Human Immunodeficiency Virus
HIV-1

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HIV continues to devastate

- At end of 2010, more than 34 million people living with HIV worldwide
- 7,000 new HIV infections daily; 2.6 million per year
- For every 1 person put on treatment, 2 people become infected
- 30 million AIDS-related deaths to date
- 260,000 children die of AIDS every year

1981
First cases of AIDS

1984
HIV discovered as the causal agent

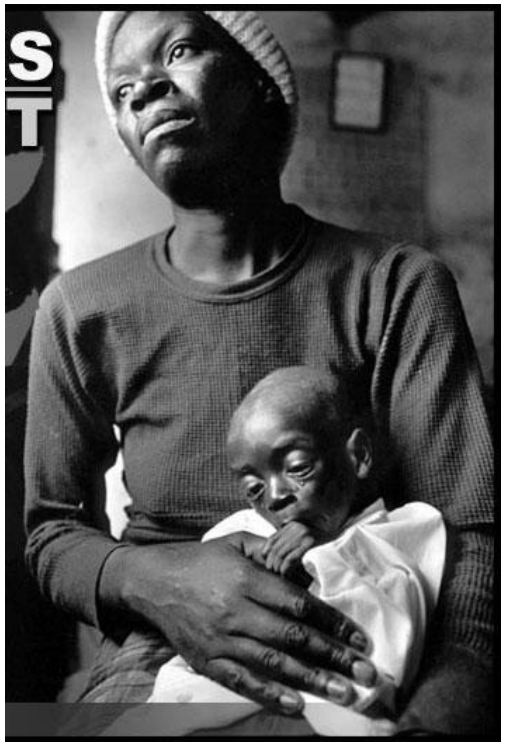
1990
7.5 million people living with HIV

1996
•Introduction of anti-retroviral therapy
•20 million people living with HIV

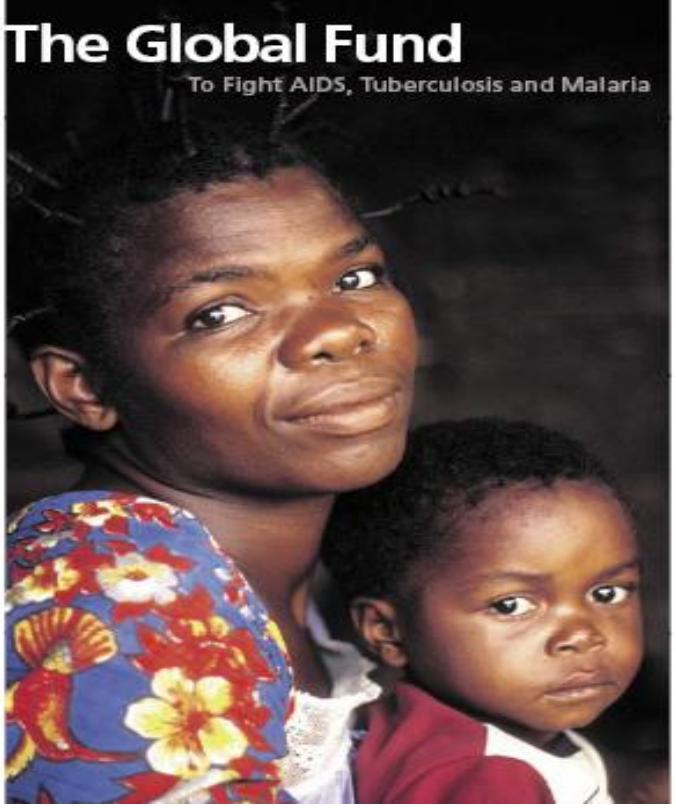
2000
28.5 million

2005
32 million

2010
34 million



Source: Joint United Nations Programme on HIV/AIDS



- HIV prevalence (33 million) constant at 0.8% of global population since 2001
- 6.6 million are now on antiretroviral treatment (ART)
- 9 million are waiting to receive it
- For every person starting ART two people are newly infected
- 20 million more people predicted to acquire HIV by 2031
- increasing potential treatment costs up to $35 billion a year[2].

"Successful provision of **universal treatment access** may be critically dependent on reducing the number of new infections"

1. UNAIDS, *AIDS at 30: Nations at the Crossroads* (2011)
2. R. Hecht *et al*., *Lancet* **376**, 1254 (2010).

Risks of HIV-1 transmission

Sexual

• Male to male	1/10 - 1/1600
• Female to male	1/700 - 1/3000
• Male to female	1/200 - 1/2000

Other

• Perinatal	1/3 - 1/4
• Isolated needle stick	1/200 - 1/300
• Blood transfusion (USA, average)	1/493,000
• Transfusion of infected blood	~ 1/1

Schreiber et al.1996. NEJM 334, 1685; Royce et al. 1997. NEJM 336, 1072

Transmission of HIV-1: Biological Requirements

Infectiousness  Susceptibility

The main route of HIV transmission continues to be sexual.

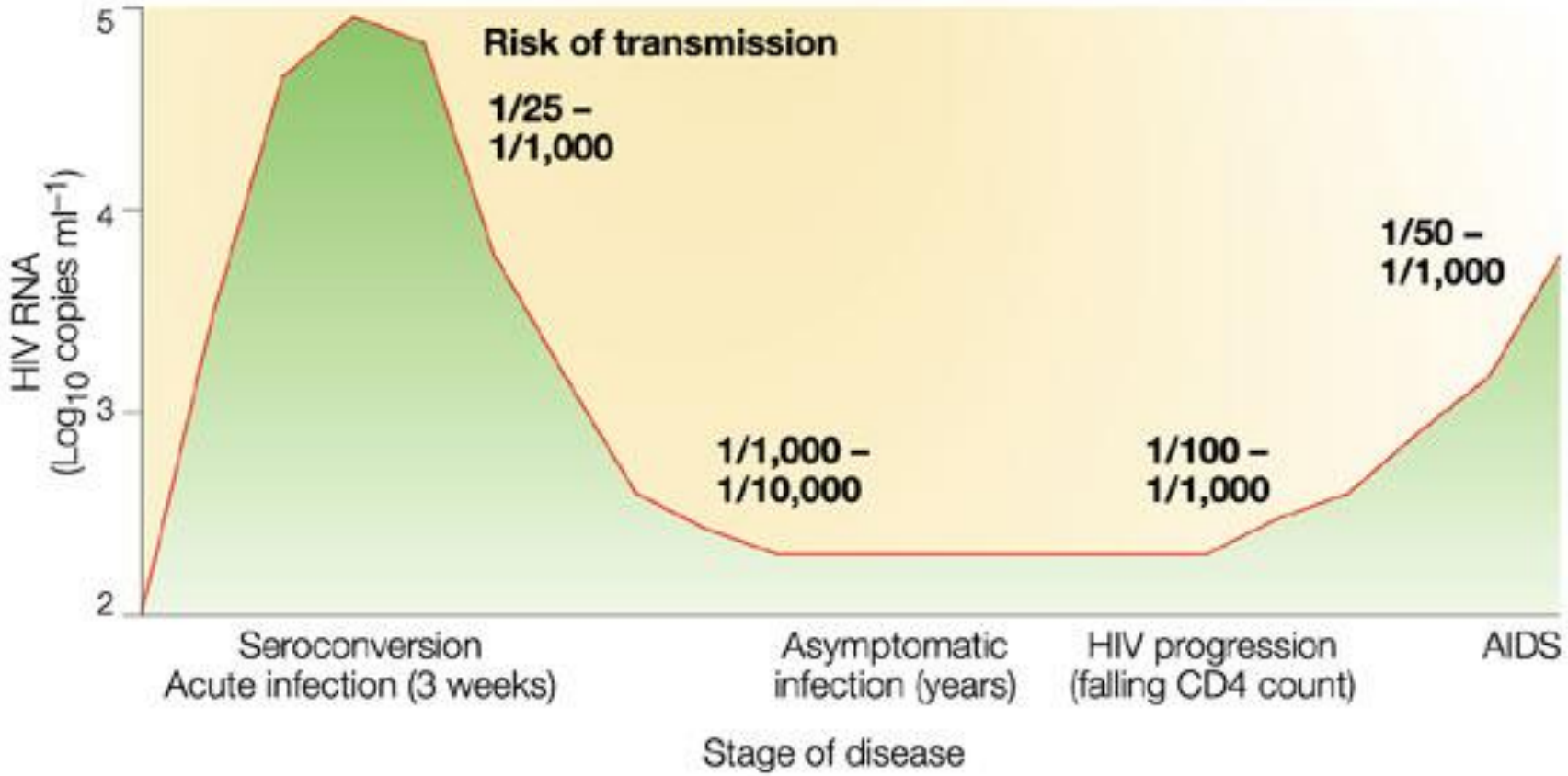
Yet it seems difficult to understand how an organism that appears to require 500-1000 episodes of intercourse for transmission could be so far reaching

Factors That Increase Transmission Across Mucosal Surfaces

High viral load during primary HIV-1 infection in the index partner
High viral load during end-stage HIV-1 disease in the index partner
Mucosal trauma, inflammation, erosion, or ulcer in the recipient partner
Mucosal infection in the recipient partner
Increased frequency of sexual contacts
Unprotected sexual contact
Receptive anal intercourse
Absence of circumcision in a male index partner

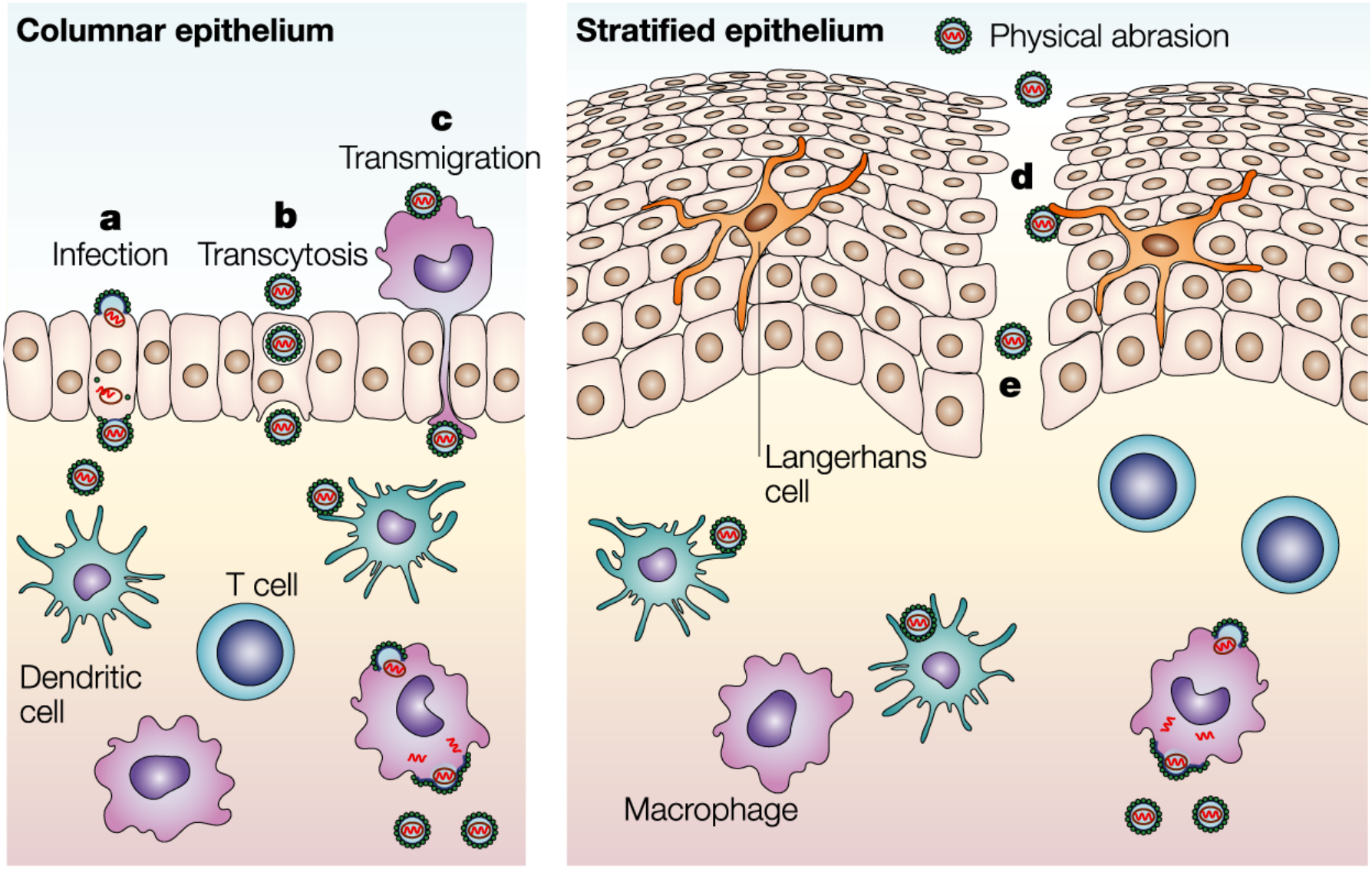
From Janoff EN and Smith PD. 2001

The risk of transmitting HIV-1 varies during the course of infection

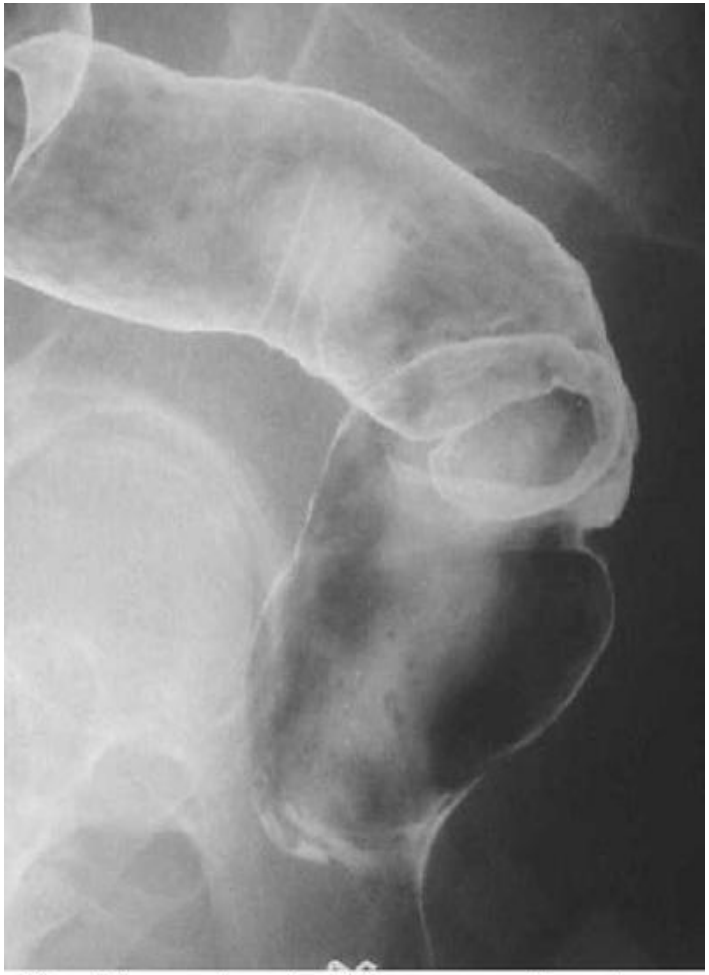


S.R.Galvin & M.S.Cohen. 2004. The role of sexually transmitted diseases in HIV transmission. Nature Reviews Microbiology 2, 33-42.

