each dose group (10, 30, & 50 mg/kg) compared to the predicted concentration at 50 mg/kg following two IM injections in rhesus macaques.

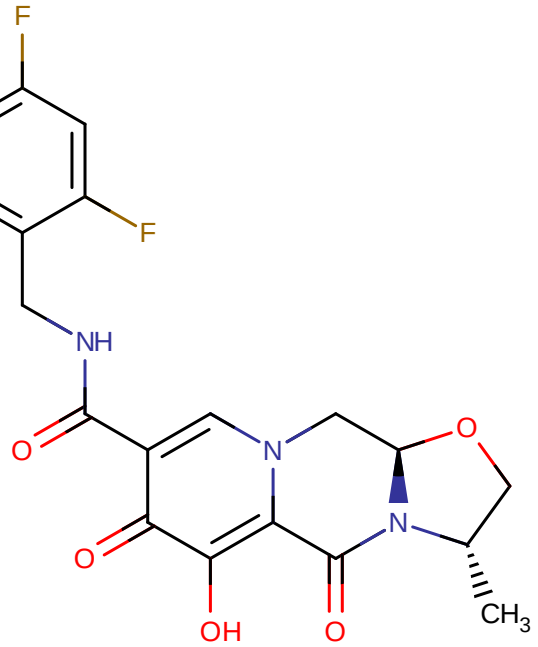
(Presented at CROI 2015, Seattle, WA, Poster 966LB)



Rate of SIV infection within various ranges of CAB plasma concentrations. The numbers above the bars represent the number of infections/ number of challenges within a plasma concentration range, percentages indicate the infection rate (+/- 95% CI).

Cabotegravir Long-Acting Injection (continued)

- **Drug Class**: Integrase inhibitor
- **Mechanism of Action**
  - Inhibits integrase, an HIV enzyme required for HIV integration and replication
- **Formulation/Dosing**
  - Long-acting injectable: 600 mg (3 mL) every 8 weeks
- **Clinical Studies (Ongoing):**
  - **HPTN-083**: Phase 2b/3 study in 4500 MSM and transgender women (≥18 years of age) in the USA (2016-2022)
  - **HPTN-084**: Phase 3 study in 3200 women (18-45 years of age) in Africa (2017-2022)
- **Sponsor**: NIH



Molecular Weight: 405.4

$C_{19}H_{17}F_2N_3O_5$

Conclusions

- Lack of efficacy and potential toxicity impeded further development of the 1st generation of HIV prevention products (PRO2000 gel and Nonoxynol-9 gel).
- Despite modest efficacy in one clinical trial, lack of product adherence in larger studies impeded further development of Tenofovir gel.
- The Dapivirine IVR is the first topical microbicide submitted for regulatory approval by the European Medicines Agency under Article 58.
  - Drug-drug interactions between Dapivirine and miconazole are currently being investigated.

Conclusions
(continued)

- Truvada pill is the only product approved by FDA for PrEP to reduce the risk of sexually acquired HIV infection in adults at high risk.
  - Available clinical trial data and modeling studies indicate that women should follow the recommended daily Truvada regimen to maintain protection against HIV.
- MPTs offer an innovative approach to combine HIV/STI prevention with contraception – with a product profile that may drive uptake and adherence.
- Long-acting injectables may offer a dosing regimen that minimize adherence requirements by allowing less frequent dosing.

Acknowledgments

Division of AIDS

NIH National Institute of Allergy and Infectious Diseases

- Jim Turpin
- Sheryl Zwerski
- Lester Freeman (C)

ABL inc. ADVANCED BIOSCIENCE LABORATORIES

- Ranajit Pal
- HK Chung
- Sharon Orndorff
- Glenn Swartz

ViiV Healthcare

- Susan Ford
- William Spreen

Supported by NIAID Contract: HHSN272200800020C, "Non-human Primate Models to Evaluate Therapeutic Strategies and Topical Microbicides for HIV"

Note: ABL conducted the nonhuman primate study with Cabotegravir provided by ViiV Healthcare.

Questions