What's new in HIV management ?

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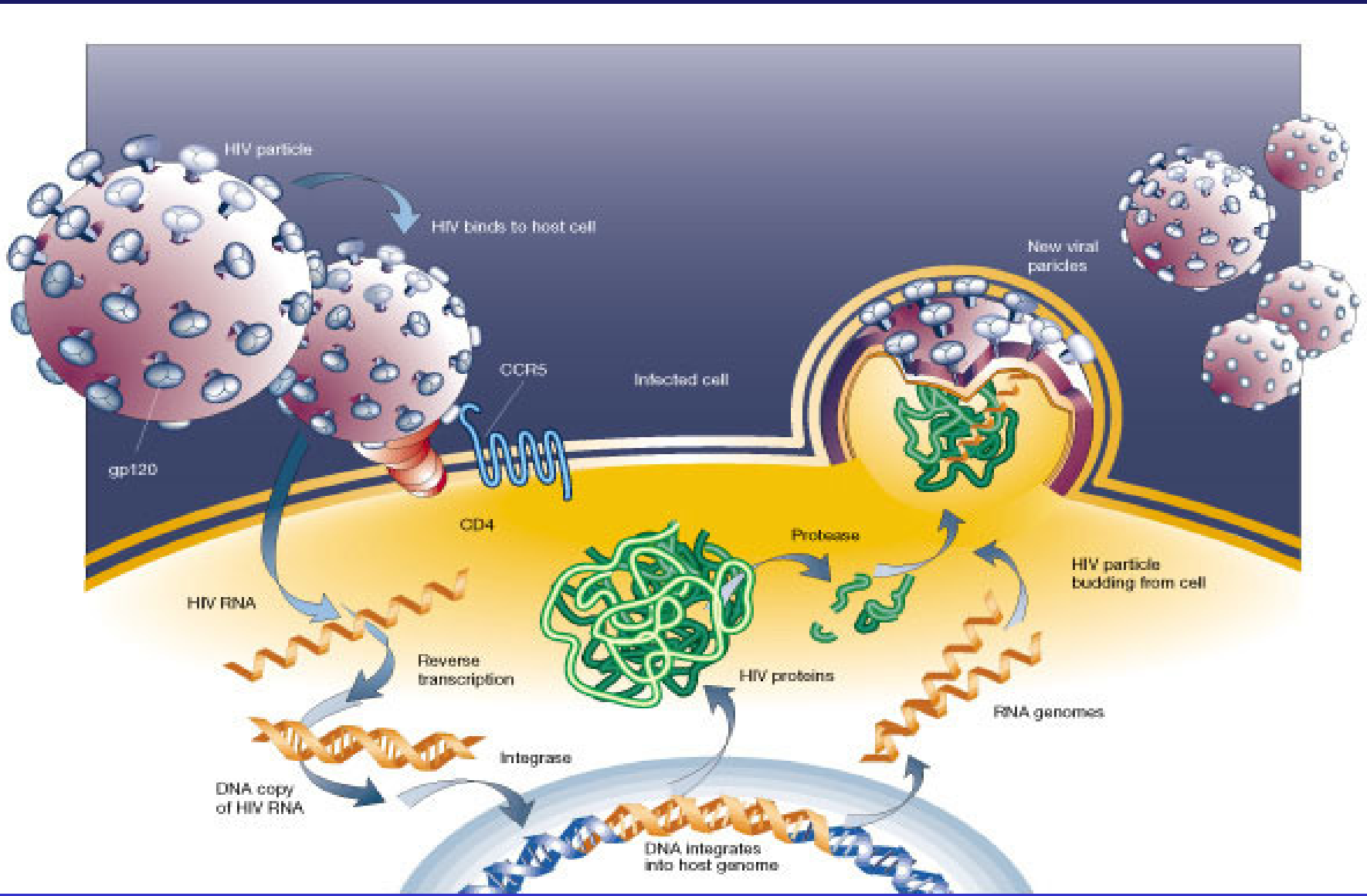
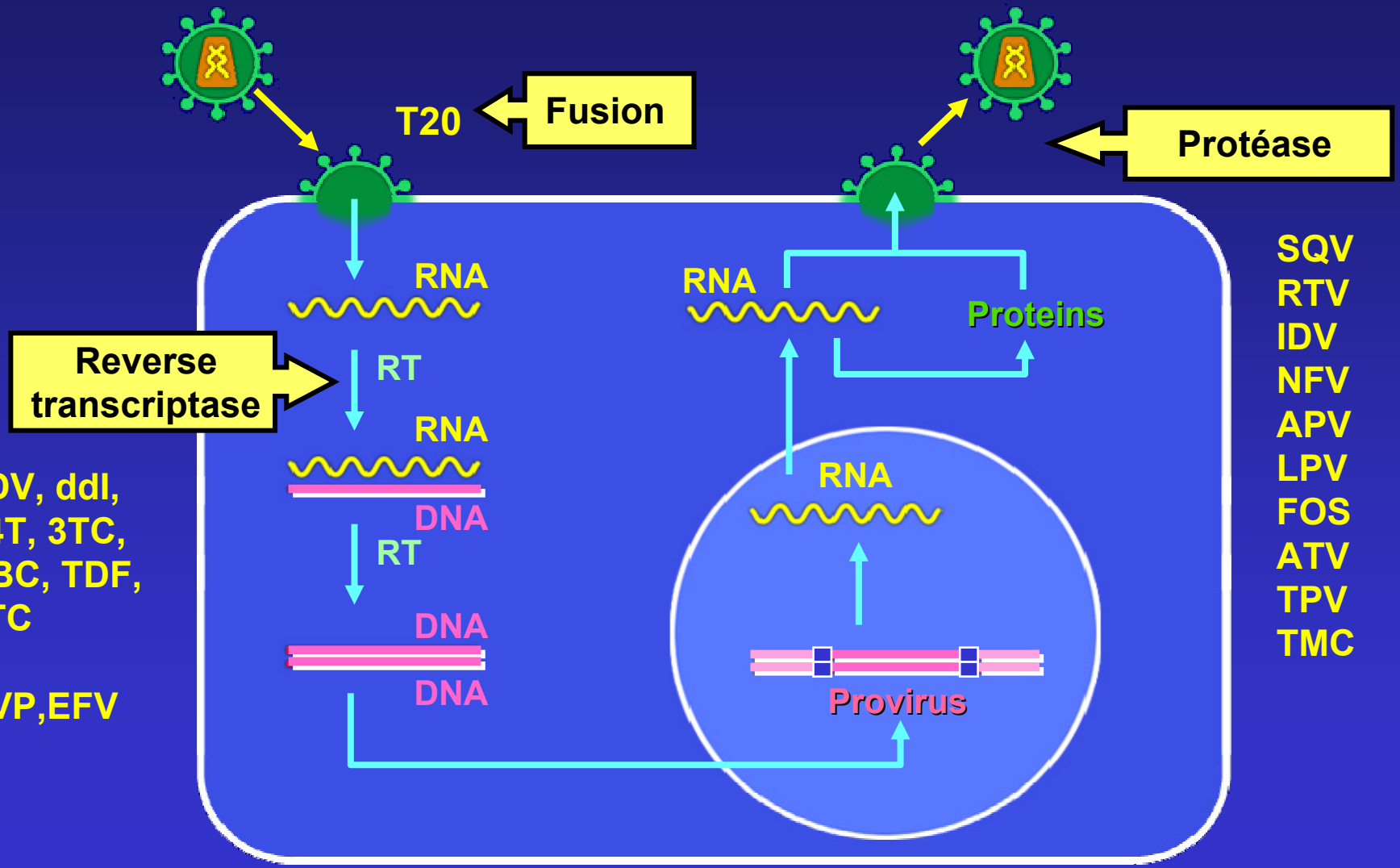
Anti HIV drugs 2005