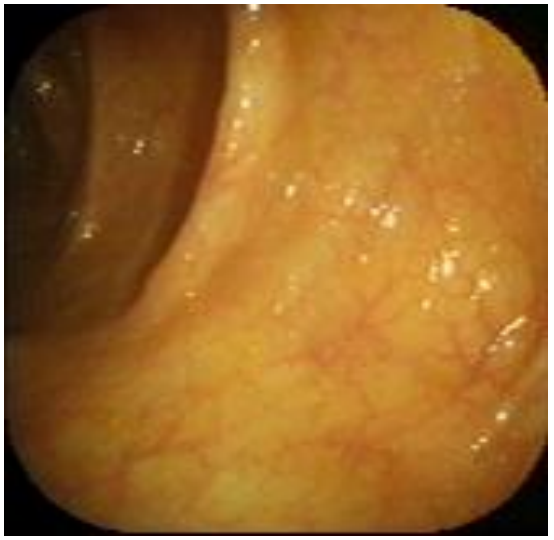
Mechanisms of transmission

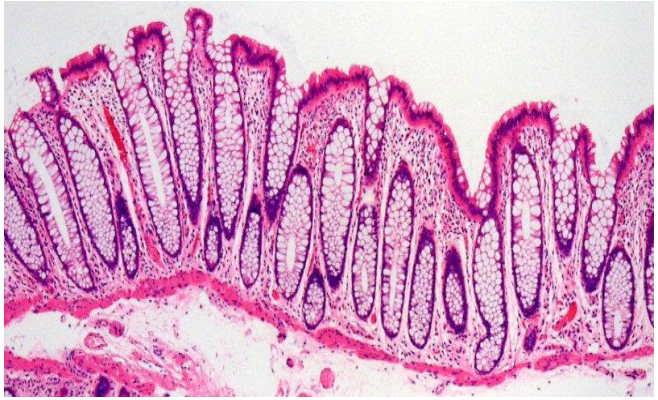


Rectal Anatomy

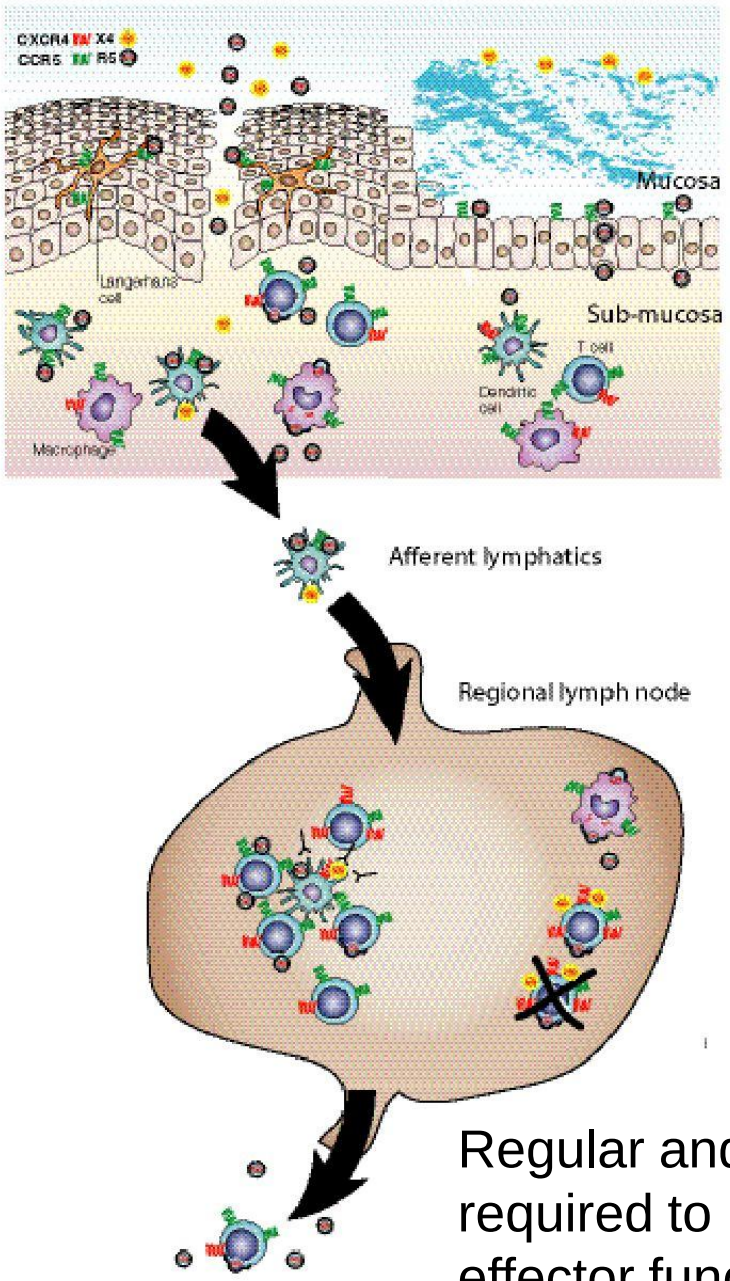


Double contrast of the normal rectum.





The time to act is short !



Exposure: 30-60 mins

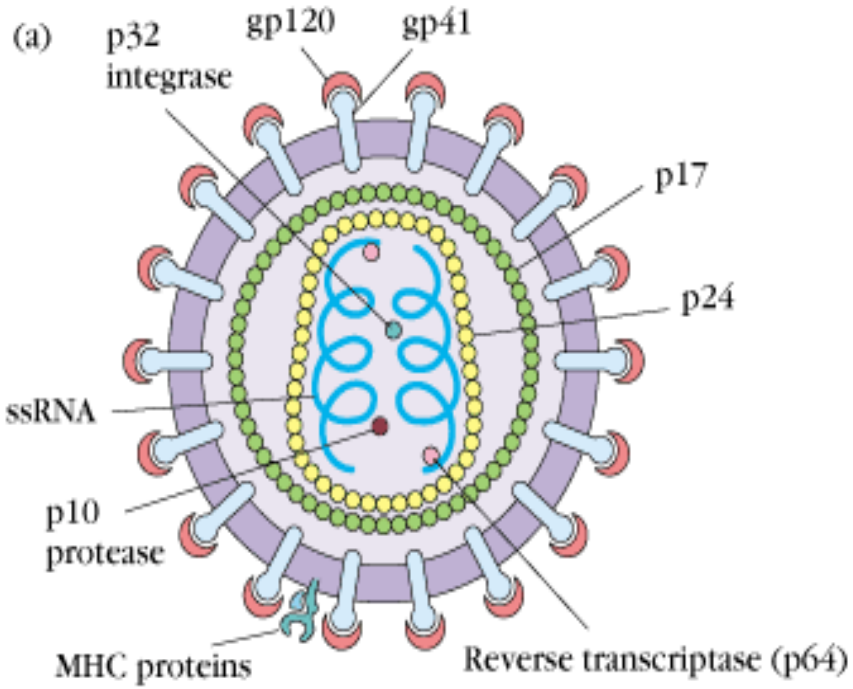
DC-T cell transfer 1-4 hours
(virological synapse)

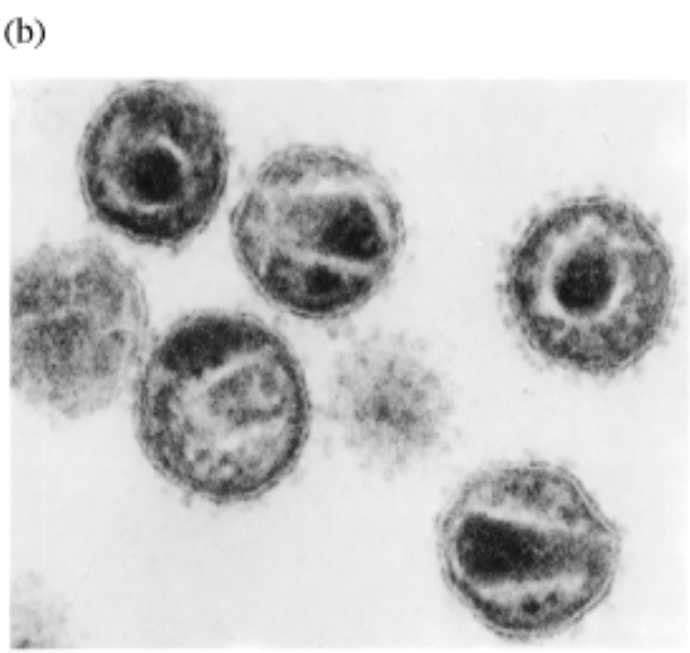
Localized infection: 16-72 hours

Dissemination to draining LN: 24-72 hours
(virological synapse)

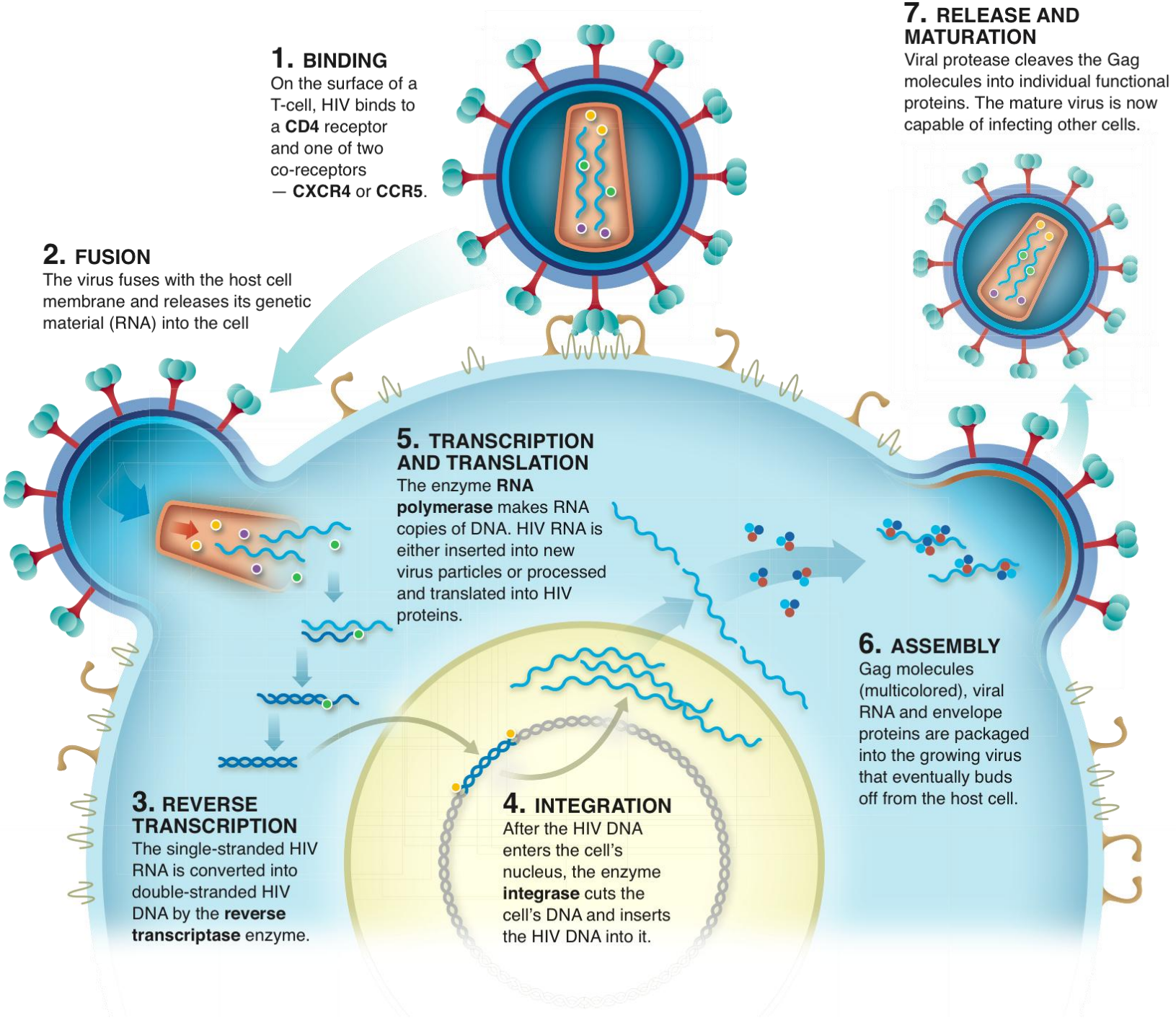
Induction of memory responses: 3-5 days

Regular and repeated mucosal vaccination may be required to maintain local protective immune effector function

