

# HIV Prevention: Condoms, Microbicides, Etc.

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# HIV Prevention: Condoms and Microbicides.

¿Which of the following is false?

- a) Condoms can reduce HIV transmission by up to 97%
- b) Introduction of the female condoms tends to lead to decreased male condom usage
- c) Clinical trials of microbicides have not yet demonstrated an effective product
- d) At least 2 microbicide candidates, in clinical trials, have been shown to increase the risk of HIV transmission.
- e) The female diaphragm is no more effective in preventing HIV infection than condom use
- f) I do not know, I'm coming to learn.

As more and more drugs with  
new mechanisms of action  
become available to treat HIV,  
we are falling behind in  
prevention

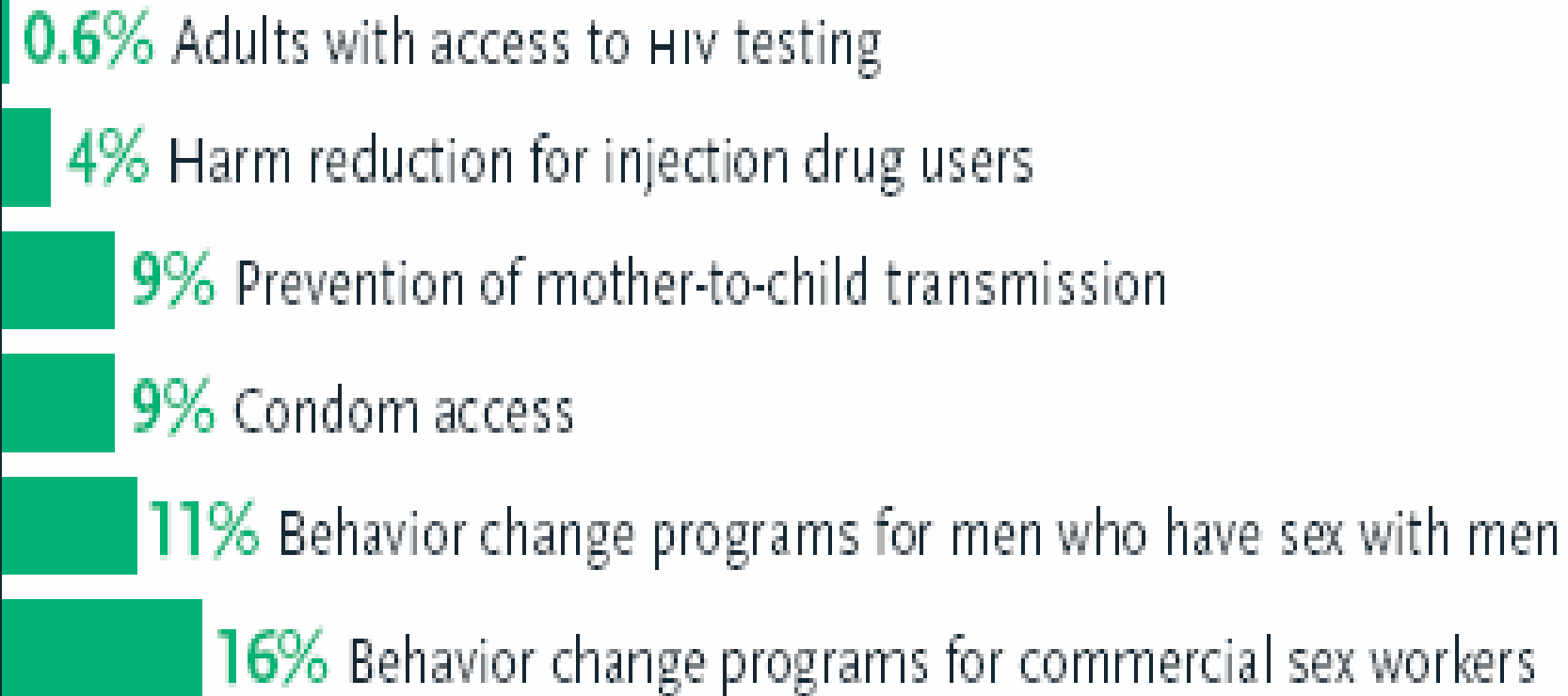
# 2006 International AIDS Conference: Time to Deliver

“Between 2003 and 2005 . . . for each new person who got treatment for HIV, about 10 people became infected. Even during our greatest advance, we are falling behind.”