Reverse transcriptase inhibitors	Protease inhibitors
nucleosides analogues	- saquinavir (SQV)
- zidovudine (AZT, ZDV)	- ritonavir (RTV)
- didanosine (ddI)	- indinavir (IDV)
- lamivudine (3TC)	- nelfinavir (NFV)
- stavudine (d4T)	- fosamprenavir (FAPV)
- abacavir (ABC)	- lopinavir/r (LPV/r)
- emtricitabine (FTC)	- atazanavir (ATV)
nucleotide analogue	- tipranavir (TPV)
- tenofovir (TFV)	- Darunavir (TMC 114)
non-nucleosides	**Fusion inhibitors**
- nevirapine (NVP)	-enfuvirtide (T20)
- efavirenz (EFV)	

HIV life cycle



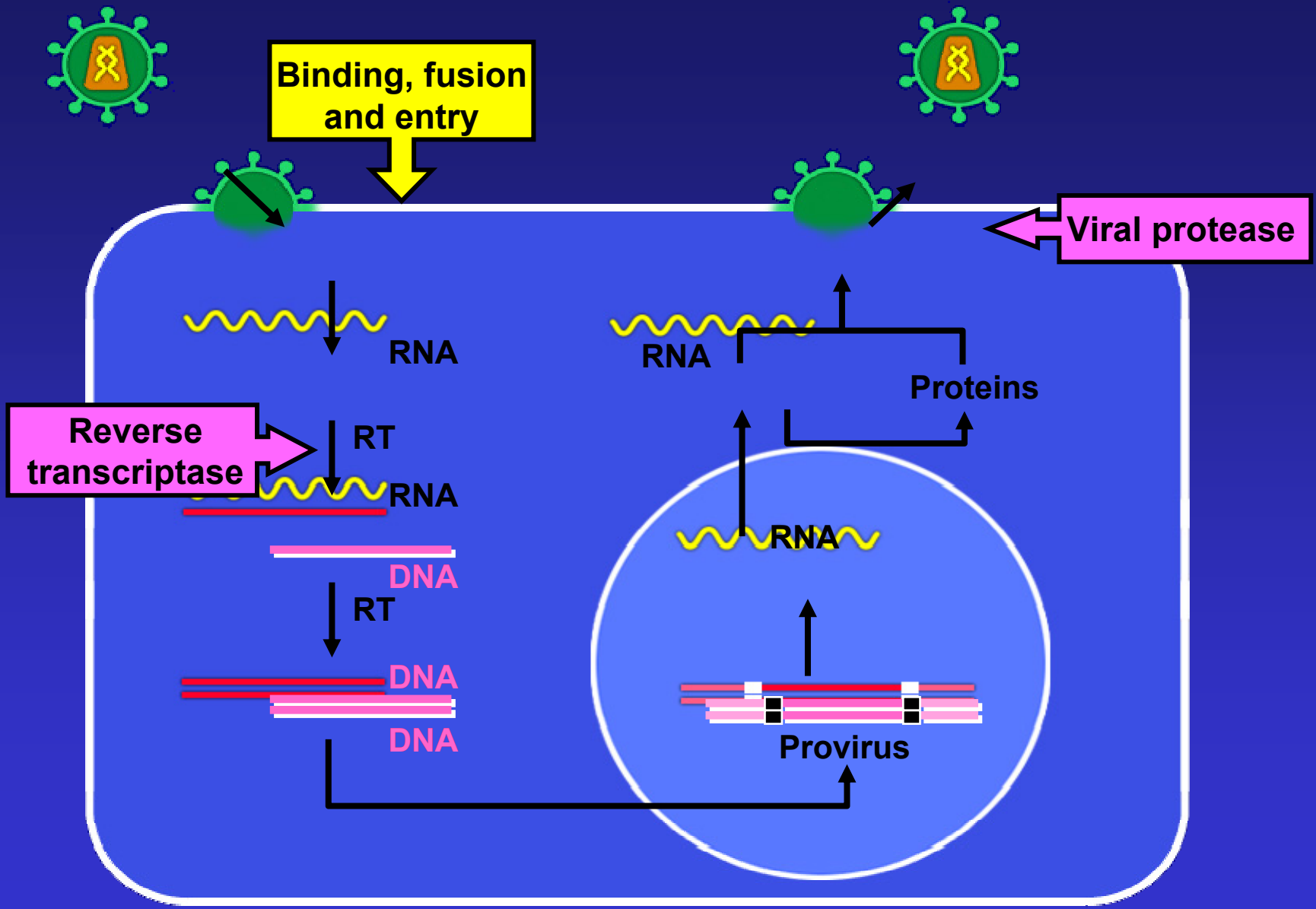
Targets for drugs available in 2005



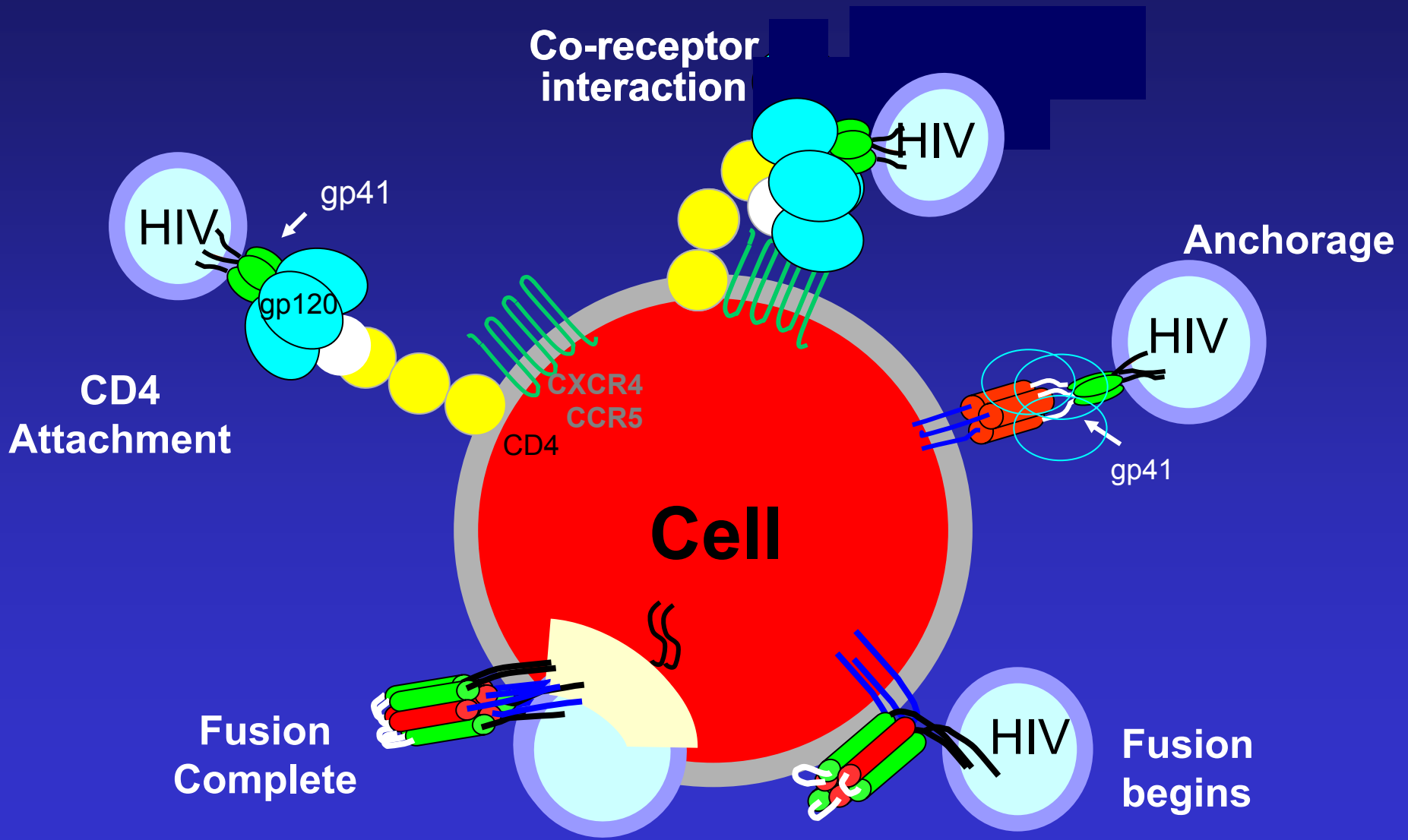
Pendulum coming back towards PI

Higher genetic barrier
Simple dosing
Improved tolerability
Less metabolic impact

New targets

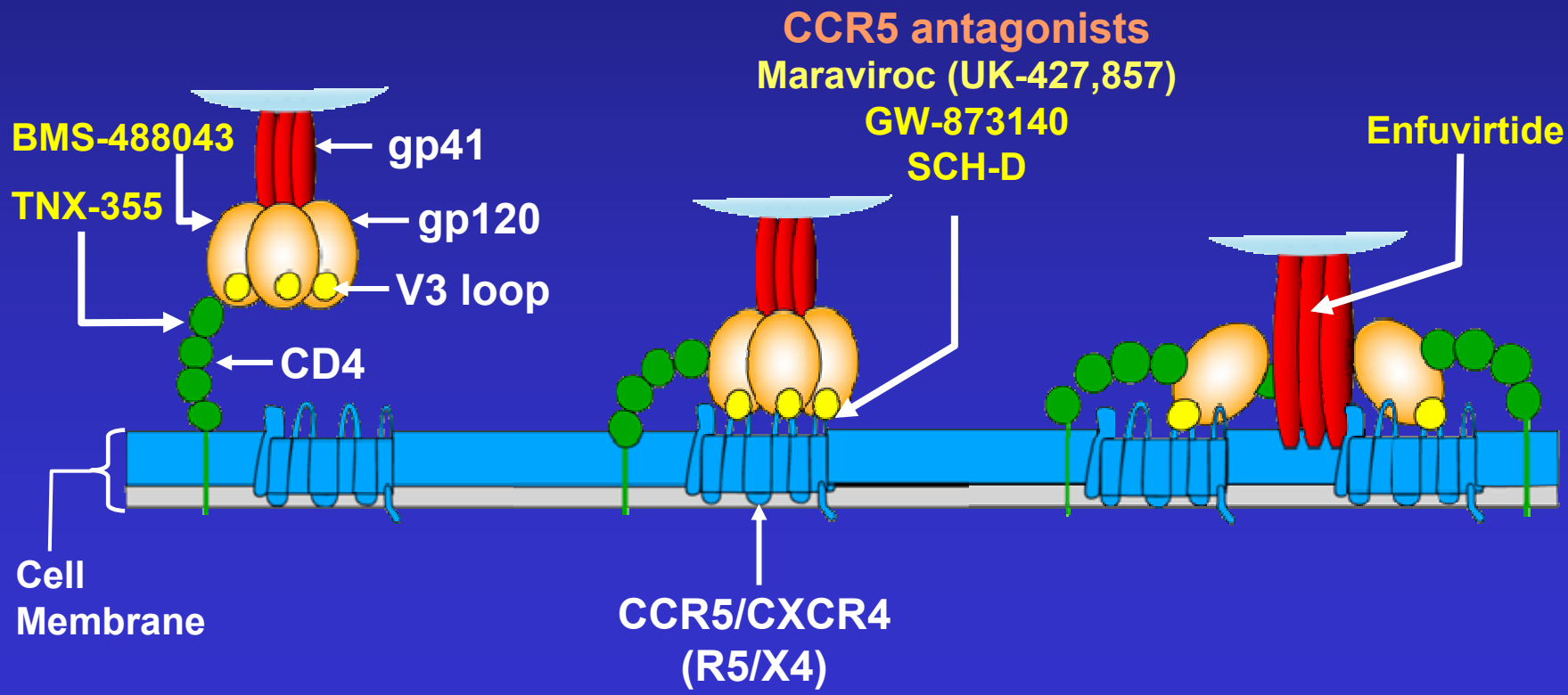