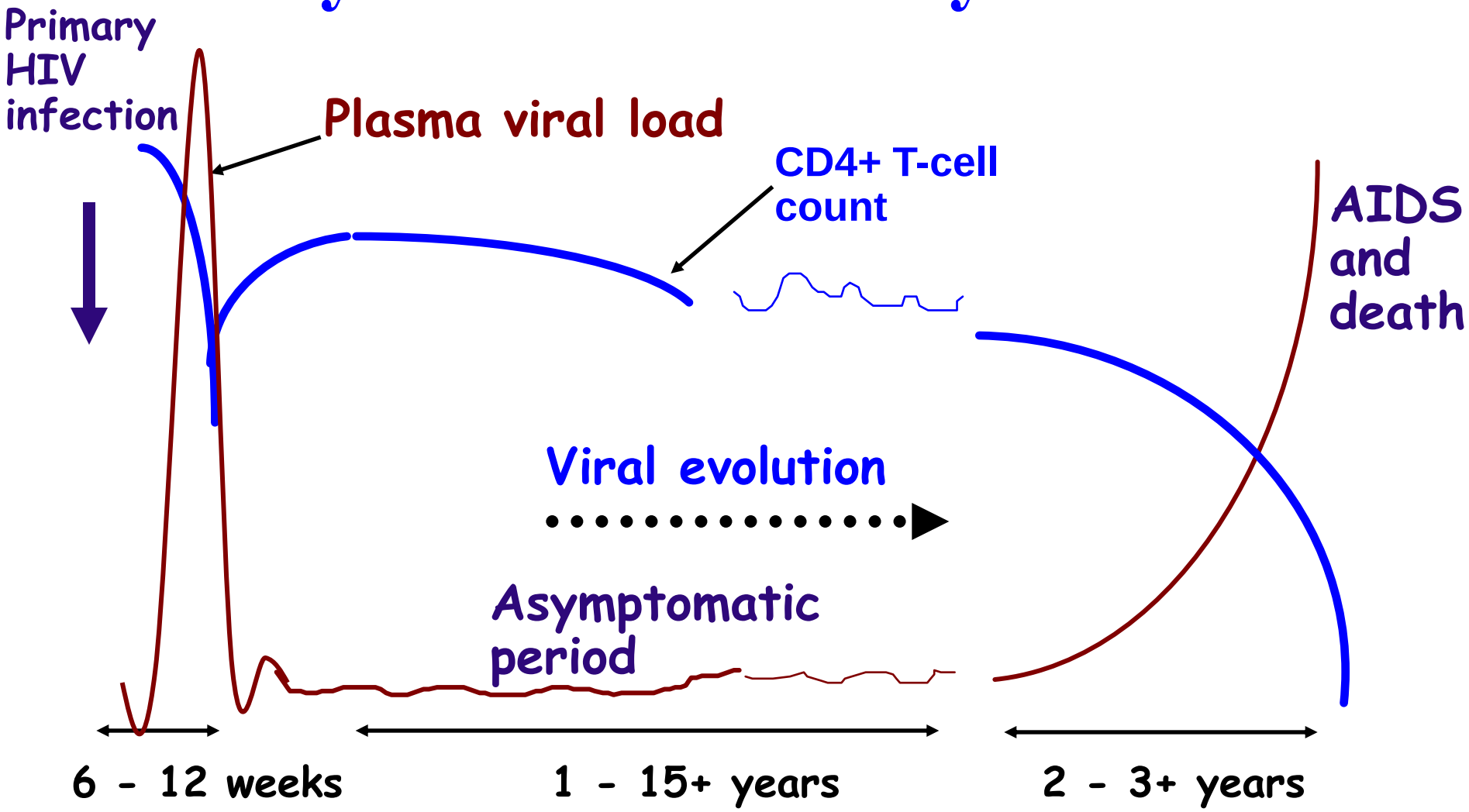




- Two identical strands of RNA (viral genome)
- Associated viral enzymes *reverse transcriptase, integrase and protease*
- Cone shaped core composed of p24 capsid protein (contains 1 & 2)
- Surrounding p17 protein matrix
- Contained within a phospholipid membrane derived from the host cell
- Virally encoded membrane proteins are bound to the envelope (gp120/gp41)

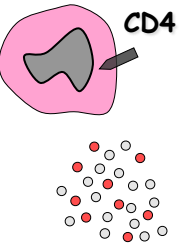

1. BINDING
On the surface of a T-cell, HIV binds to a CD4 receptor and one of two co-receptors — CXCR4 or CCR5.
2. FUSION
The virus fuses with the host cell membrane and releases its genetic material (RNA) into the cell
3. REVERSE TRANSCRIPTION
The single-stranded HIV RNA is converted into double-stranded HIV DNA by the reverse transcriptase enzyme.
4. INTEGRATION
After the HIV DNA enters the cell's nucleus, the enzyme integrase cuts the cell's DNA and inserts the HIV DNA into it.
5. TRANSCRIPTION AND TRANSLATION
The enzyme RNA polymerase makes RNA copies of DNA. HIV RNA is either inserted into new virus particles or processed and translated into HIV proteins.
6. ASSEMBLY
Gag molecules (multicolored), viral RNA and envelope proteins are packaged into the growing virus that eventually buds off from the host cell.
7. RELEASE AND MATURATION
Viral protease cleaves the Gag molecules into individual functional proteins. The mature virus is now capable of infecting other cells.

Why does HIV make you sick?



The relentless destruction of CD4 T cells leads to the eventual collapse of the immune system

HIV immunopathogenesis

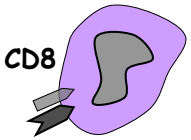


Functional CD4 T cell help & regulation

Decline in CD4 T cells

Proliferation < Apoptosis

CD4 and CD8 T cell exhaustion



CD8 T cells

HLA type-dependent

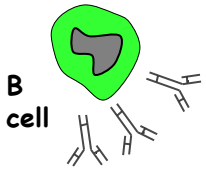
VL driven

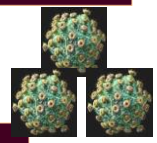
Super infections

Loss of Tregs

Rise in immune activation

Neutralizing Ab





Rise in VL

Viremia control

Viral Escape

Loss of CD8 T cells

Loss of neutralizing Abs

What about treatment?

- Expensive
- Lifelong medication
- Side effects / Toxicity
- Adherence
- Does not eradicate virus
- High levels of mutation (RT - 1 error per 10K nucleotides, 109 virus/day)
- Rapid development of resistance to monotherapy led to combinations of drugs being employed – HAART (Highly Active Anti-Retroviral Therapy)
- Initial therapy: 2NRTIs + PI / NNRTI

HIV-1 therapy

Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTIs)

Abacavir (ABC)
Didanosine (ddI)
Emtricitabine (FTC)*
Lamivudine (3TC)*
Stavudine (d4T)
Tenofovir (TDF)*
Zalcitabine (ddC)
Zidovudine (ZDV)
3TC/ABC
3TC/ABC/ZDV
3TC/ZDV
FTC/TDF*

Nonnucleoside RTIs (NNRTIs)

Delavirdine (DLV)
Efavirenz (EFV) , MIV-150*
Nevirapine (NVP), Dapivirine (TMC-

Multiple Class Combinations

EFV/FTC/TDF

Integrase Inhibitors

Raltegravir*

Protease Inhibitors (PIs)

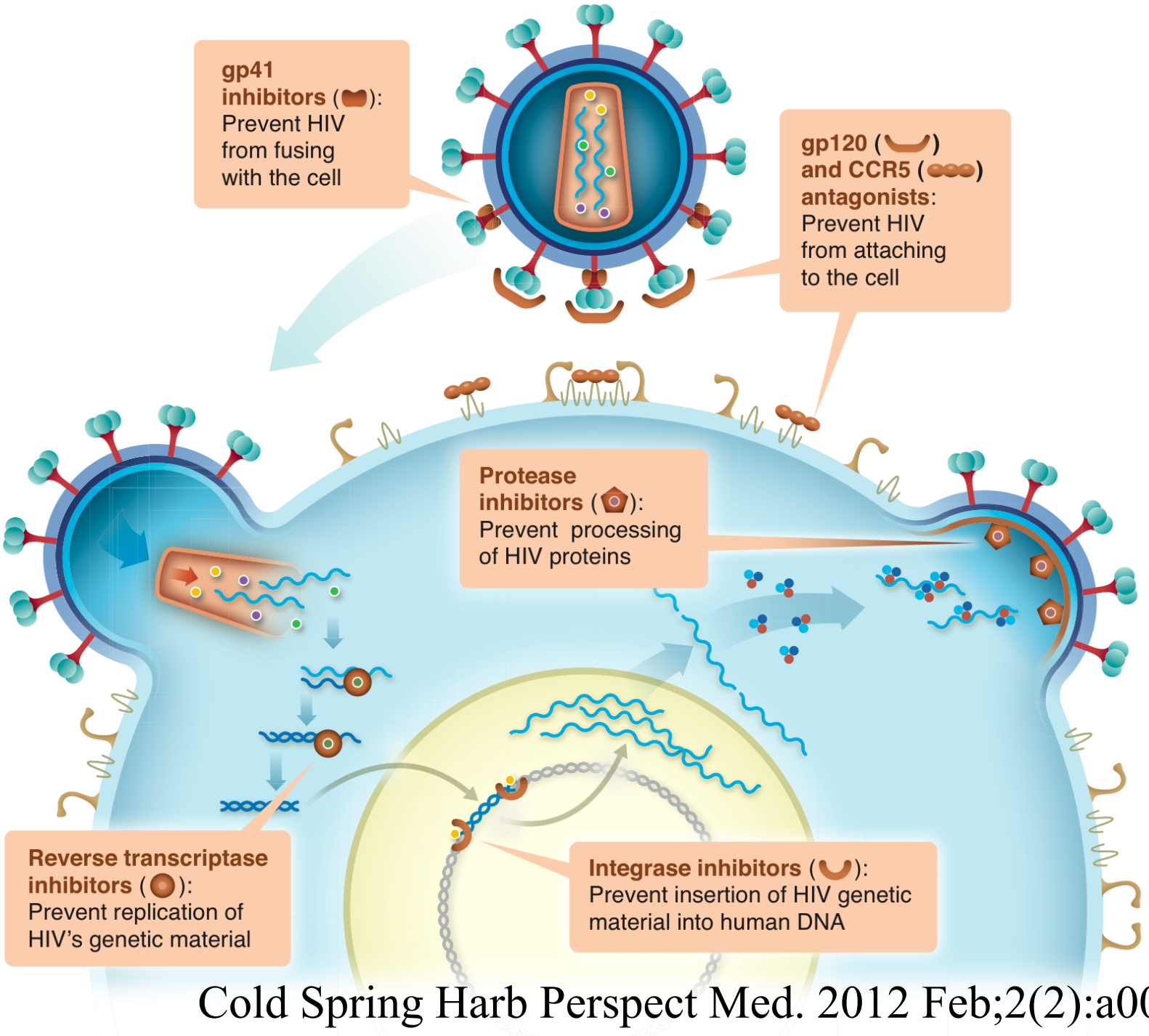
Amprenavir (APV)
Atazanavir (ATV)
Darunavir (DRV) *
Fosamprenavir (FPV)
Indinavir (IDV)
Lopinavir/ritonavir (LPV/r) *
Nelfinavir (NFV)
Ritonavir (RTV) *
Saquinavir (SQVhgc) *
Tipranavir (TPV)

Fusion Inhibitors (FIs)

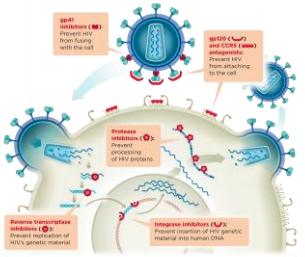
Enfuvirtide (ENF)

Chemokine Receptor 5 (CCR5) Inhibitors

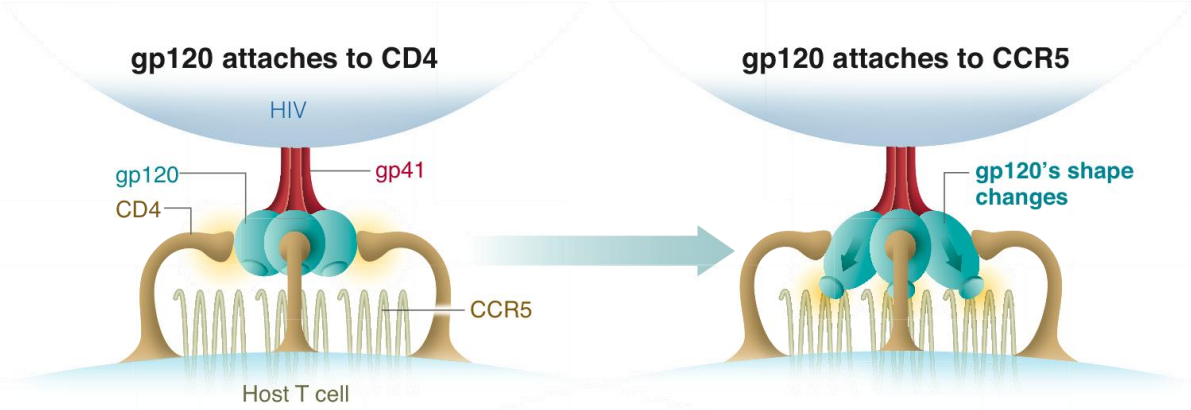
Maraviroc (MVC)*



Cold Spring Harb Perspect Med. 2012 Feb;2(2):a007385.