- Bill Gates



# Percentage of Individuals at Risk with Access to HIV Prevention

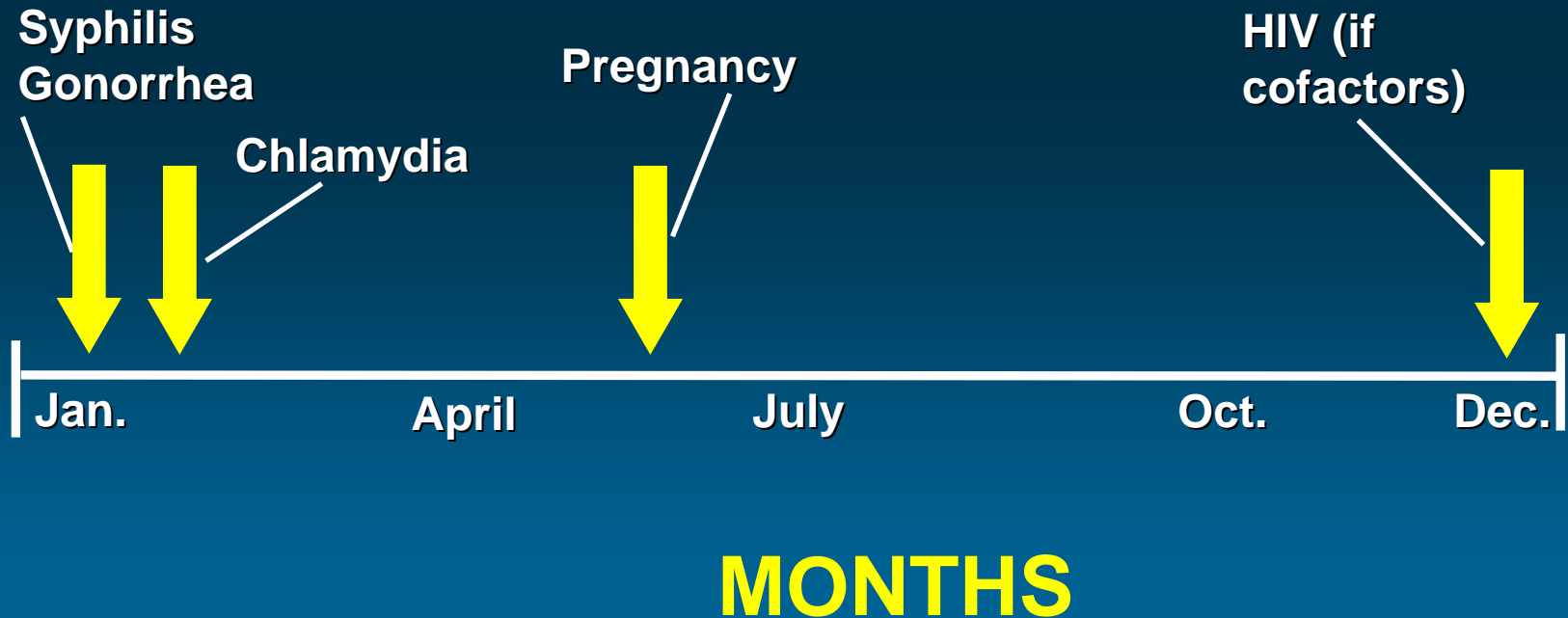


Sources: UNAIDS, 2006; USAID et al., 2004

# Condom Efficacy

## Estimated Risks from 2 Acts of Unprotected Intercourse Per Week

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Source: Cates, *STD*, 2002;29:350-52

# But If Protected by Condoms

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Source: *Cates, STD, 2002;29:350-52*

# The Efficacy of Condoms

- **In longitudinal studies among heterosexuals condoms have been shown to decrease the risk of HIV by 80-97%**

*Source: Weller S & Davis K, The Cochrane Library 2004*

- **Sero-conversions in discordant couples who used condoms:**
  - **Consistently = 0% per person-year (n=124)**
  - **Inconsistently = 4.8% per person-year (n=121)**