Binding, fusion and entry
Viral protease
RNA
RNA
Proteins
Reverse transcriptase
RT
RNA
DNA
RT
DNA
DNA
RNA
Provirus

Interactions between HIV, CD4 and coreceptors



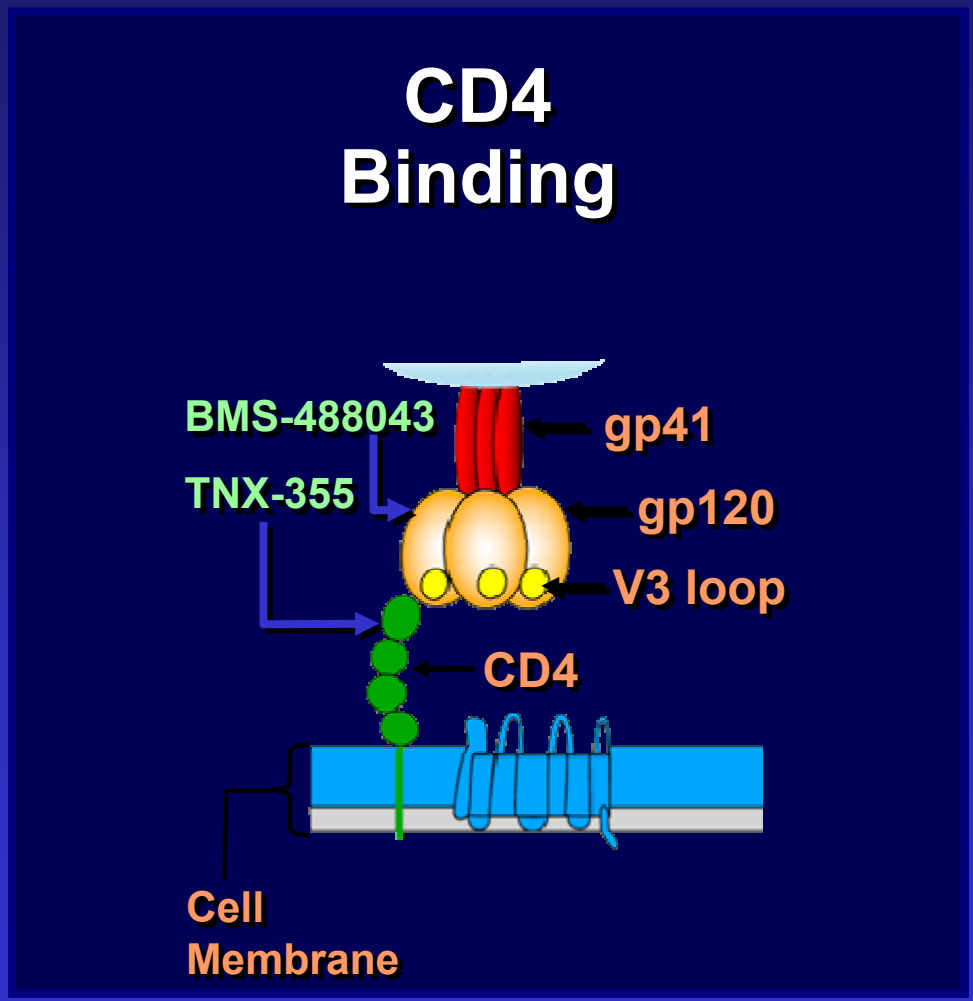
HIV Attachment and Fusion Targets for Inhibition

CD4 Binding → **Co-receptor Binding** → **Virus-Cell Fusion**



Adapted from Moore JP *et al*. PNAS 2003;100:10598-10602.