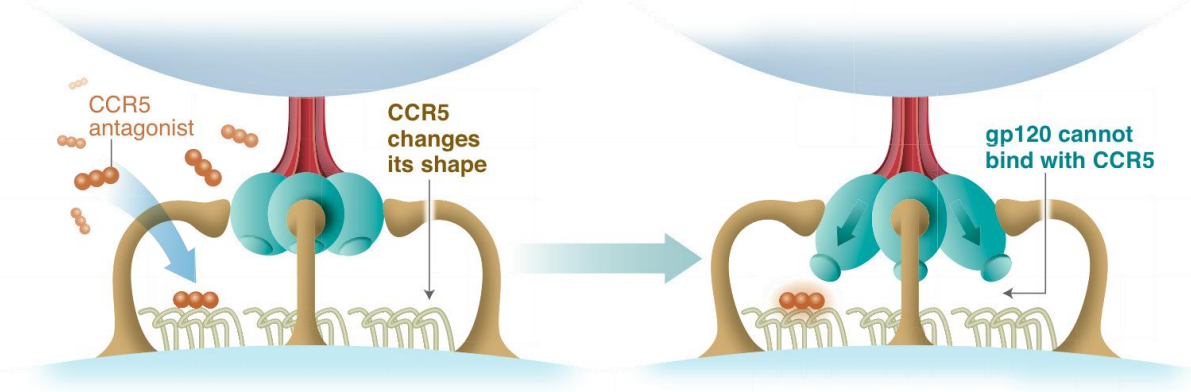


How CCR5 Antagonists Like Maraviroc Work



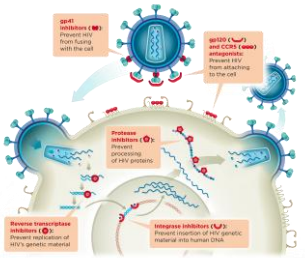
1. HIV ATTACHMENT

The HIV life cycle begins when a protein on the virus—**gp120**—binds to a **CD4** receptor on the cell. This in turn induces conformational change in gp120, facilitating its binding to a **CCR5** or **CXCR4** coreceptor and triggering viral fusion with the cell.

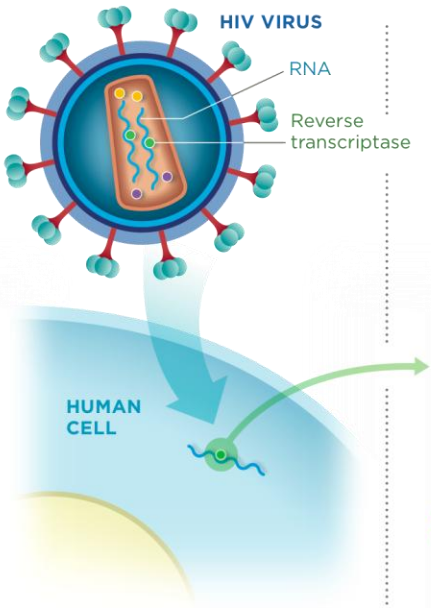


2. CCR5 ANTAGONISTS

CCR5 antagonists like **maraviroc** change the shape of CCR5, making it impossible for gp120 to bind to the CCR5 receptor, thereby inhibiting HIV attachment.

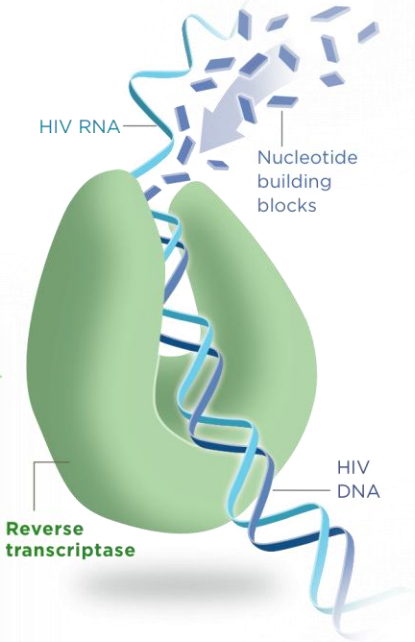


How NRTIs Like Tenofovir Work



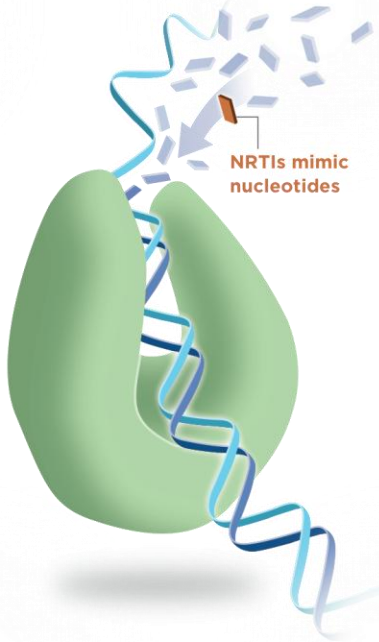
1. HIV REVERSE TRANSCRIPTASE

HIV carries a protein called **reverse transcriptase**. This protein creates the HIV DNA that is inserted into the human cell's DNA.



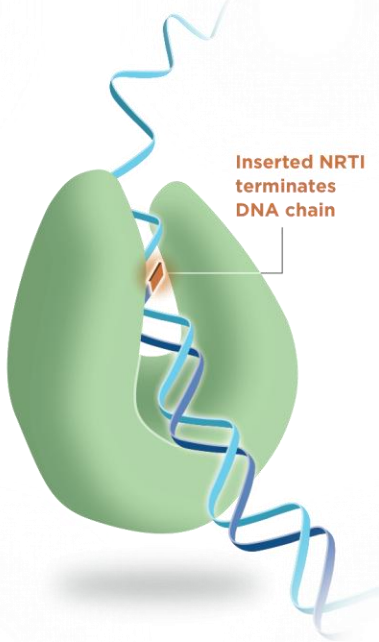
2. REVERSE TRANSCRIPTION

After HIV enters a cell, reverse transcriptase converts single-stranded HIV RNA into double-stranded HIV DNA using **nucleotides,** the building blocks of DNA.



3. NRTIs

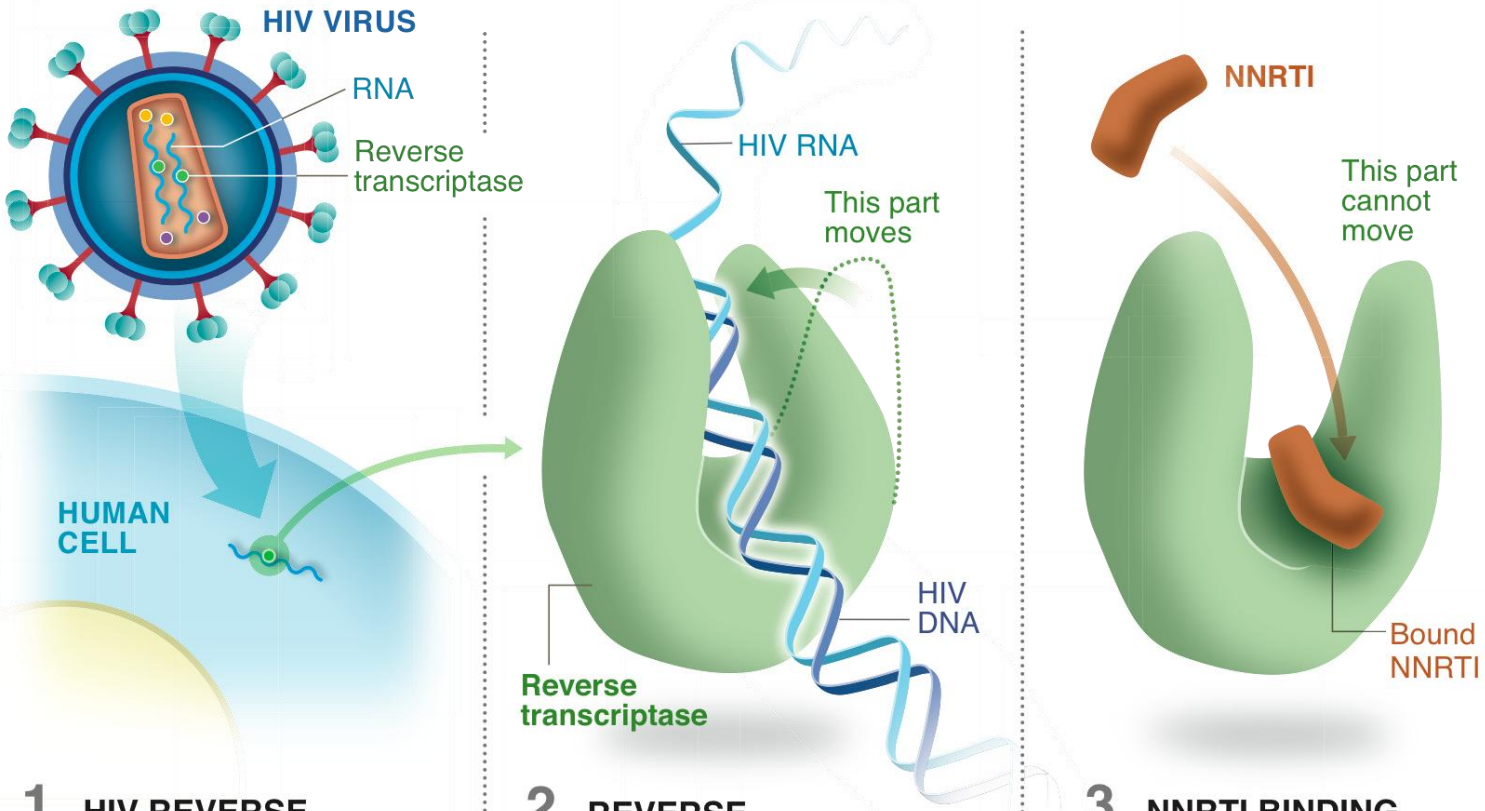
NRTIs, like **tenofovir**, are small molecules that mimic the nucleotides, so reverse transcriptase inserts them into the new HIV DNA chain.



4. DNA CHAIN TERMINATION

When an NRTI is incorporated into the virus's DNA, the DNA chain stops and replication of the virus is interrupted.

How NNRTIs Like Dapivirine Work



1. HIV REVERSE TRANSCRIPTASE

HIV carries a protein called reverse transcriptase. This protein creates the HIV DNA that is inserted into the human cell's DNA.

2. REVERSE TRANSCRIPTION

Reverse transcriptase uses the HIV RNA chain to synthesize the HIV DNA. In order to do so, the protein must change shape.

3. NNRTI BINDING

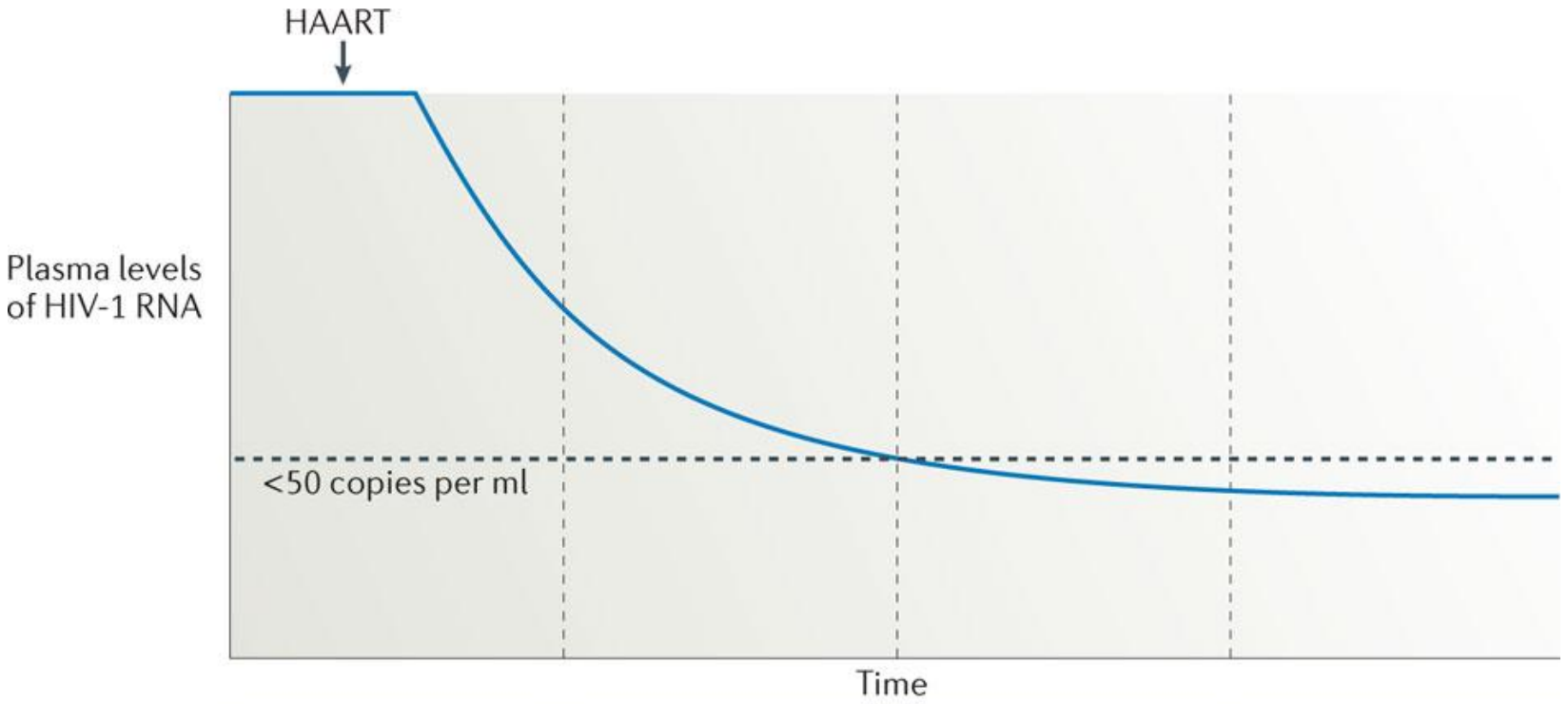
NNRTIs attach to reverse transcriptase, making it impossible for the protein to bind to HIV RNA, thereby preventing the creation of HIV DNA.

Antiretroviral treatment (ART) works!!

Haitian Patient, before and after Receiving Free Treatment for HIV Infection and Tuberculosis.