*Source: De Vincenzi I, N Engl J Med 1994*

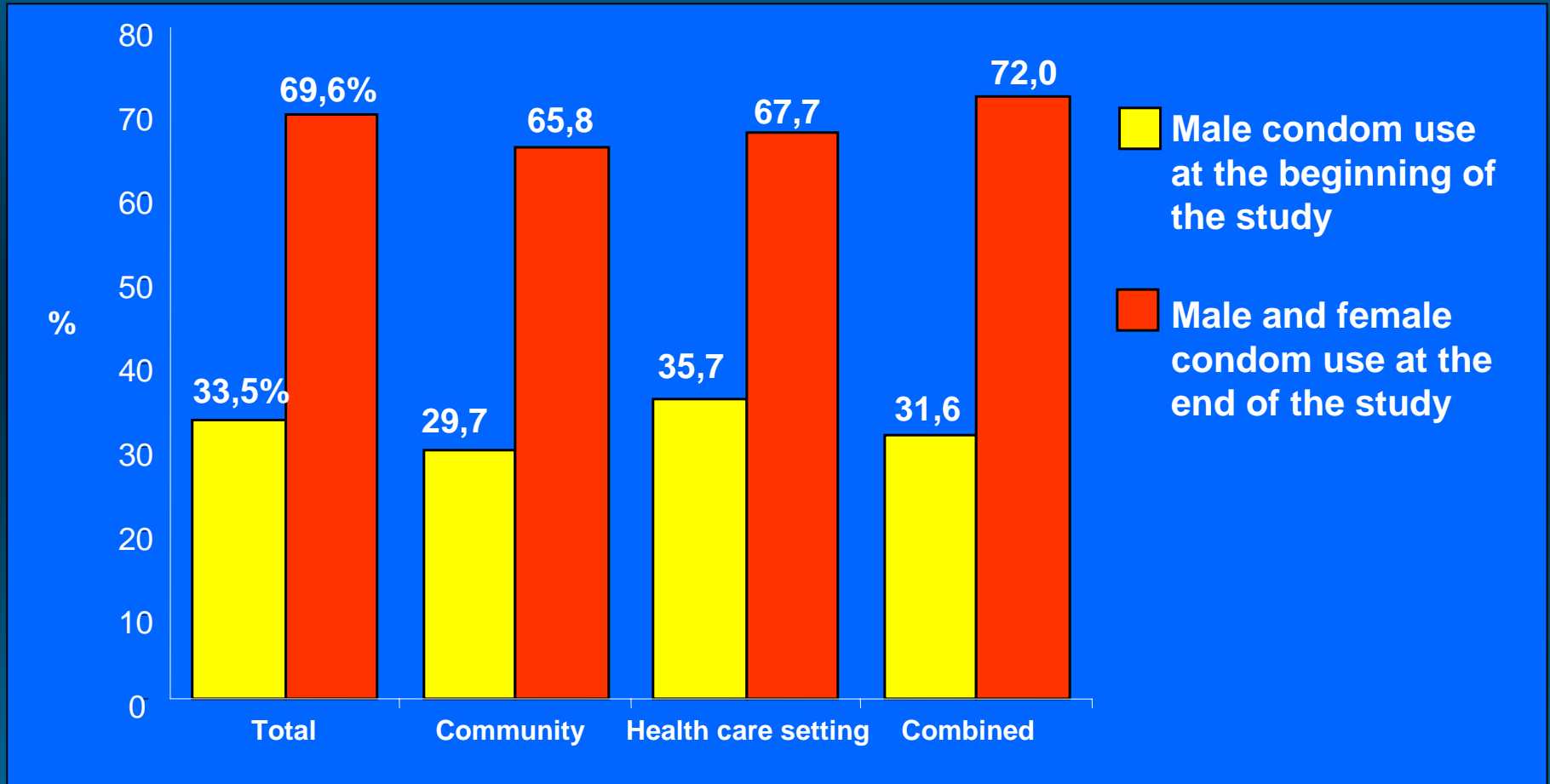


# Female Condoms

- As effective as male condoms in preventing STIs
- In-vitro data support impermeability to HIV
- Generally used to complement male condoms
- Are several times more expensive than male condoms
- Issues related to reuse are not totally defined

*Source: French PP et al, Sex Trans Dis 2003; Fontanet et al, AIDS 1998; Feldblum et al, AIDS 2001 Source: Drew W et al, Sex Trans Dis 1990*

# Female condoms in prevention programs increase overall condom use



**Proportion of safe sex acts in the last sexual intercourse at start and end of female condom promotion in various health care settings in Brazil**

Source: Barbosa R et al, XIIIth Int AIDS Conference, 2000

How Do We Increase the Use of  
Condoms?

# Condom Success Stories: Thailand

Nelson et al. NEJM. 1996

- Due to high prevalence of HIV among CSWs, and military recruits, the Thai Ministry of Public Health began a “100% condom campaign” in brothels along with a media campaign and an enforcement program in 1990
- Successive cohorts of military conscripts demonstrated decreased CSW contacts, increased condom use and decreased HIV infection rates

# Condom Success Stories: Thailand

Nelson et al. NEJM. 1996

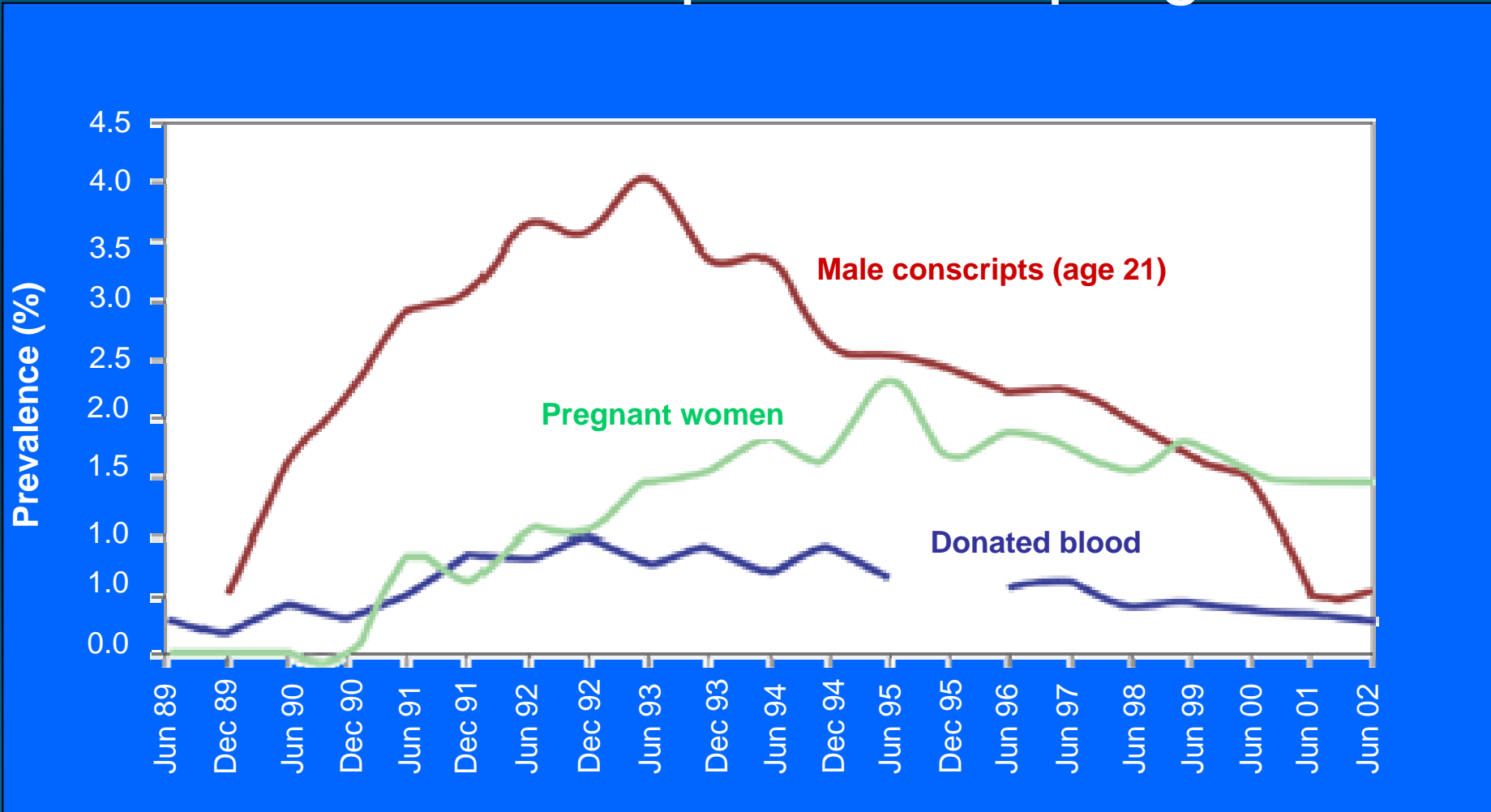
**TABLE 2. HIGH-RISK BEHAVIOR REPORTED BY THE 21-YEAR-OLD MILITARY CONSCRIPTS IN THE 1991, 1993, AND 1995 STUDY COHORTS.**