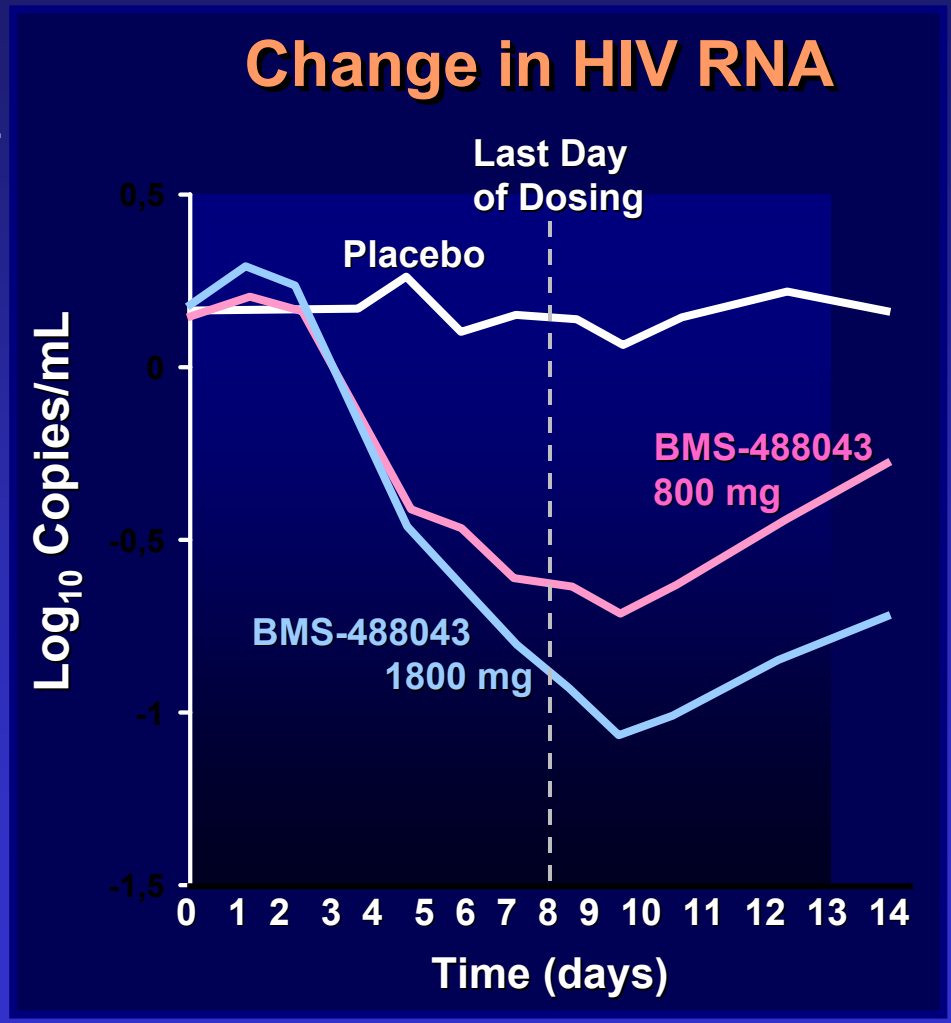
HIV Attachment and Fusion Targets for Inhibition



Moore JP, et al. *PNAS.* 2003;100:10598-10602.

BMS-488043: Proof-of-Concept Study

- 30 treatment-naïve patients
  - HIV RNA: 4.66 $\log_{10}$ copies/mL
  - CD4: 403 cells/μL
- Monotherapy for 8-days, then 7-day follow-up
  - Placebo
  - BMS-488043
    - 800 mg q12 hours
    - 1800 mg q12 hours
- Change in viral load
  - >1.0 log reduction
    - BMS-488043: 58% of patients
    - Placebo: 0%
- Dose-response relationship
- Generally well-tolerated



Hanna G, et al. 11th CROI. San Francisco, 2004. Abstract 141.

Two groups of HIV-1 variants with distinct biological phenotypes

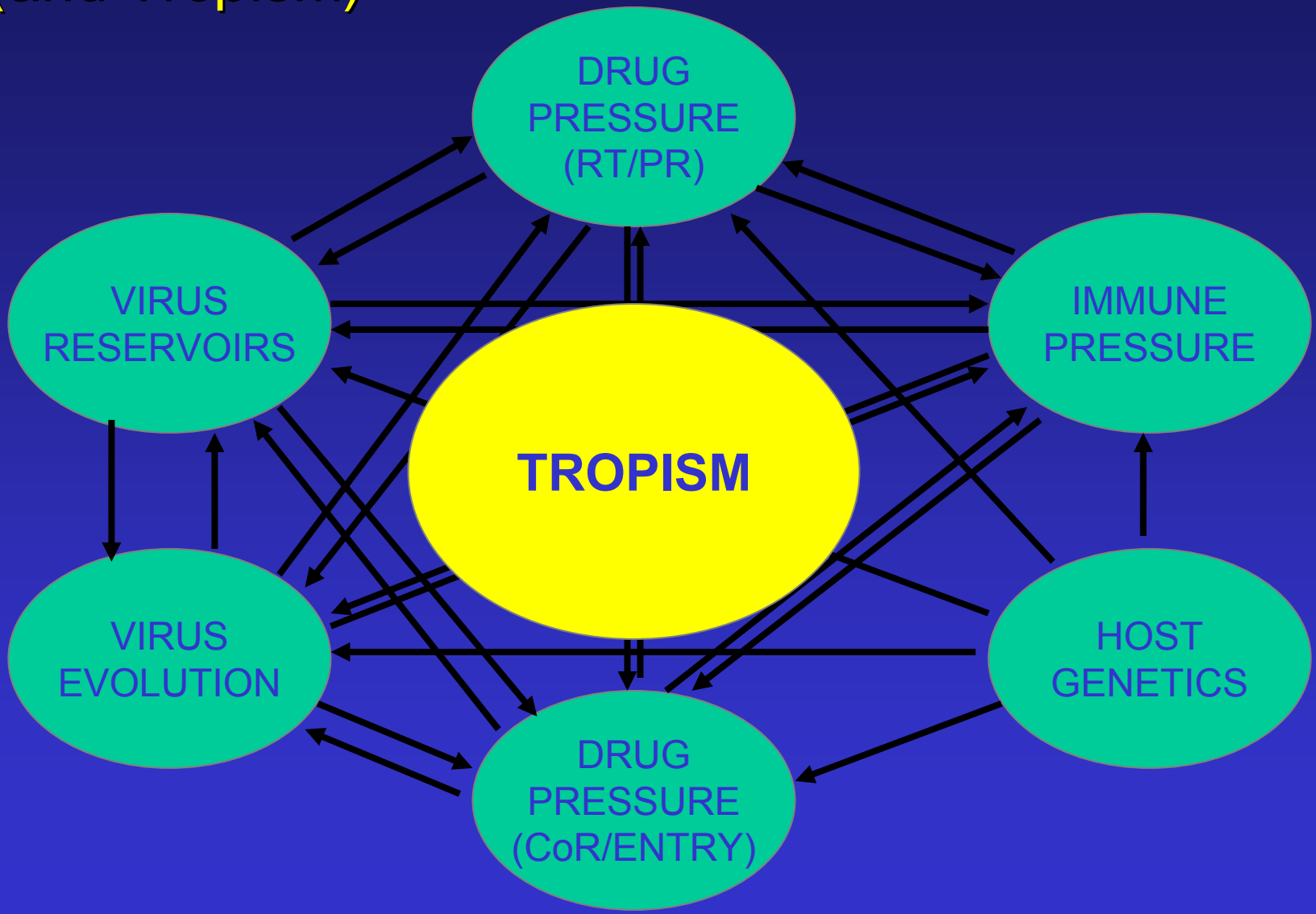
CCR5 using variants (R5 HIV)