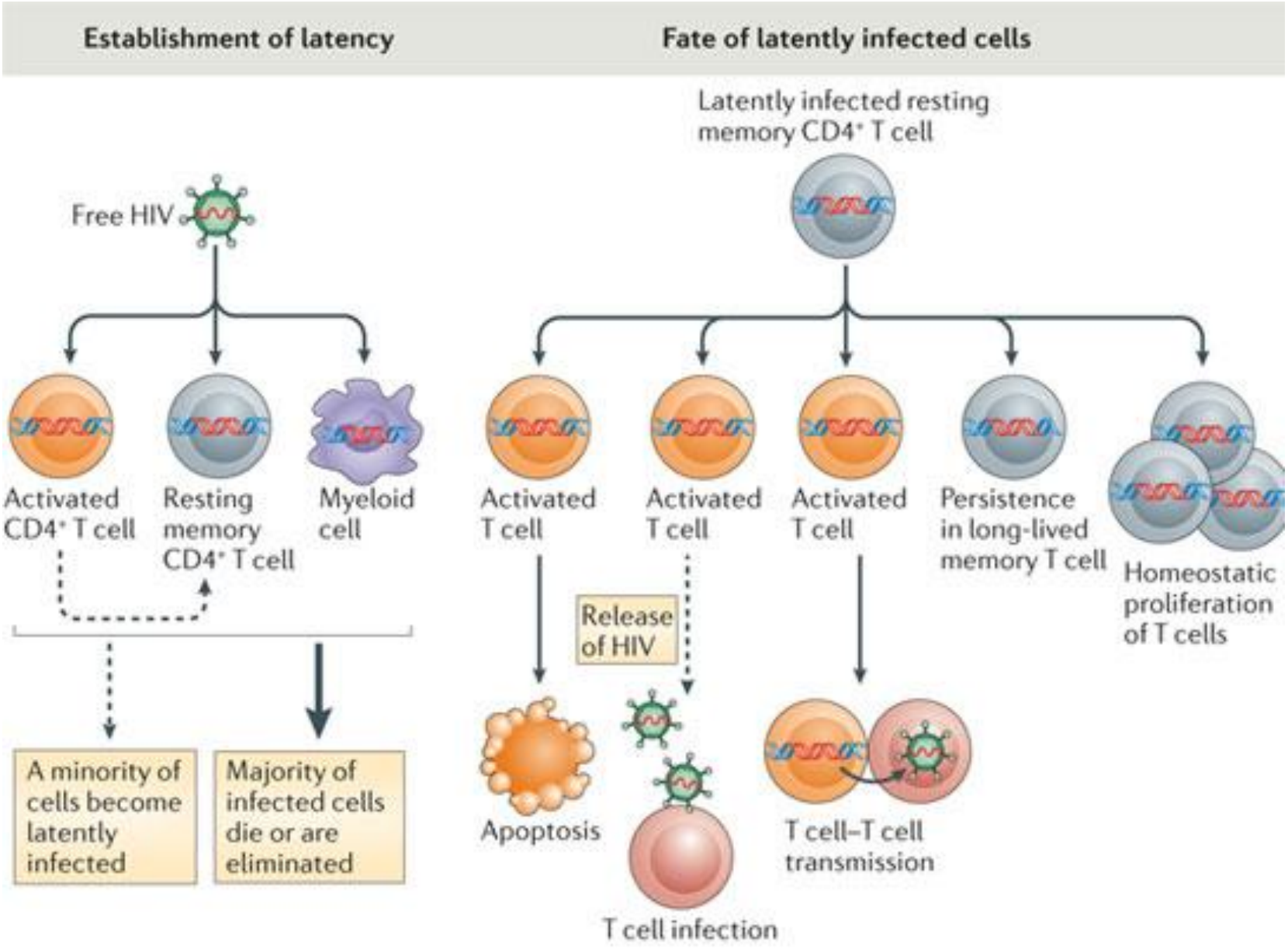
The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public–private partnerships.

But can we deliver it to all those in need



Nature Reviews | Immunology

International AIDS Society. Nat Rev Immunol. 2012:607-14. doi: 10.1038/nri3262.



International AIDS Society. Nat Rev Immunol. 2012:607-14. doi: 10.1038/nri3262.

But some issues remain….

- Resistance
- The requirement for high compliance <95%
- The need for “simpler” regimens
- Management of long-term toxicity
- Treatment not cure

Next steps - towards elimination of viral latency…

- Very early treatment – treatment for prevention
- Therapeutic vaccines
- Immune modulation
- Gene therapy …..

The growing global interest in curing HIV infection

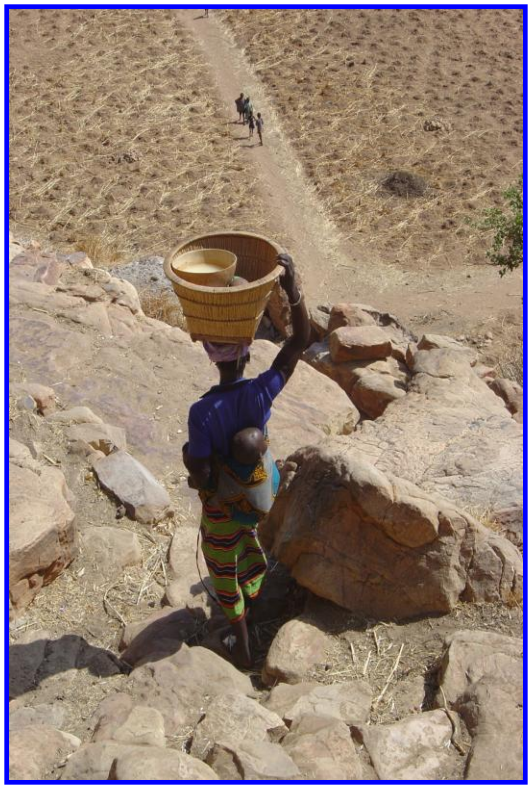
Due, in part, to a remarkable case report.

A HIV-infected man given bone marrow transplant homozygous for the CCR5 Δ32 deletion (co-receptor for HIV) following depletion of his haematopoietic system.

Antiretroviral therapy was discontinued at the time of transplantation.

Remarkably, viraemia remained undetectable throughout the post-transplant period, which has now lasted for more than 5 years.

But what are the prospects for curing HIV?



- A "cure" would require elimination of all free HIV particles and all infected cells
- Latently-infected cells persists for years, and HIV starts replicating again immediately when therapy is stopped
- It would take 70 years to eliminate all virus and infected cells with current therapy
- The new goal is to identify new strategies to eliminate latent infection

Treatment works so why isn't everyone on it?

- ACCESS
- Resources
- Belief systems
- Drug availability
- Health care facilities
- Stigma
- "TEST AND WE WILL TREAT!

What are the challenges?

- Money
- Drug supply chains
- Trained staff
- Capacity within failing health care system
- Stigma
- Gender based violence
- Human rights/coercion
- Acceptability at a population level

Can treatment reverse the epidemic?

HAART
cost in the West:
$7000/patient/year - for life

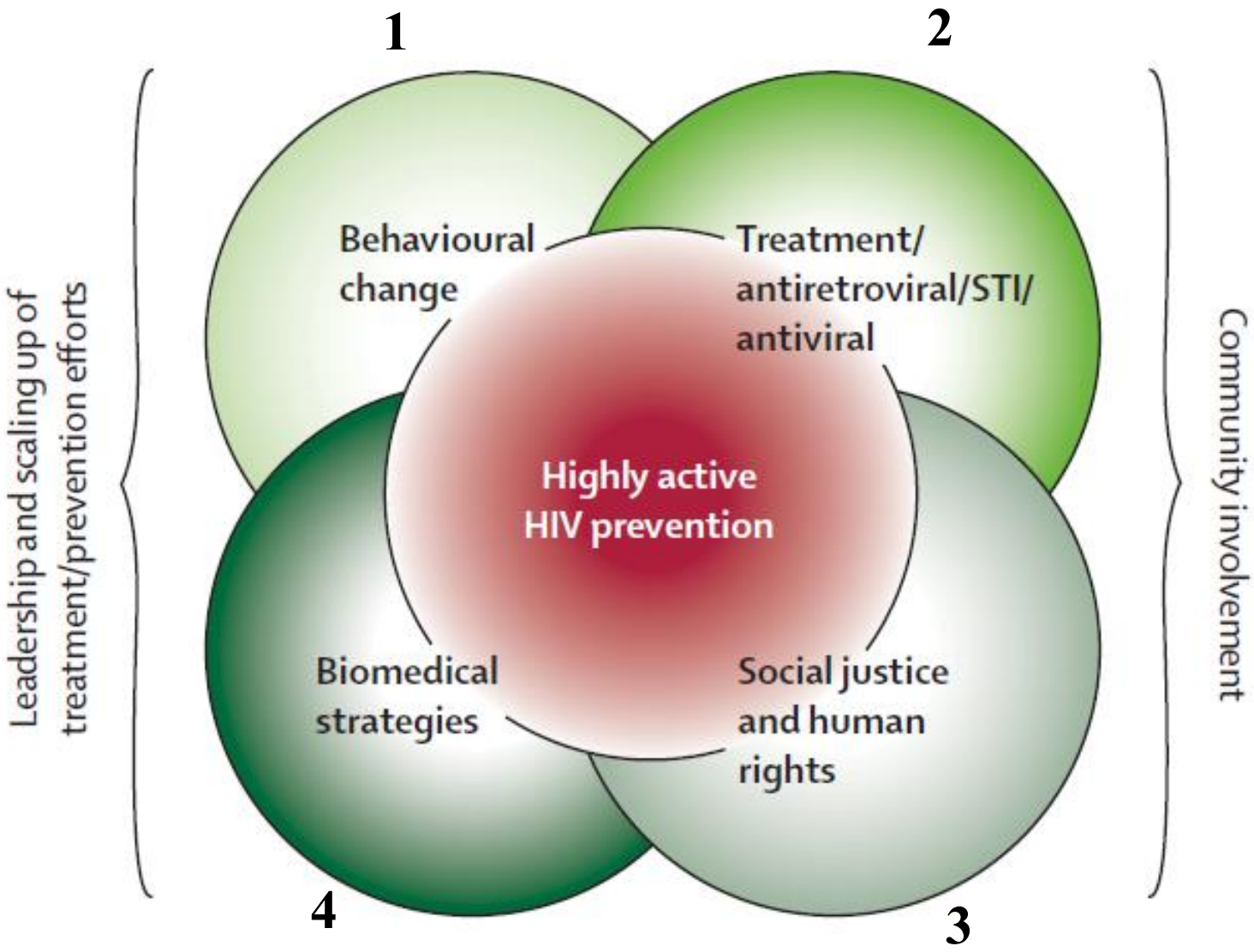
Cost in the developed world:
$500

Average health budget in
Africa $10-20/person/year

Implications of distribution, storage, infrastructure and access

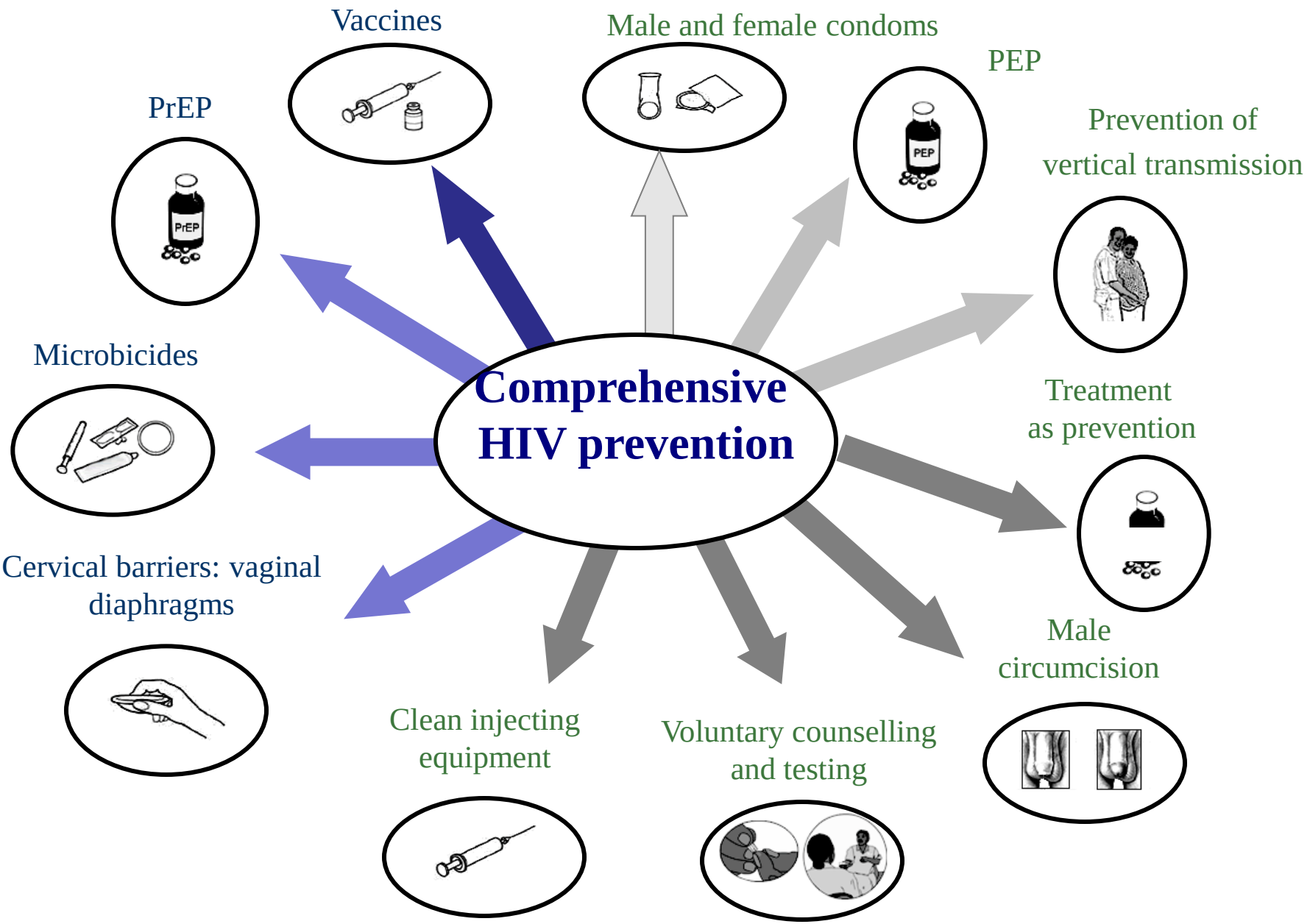

BROKEN
PROMISES
KILL
NO RETREAT
FUND AIDS
www.FundGlobalAIDS.org

What about prevention?