| TYPE OF BEHAVIOR                          | 1991             | 1993        | 1995       |
|---|------------------|-------------|------------|
|   | (N = 1819)       | (N = 1667)  | (N = 821)  |
|   | no. positive (%) |             |            |
| Sexual activity                           |                  |             |            |
| Any                                       | 1679 (92.3)      | 1553 (93.2) | 716 (87.2) |
| Before the age of 17 yr                   | 660 (36.3)       | 775 (46.5)  | 345 (42.0) |
| Visits to sex workers*                    |                  |             |            |
| Ever                                      | 1482 (81.5)      | 1346 (80.7) | 524 (63.8) |
| In past year                              | 1039 (57.1)      | 738 (44.3)  | 195 (23.8) |
| Condom used on most recent visit†         | 904 (61.0)       | 1125 (83.6) | 485 (92.6) |
| Sexual activity with others*              |                  |             |            |
| With girlfriend                           | 421 (23.1)       | 451 (27.1)  | 231 (28.1) |
| With male partner                         | 51 (2.8)         | 63 (3.8)    | 39 (4.8)   |
| Sexually transmitted disease at any time* | 767 (42.2)       | 539 (32.3)  | 129 (15.7) |
| Any use of illicit injection drugs*       | 20 (1.1)         | 17 (1.0)    | 23 (2.8)   |

\* $P \leq 0.001$  for the comparison between cohorts by the chi-square test for trend.

†Percentages shown for condom use were based on the numbers of men who reported any sexual relations with a sex worker.

# Prevention of heterosexual HIV works! Evidence from the Thai 100% condom promotion program



# Brazil: Aggressive Condom Promotion

Okie. NEJM. 2006

- The first middle income country to offer universal access to HIV treatment, Brazil has been equally aggressive in prevention
- HIV seroprevalence in Brazil has decreased from 1.5% to 0.6%
- Aggressive media promotion of condoms, especially at carnival time, has been key to prevention activities
- Both heterosexuals and homosexuals are targeted
- Condoms (and needle exchange) are also available to prisoners in Brazil

# Brazil: Aggressive Condom Promotion



**“Condom — Don’t Go without It.”**



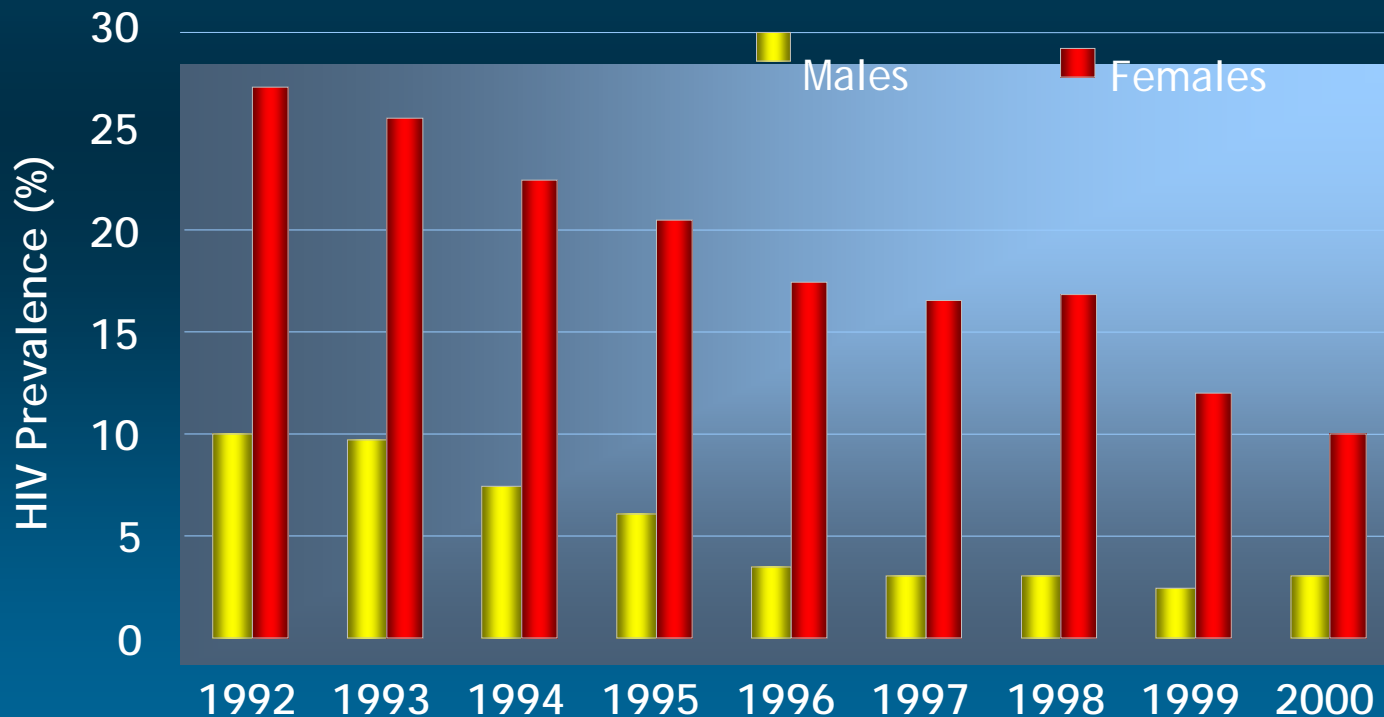
# Cambodia: 100% Condom Program

Cohen. Science.2003.