- establish new infections and predominate in early infection
- persist throughout infection (also after X4 conversion)
- T cell and macrophage-tropic
- associated with slow CD4 decline

CXCR4 using variants (X4 HIV)

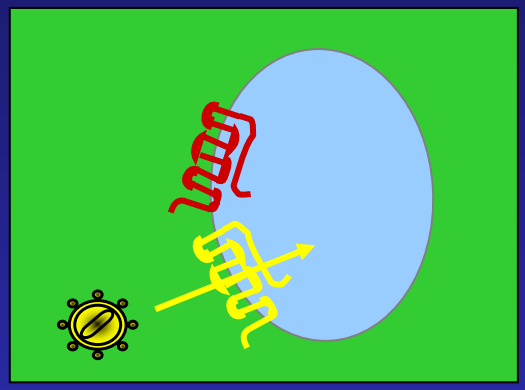
- emerge during the course of infection
- evolve from R5 HIV variants
- present in 50% of AIDS patients
- replicate in T cell lines (MT-2)
- associated with rapid CD4 decline
- predictive of rapid progression

Factors That Influence Virus Quasispecies (and Tropism)

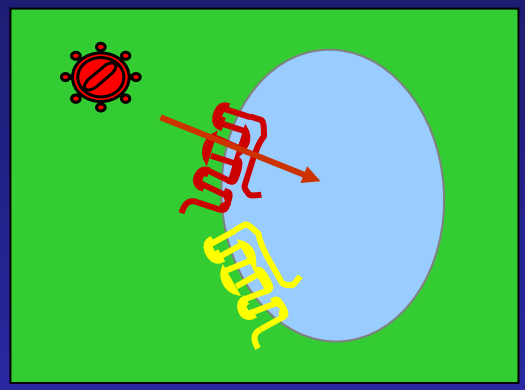