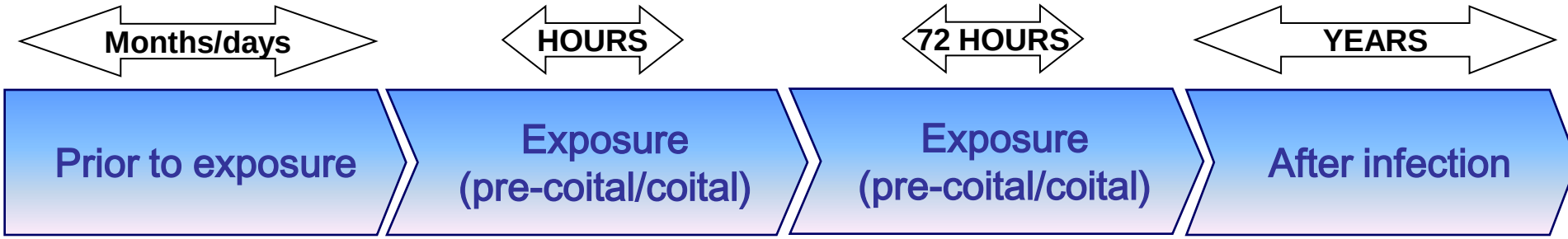


Coates et al., Lancet 2008

HIV prevention strategies



Opportunities for biomedical interventions



- Oral pre exposure prophylaxis (daily PrEP)
- Topical PrEP (daily gels or intra-vaginal rings (microbicides)
- Preventive Vaccines

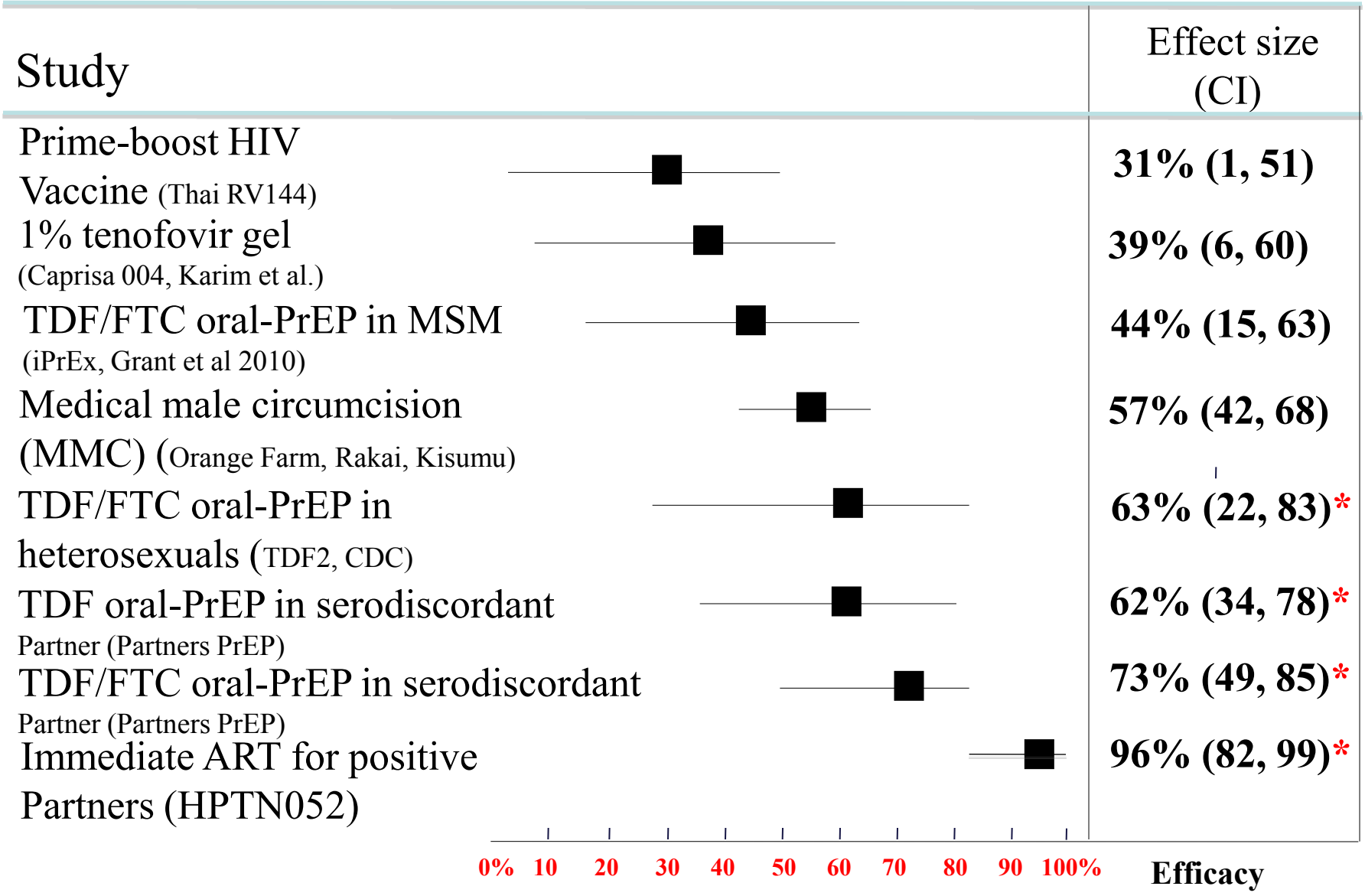
- Oral pre exposure prophylaxis (intermittent PrEP)
- Coitally dependent topical PrEP (microbicides)

- Oral post exposure prophylaxis following sexual exposure (PEPSE)

- Treatment of positive partners in discordant couples (T4P)
- Universal Test and Treat (UTT)

All have a behavioral and structural components

New biomedical intervention strategies



*Provisional

What options are currently available

Partner reduction

Condoms

Require partners consent
Issues of trust

Male circumcision (>57% reduction)

Gray R, et al. AIDS. 2012;26:609-15

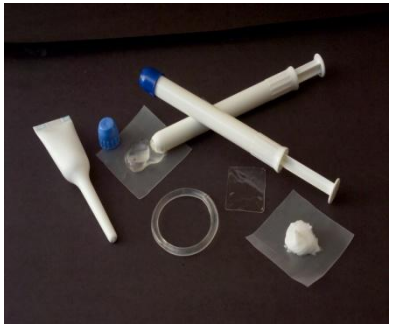
On demand products

- Used before or after intercourse
- Appropriate for discrete use
- Providing control over protection

Sustained release devices

- User initiated but do not require daily action
- Should increase adherence and therefore overall effectiveness

Pill/tablet



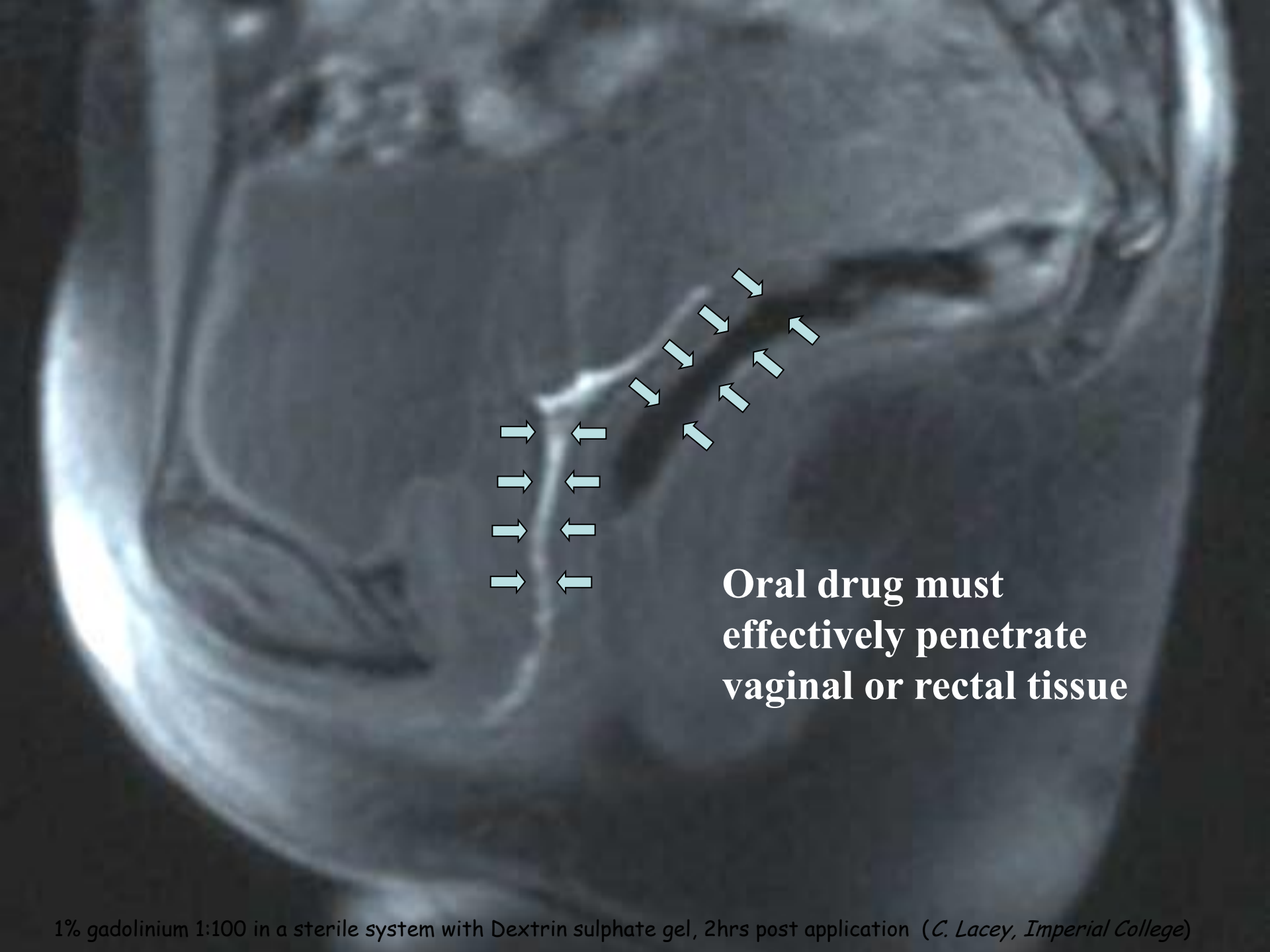
Gel / applicator

Vaginal film

Vaginal ring

Injectable

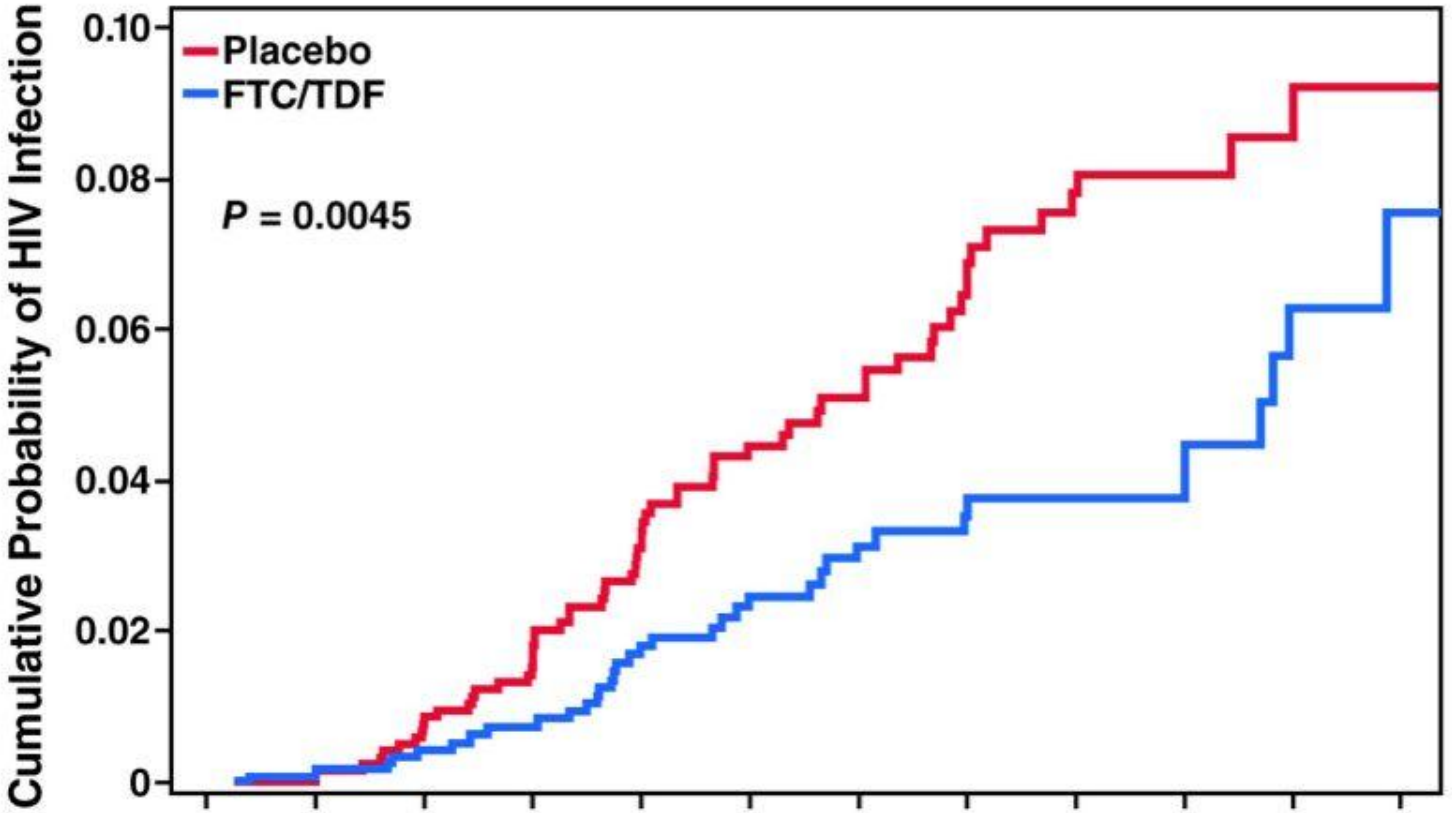
What of oral prophylaxis (PrEP



1% gadolinium 1:100 in a sterile system with Dextrin sulphate gel, 2hrs post application (*C. Lacey, Imperial College*)