- Supported by government and NGOs
- Consistent condom use by CSWs increased from 51.9% to 89.8% and HIV prevalence in that group decreased from 42.6% to 28.8%
- Decrease in HIV seroprevalence from 4% in 1999 to 2.6% in 2002

# ¿Can we change behavior?

## HIV Prevalence in 15-24 years old first time testers in Kampala, Uganda: 1992-2000



# Prevention Success in Uganda

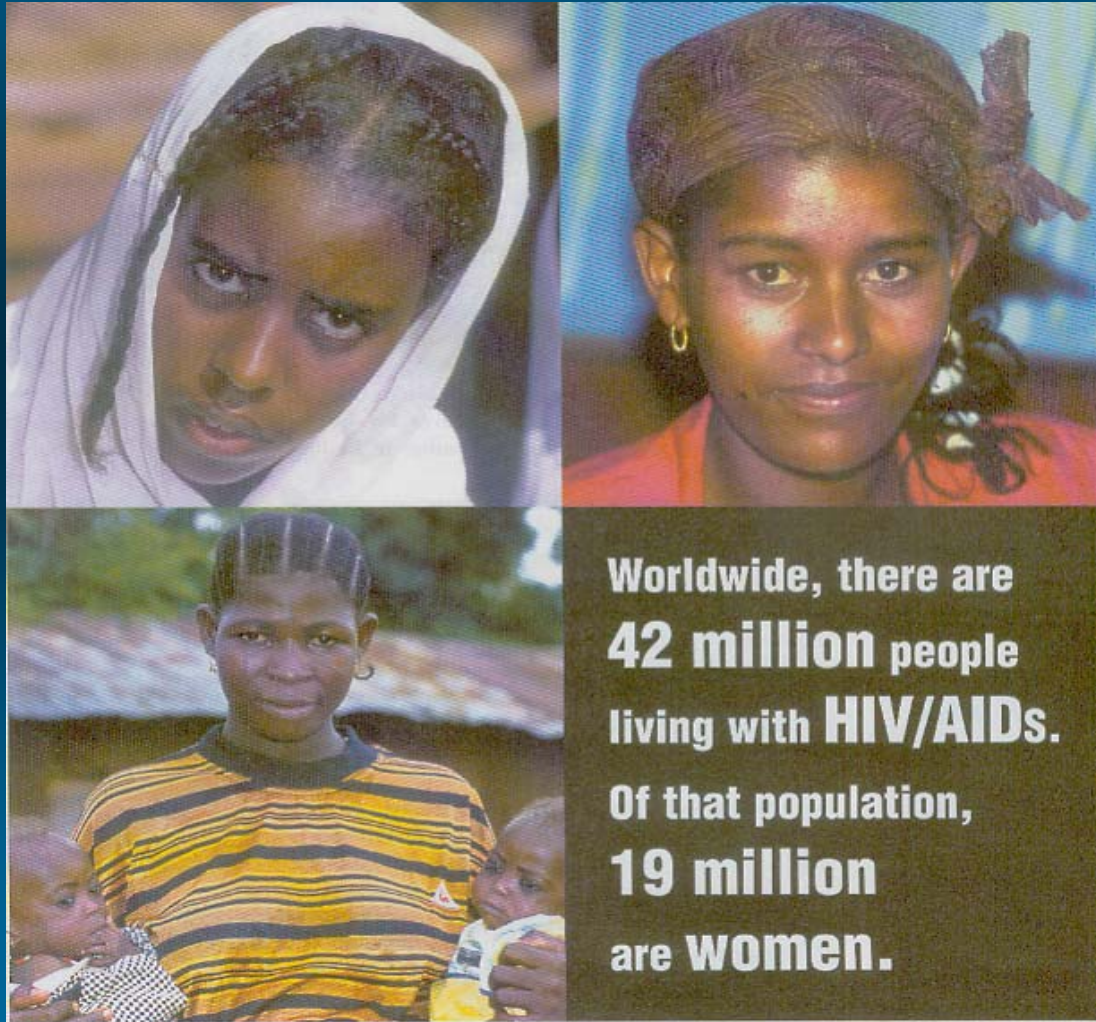
- Massive governmental and NGO campaign
- President of the country personally involved in spreading the message
- Decreased seroprevalence accompanied by increase in the age of sexual debut, decrease in casual partners, increase in condom use

# CDC Systematic Review of HIV Behavioral Interventions for US Populations at High Risk, 2000-2004

- 18 meet specifications of providing best evidence of efficacy in reducing HIV risk
- Significant intervention effects included increased condom use reductions in unprotected sexual intercourse, number of sexual partners, injection drug use, needle sharing and newly acquired sexually transmitted infections.
- All interventions relied on at least one behavioral change theory or model (Social Cognitive Theory, Social Learning Theory, etc)
- All had at least 70% retention rates in both arms and minimal 3 month follow up.