HIV Envelope Tropism

R5-Tropic

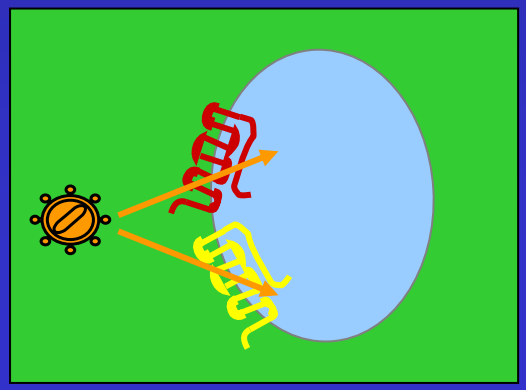


X4-Tropic

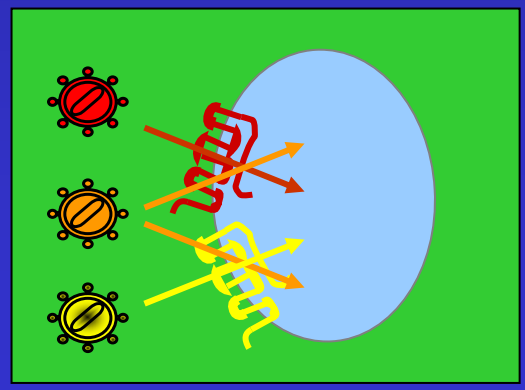


R5/X4-Tropic

Dual-Tropic



Mixed-Tropic



CXCR4

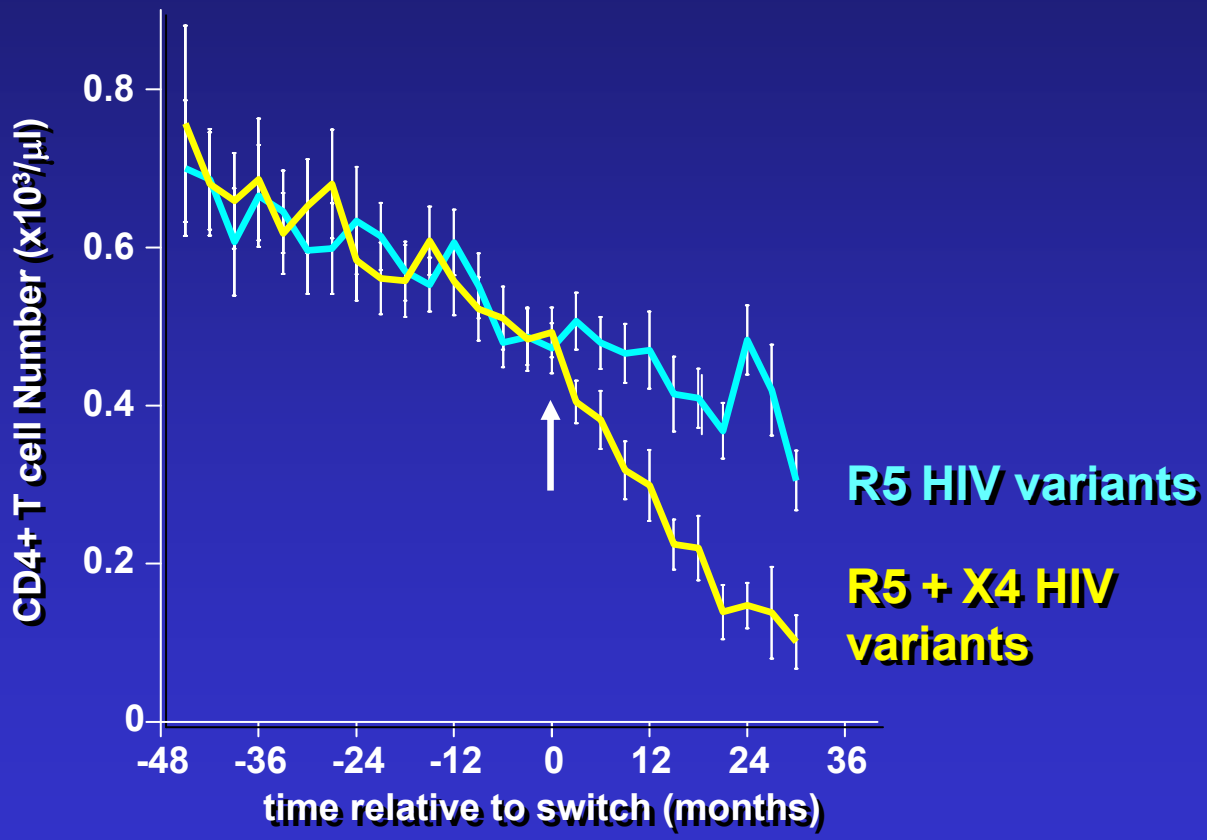
CCR5

X4-tropic HIV

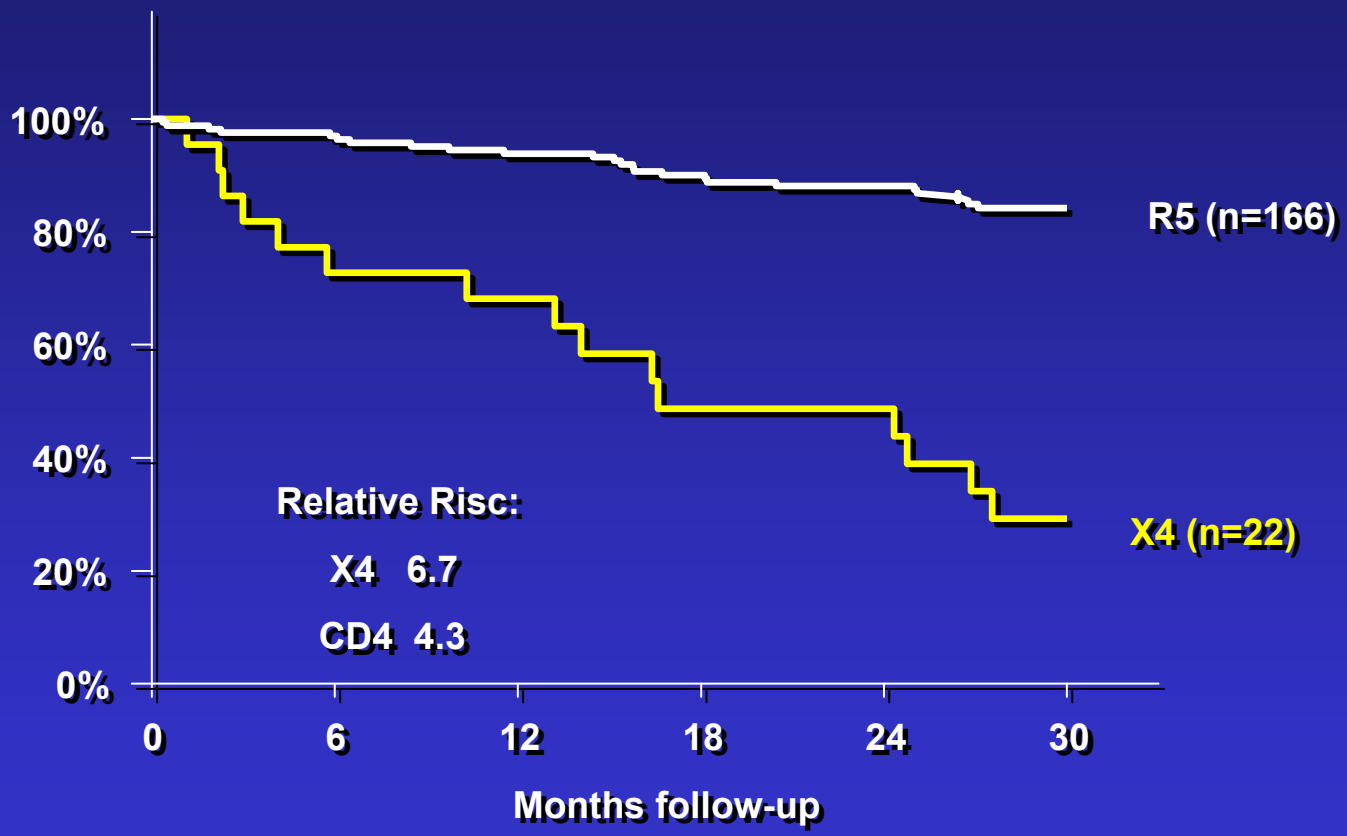
R5-tropic HIV

dual-tropic HIV

CD4+ T cell decline in relation to the presence of R5 and X4 HIV-1

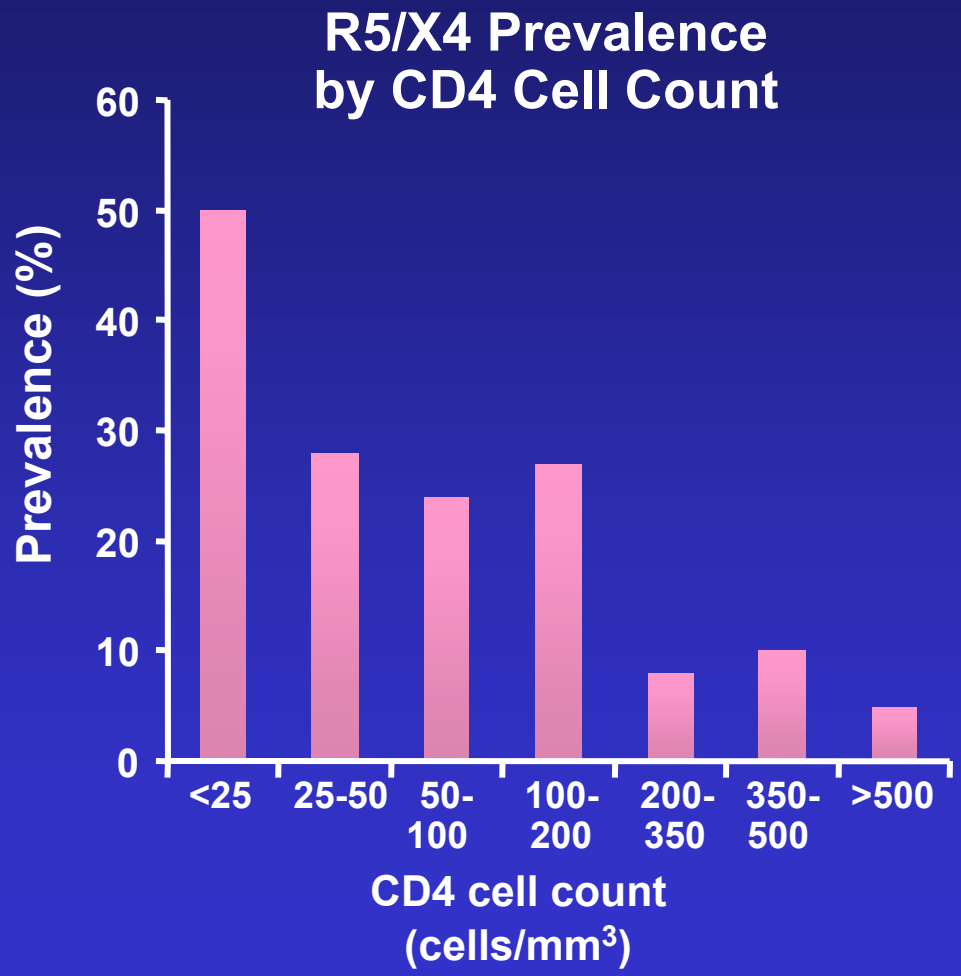


AIDS free survival in relation to the R5/X4 phenotype of HIV



Prevalence, Predictors, and Clinical Impact of HIV Co-receptor Usage