PrEP for HIV prevention in men who have sex with men

Efficacy (MITT) 44% (15-63%)
Infection Numbers: 64 – 36 = 28 averted

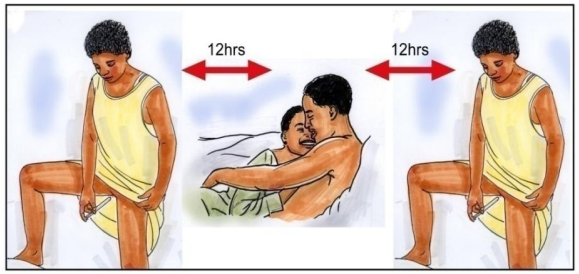


N =												
Placebo:	1248	1194	1108	1005	852	674	546	444	370	258	137	60
FTC/TDF:	1251	1188	1097	988	848	693	558	447	367	267	147	65

10.200B2

New England Journal of Medicine, online Nov 23, 2010

CAPRISA 004: HIV infection rates in the tenofovir and placebo gel groups: Kaplan-Meier survival probability



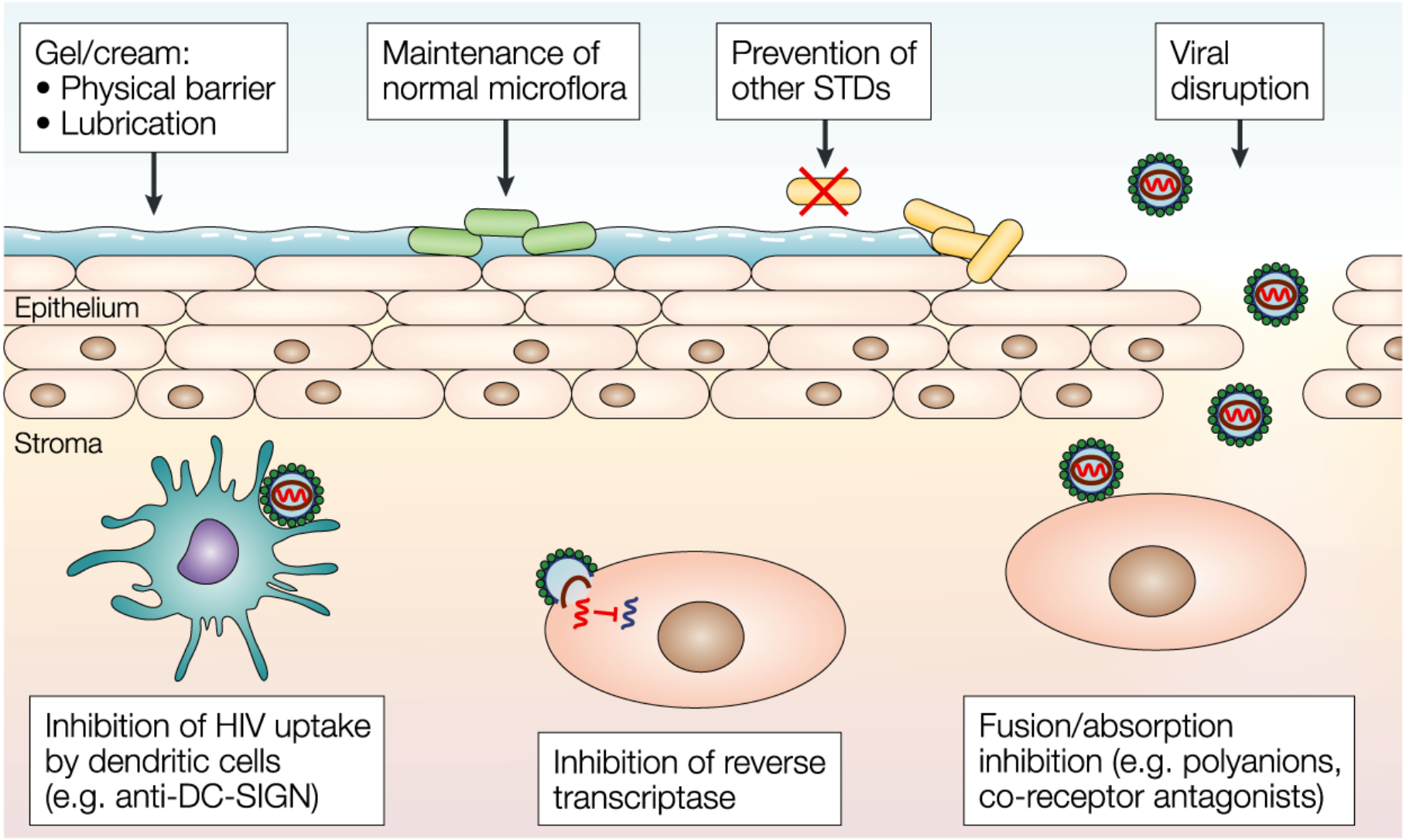
CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Months of follow-up	**6**	**12**	**18**	**24**	**30**
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 9.4	5.6 vs 9.1
Effectiveness (p-value)	**47% (0.069)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

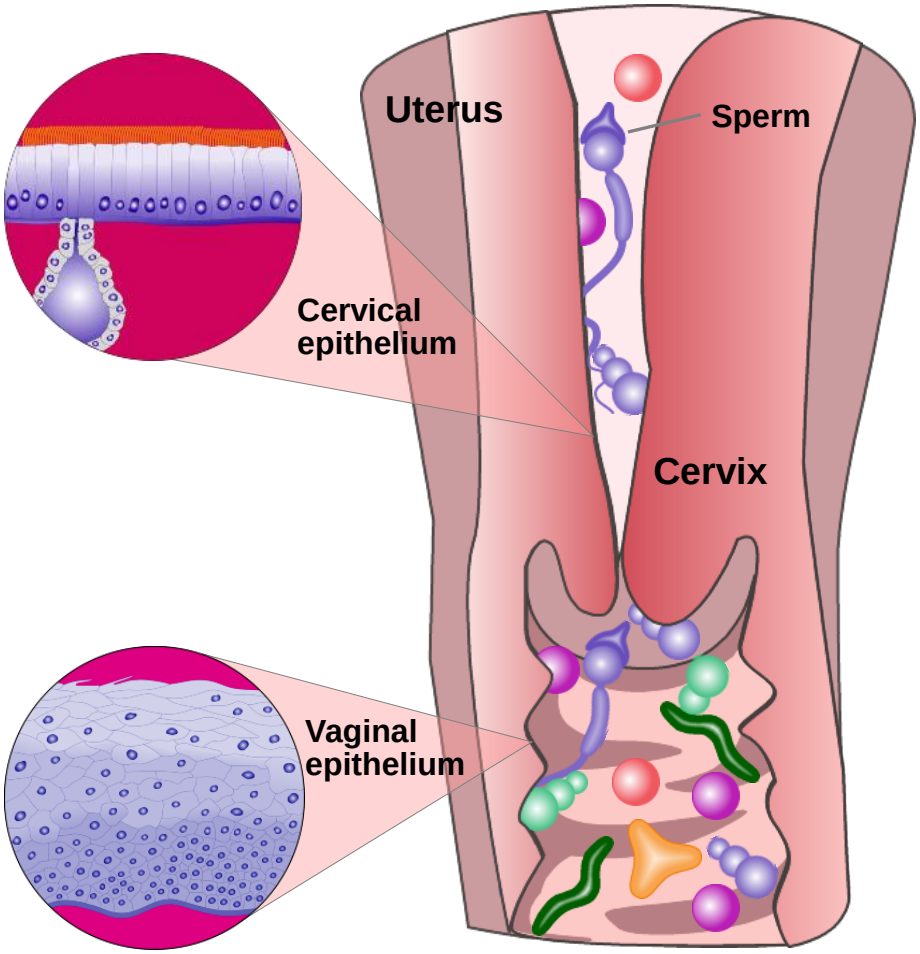
Microbicides – topical PrEP?

- Substance that can substantially prevent or reduce transmission of HIV when applied to the vagina or rectum
- Could potentially be made in many forms:
  - gel or cream
  - sponge
  - film
  - suppository
  - ring or diaphragm

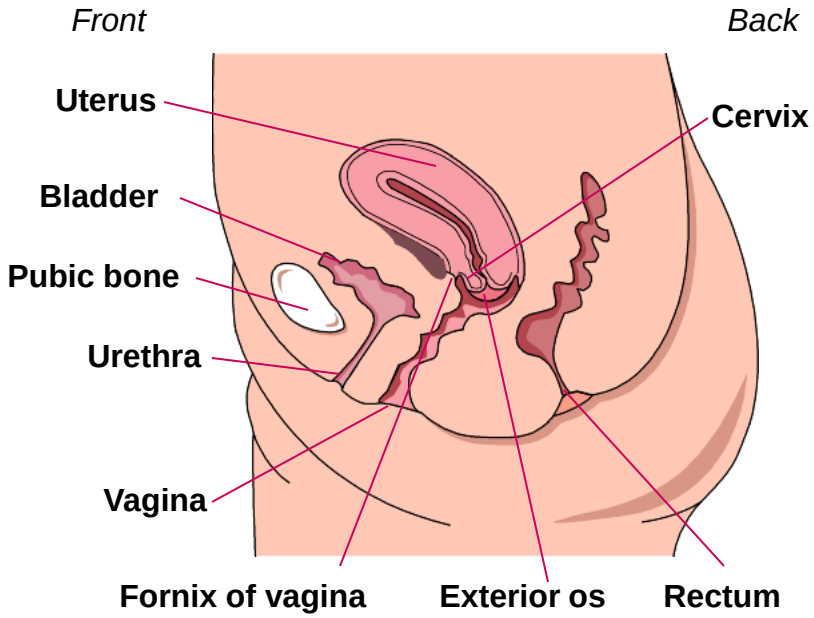
How would they work



Nature Reviews | Microbiology



Female Anatomy



Fungi

Candidiasis

Protozoa

Trichomonas

Viruses

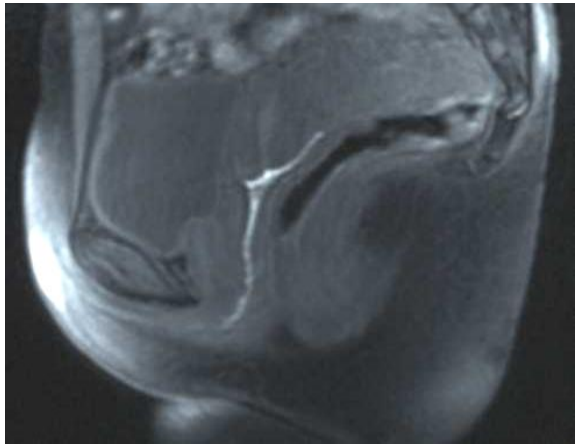
HIV

Human papilloma
Cytomegalovirus
Hepatitis

Bacteria

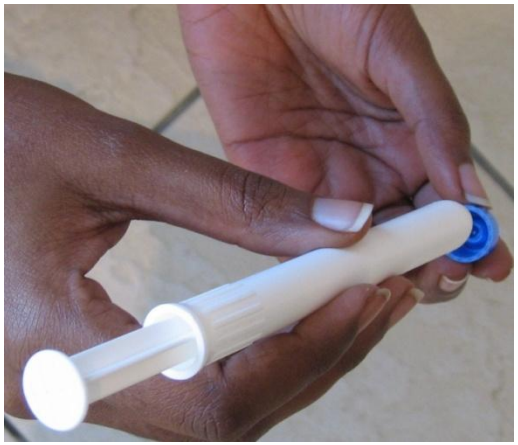
N.gonorrhoeae
C.trachomonas
T.pallidum
Haemophilus