The problem with behavioral interventions appears to be sustaining change over time

For every person initiating HIV treatment,  
10 more are newly infected



Worldwide, there are  
**42 million** people  
living with **HIV/AIDs**.  
Of that population,  
**19 million**  
are **women**.

# Female Controlled Methods

- Diaphragm
- Microbicides

# The Diaphragm: Rationale for Exploration

- Female initiated and controlled
- Worn inside the vagina- unobtrusive
- Creates a physical barrier over the cervix- site believed to be most vulnerable to HIV infection
- If effective, could be combined with an effective microbicide



# Vaginal Diaphragm Clinical Trial



- Mira Vaginal Diaphragm with Replens
- Over 5000 women enrolled in Africa
- 32% HIV seroprevalence baseline
- Results published July 2007 in the Lancet.

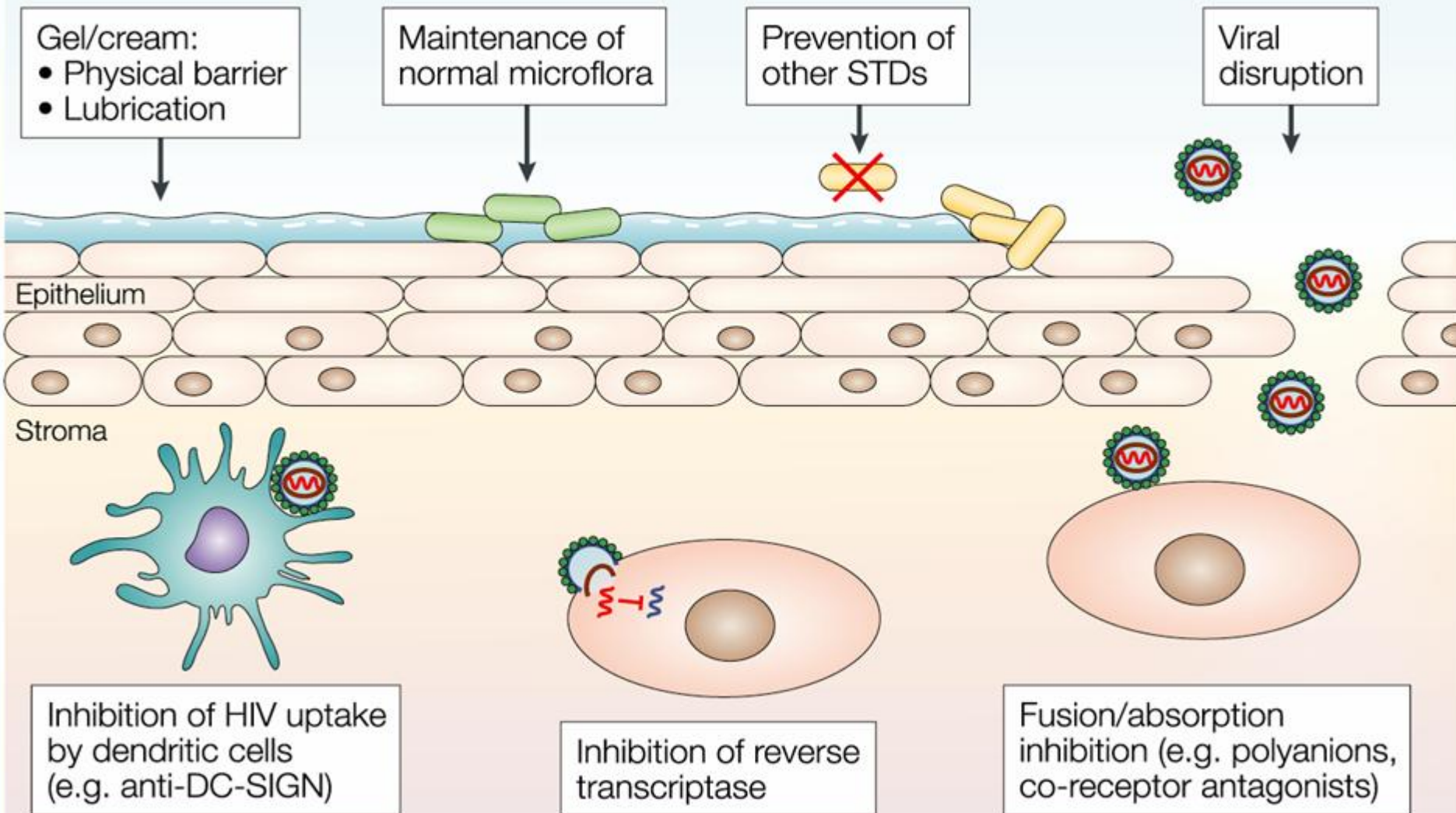
# Vaginal Diaphragm Clinical Trial

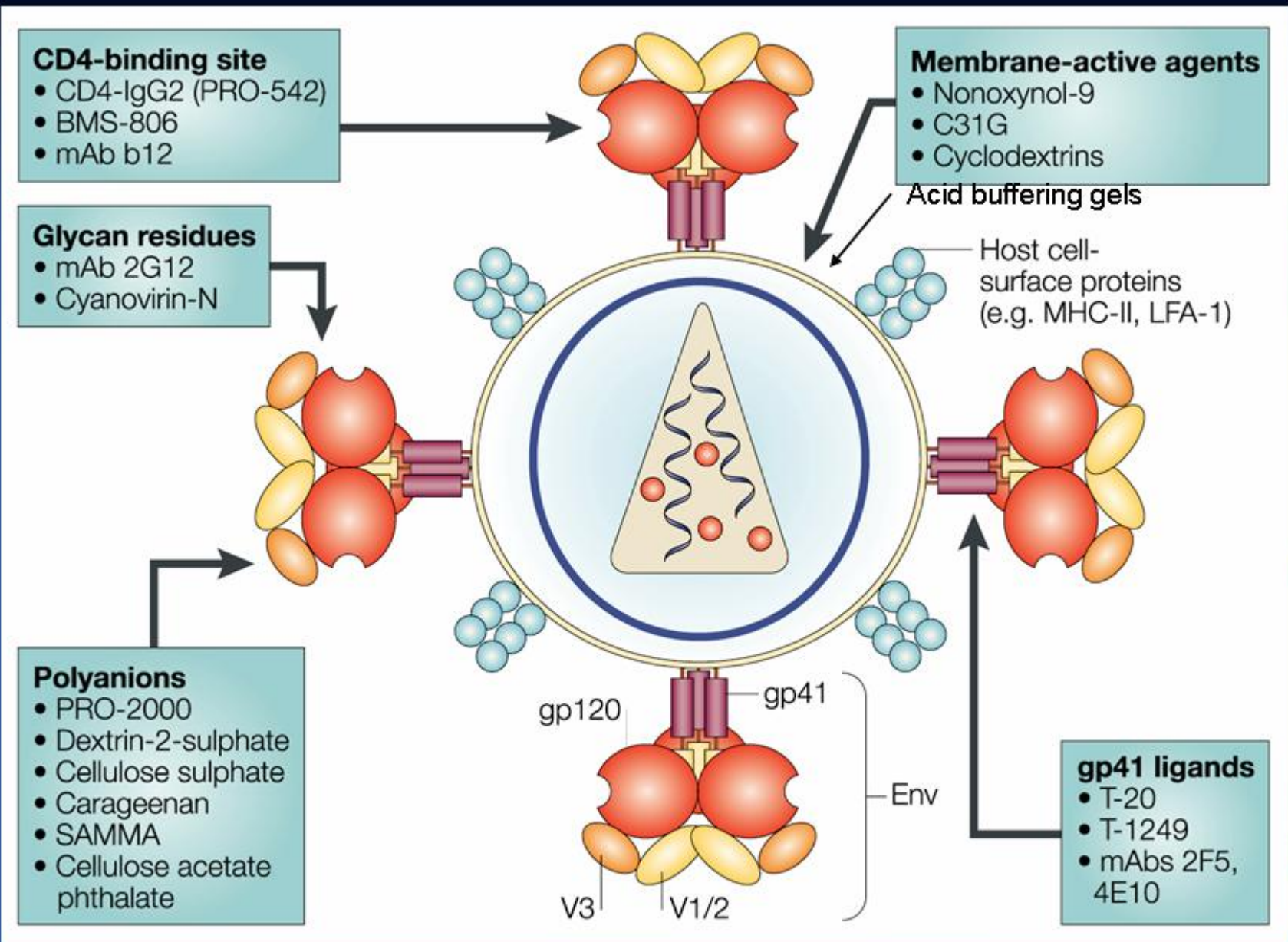
- Incidence rates of HIV in the intervention group (4%) and condom group (3.9%) virtually identical
- Both groups had been counseled to use condoms and were given condoms
- Women randomized to the diaphragm group were significantly less likely to use condoms, but there weren't enough in the study to make valid statistical inferences
- Condom use increased significantly in both arms over time, indicating women were able to negotiate condom use.

# Microbicides

- Drugs or biologic products, for use primarily by women, that can be applied to the vagina prior to intercourse in order to reduce the transmission of HIV
- May or may not have spermicidal activity
- May be available as gels, intravaginal rings, or in other forms
- May be coitally dependent or provide continuous protection
- Potentially may be protective for rectal use as well

# Sites of Action of Microbicides





# Microbicide Trial Challenges

- No validated surrogate endpoints exist, primary endpoint is HIV infection
- Thousands of high risk women required for trials
- Efficacy trials must measure the incremental effect of the potential microbicide over and above known effective methods- condom use and HIV treatment
- If efficacy is less than condoms, it may be hard to show
- Placebo gel may be protective through lubricating effects
- Adherence of participants may be difficult to measure

# Vaginal Microbicides: Randomized Controlled Trials to Date

- Nonxynol 9 (2002)  
First microbicide to fail, increased HIV risk among users.  
Found to be cytotoxic at higher levels of concentration
- Cellulose Sulfate (2007)  
Clinical trials halted after a trend towards increased HIV risk among users of the product.
- SAAVY (2007)  
Two Phase 3 trials discontinued due to low HIV incidence
- Carraguard (2008)  
Trial halted after it was shown to have no protective value

# Planned Phase III Trials

| Network/<br>Sponsor                  | Product/s                              | N (design)                     | Countries   | Sites | Start |
|--------------------------------------|--|--------------------------------|---|-------|-------|
| HPTN [NIAID]<br>Indevus<br>Reprotect | Pro 2000/5<br>Buffergel<br>(Phase IIb) | 3,200 (4 arm)                  | Malawi [Blantyre, Llongwe]<br>South Africa [Durban, Hlabisa]<br>Tanzania [Moshi]<br>Zambia [Lusaka]<br>Zimbabwe [Chitungwiza, Harare]<br>USA [Philadelphia] | 9     | 2/05  |
| Biosyn/<br>GMP/FHI                   | Saavy [C31g]                           | 4,284 (2-arm<br>phase III × 2) | Ghana [Accra, Kumasi]<br>Nigeria [Lagos, Ibadan]  | 4     | 4/04  |
| CONRAD/<br>GMP                       | Cellulose<br>sulfate                   | 2,500 (2-arm)                  | India [Chennai]<br>Kenya [ACCT-Nairobi... rural?]<br>Uganda [Kampala-Makerere]<br>Benin [CIDA]  | 4     | 6/05  |
| FHI                                  |  | 2,700 (2-arm)                  | Cameroon [Yaounde]  | ~2    | 2004  |
| Population<br>Council/CDC            | Carraguard                             | 6,000 (2-arm)                  | Botswana<br>South Africa [CapeTown, Soshanguve]   | 3     | 3/04  |
| MRC [DFID]<br>Indevus                | Pro 2000/5<br>(0.5 vs 2% vs<br>HEC)    | 12,000 (3-arm)                 | Cameroon<br>Durban<br>Johannesburg<br>Tanzania<br>Uganda  | 5     | 3/05  |
| Total                                |  | ~30,000                        |   | ~30   |       |