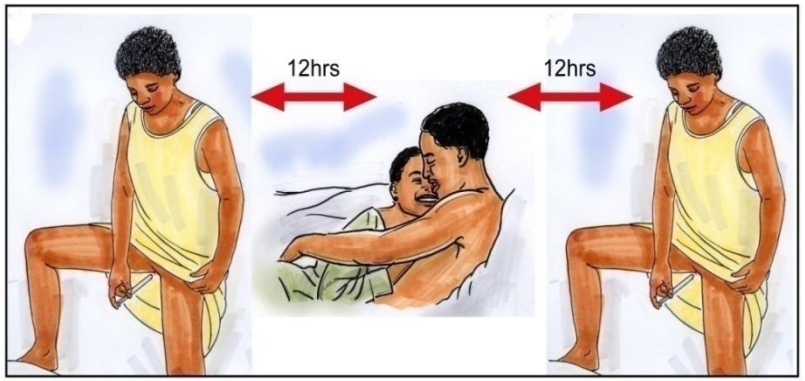
Lactobacillus



C. Lacey. Imperial Collage

CAPRISA 004 result, July 2010



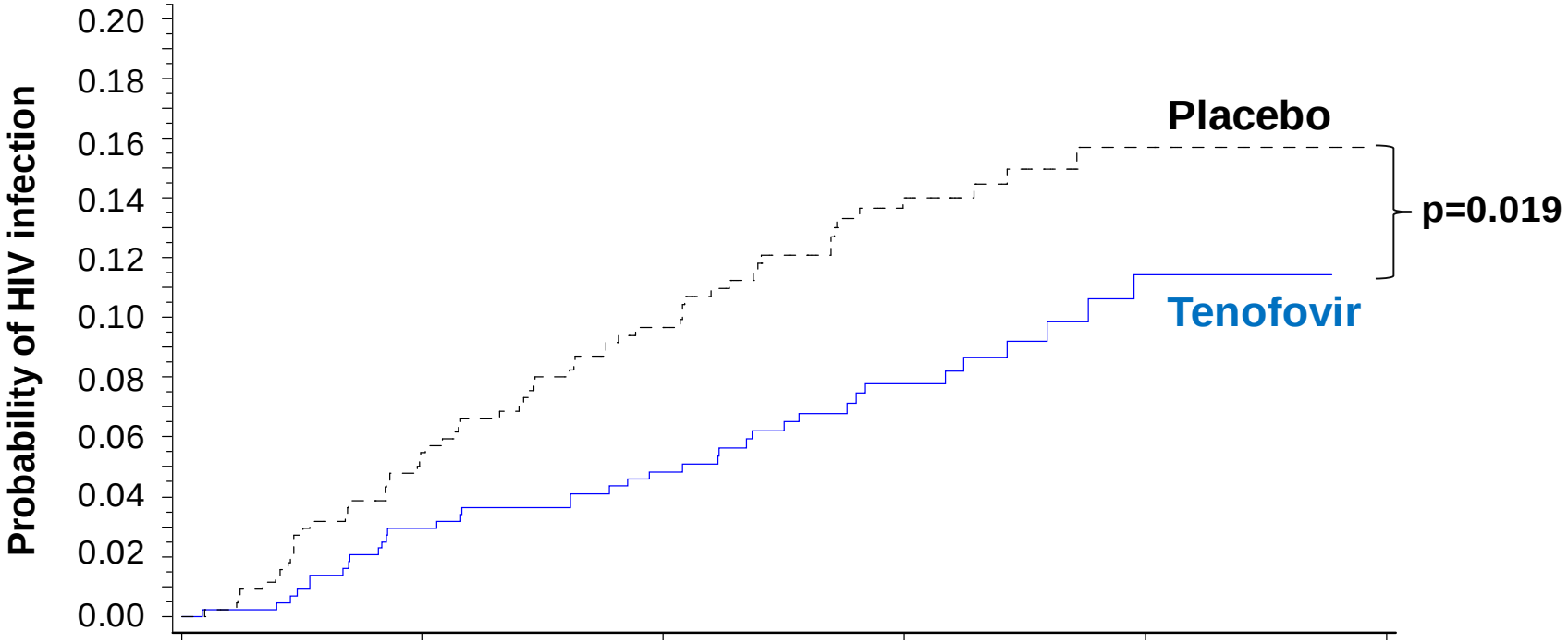


Karim et al,
Science. 2010 ;329(5996):1168-74.

CAPRISA 004 assessed the safety and effectiveness of 1% tenofovir gel applied

12 hours Before sex, and as soon as possible within 12 hours After sex, no more than Two doses in 24 hours

HIV infection rates in the tenofovir and placebo gel groups: Kaplan-Meier survival probability



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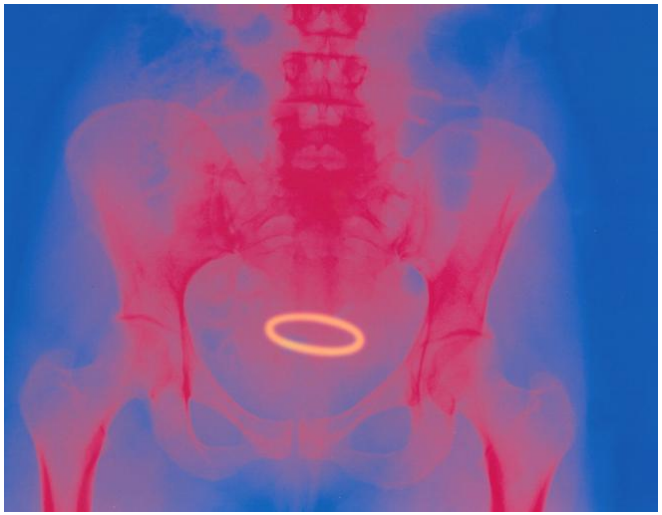
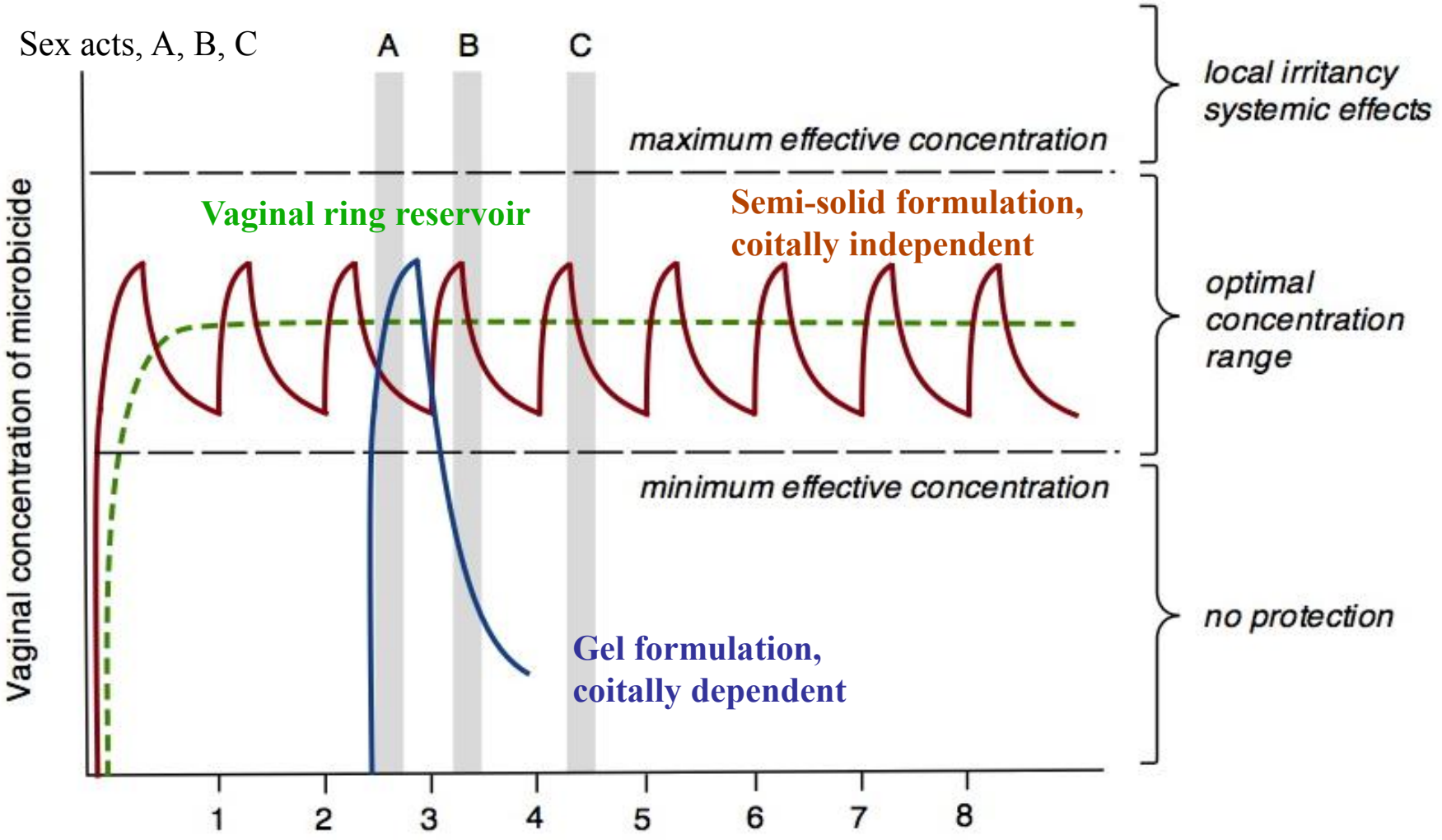
Impact of adherence on effectiveness of tenofovir gel

	# HIV	N	HIV incidence		Effect
			TFV	Placebo	
High adherers (>80% gel adherence)	36	336	4.2	9.3	**54%**
Intermediate adherers (50-80% adherence)	20	181	6.3	10.0	**38%**
Low adherers (<50% gel adherence)	41	367	6.2	8.6	**28%**

Sustained release for increased effectiveness?

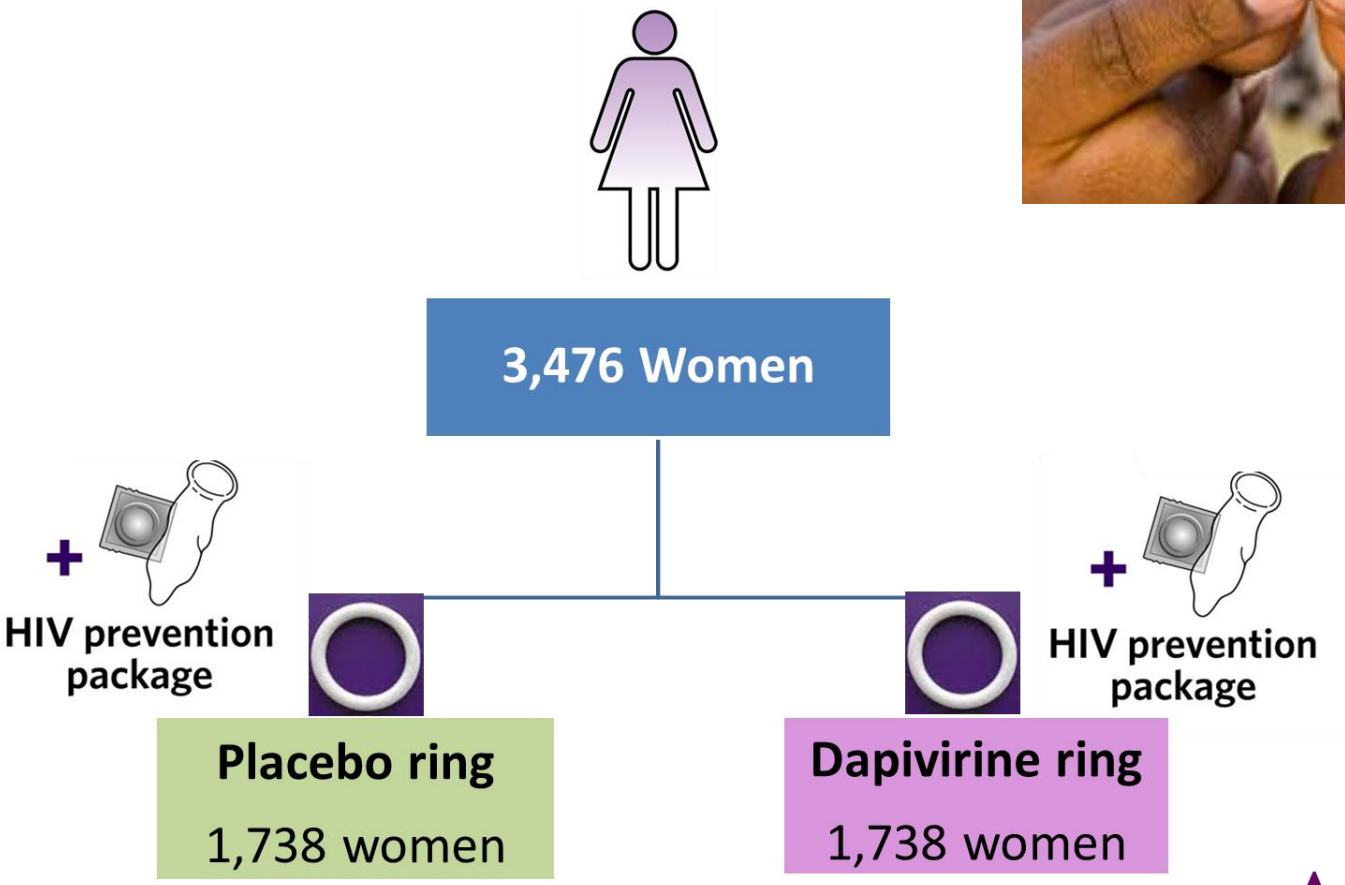


Sustained delivery devices and vaginal rings offer a path away from coitally-dependent microbicides



Karl Malcolm - Queen's University Belfast

Aspire: Dapivirine ring trial



ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

Proving Effectiveness will be Difficult...

- **Large Phase III trials**
- **Limited clinical trial capacity**
- **Prevention of an infection with relatively low incidence after counseling about safe sex practices**
- **Requires a high level of compliance by those not, or infrequently, using condoms**
- **Vast majority of resources required in late stage development therefore only limited candidates can be taken into trials**

Treatment for prevention (T4P) HPTN052

- Early use of ART by an HIV-infected individual reduces heterosexual transmission to an uninfected partner by 96%
- However in at least 7 of the 39 (18%) infections virus was likely acquired from outside the primary relationship
- Implementation may be feasible for discordant couples in many settings,
- But offering immediate T4P to all who test HIV-positive is challenging in settings where barely 50% of those medically eligible are currently receiving ART.
- Even more challenging will be identifying those in acute infection and encouraging them to join treatment programs

Is ART for prevention a ‘game changer’ The reality

- The humanitarian dilemma
- Clean water, education, malaria, TB, infant mortality, death in childbirth.....
- Only with unlimited resources not only funding but trained personnel, laboratory trained staff and equipment can ART on a population level be sustainable
- Sustainability is the critical challenge ART is for life and because it works it must be for the next 40-50 years

Can we treat our way out of the epidemic?
Is the science credible?

- Yes
- ART can eliminate MTCT (Mother To Child Transmission)
- ART can prevent sexual transmission (052)
- ART can reduce the transmission if given before sexual exposure
- There are flaws: but all in terms of implementation

The Economist June 4, 2011

" Thirty years on, it looks as though the plague could now be beaten, if the world has the will to do so"

Thank you for attention