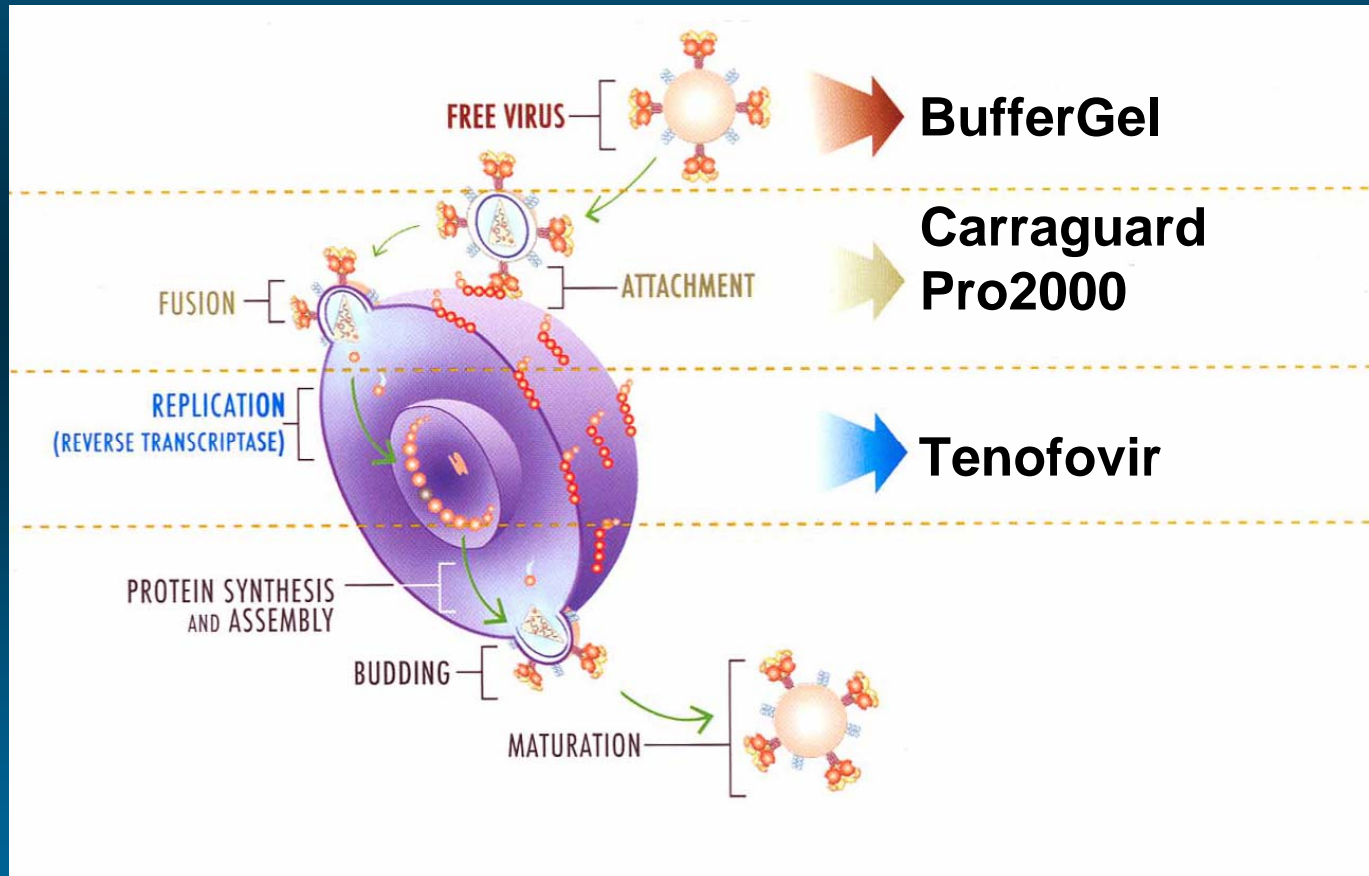
Number of women ~ 30,000. Cost per trial > \$30M. Total cost \$200-500M.



# Possible mechanisms of increased susceptibility to HIV

- Microbicide induced changes in genital epithelial integrity or permeability
- Microbicide induced genital inflammation, increased immune activation and/or decreased immunity
- Microbicide induced vaginal flora changes

# Topical Microbicides – Current Products



# ARV Containing Vaginal Rings

- Could provide more specific, longer acting agents, including ARVs that enter genital tissues, but not the plasma
- Could provide coverage for 30 days or longer
- Would be unobtrusive, easy to use



# Conclusion

- Both male and female condoms reduce HIV transmission risk
- Aggressive government efforts to promote condom use have been successful in several countries
- Behavioral change interventions have been demonstrated effective in some scenarios, but maintaining the change is difficult
- The search for an effective female microbicide has been frustrated by several failed trials

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