- **Homer cohort** (1996-1999)
  - 806 patients
  - Treatment-naïve
  - Median follow-up: >4 years
- **Overall prevalence**
  - R5/X4 or X4: 16.7%
    Markedly dependent on baseline CD4 cell count
- **X4 not predictive of mortality or CD4 cell count decline below baseline**



Harrigan PR *et al*. 15th IAC 2004. Abstract MoPeB3117

Prevalence of HIV Co-receptor Usage

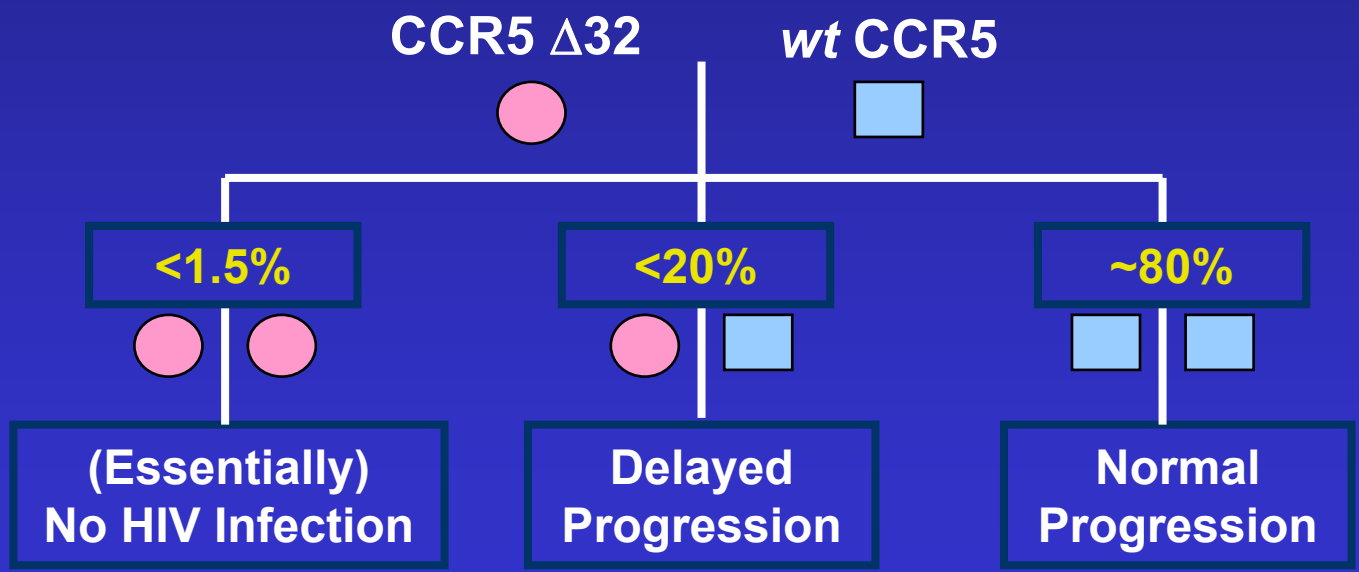
Study/Source	Population	R5	X4	R5/X4
Maraviroc (UK-427,857) Phase 2[a]	Naive	94	0	6
Homer cohort[b]	Naive	83	<1	17
C & W cohort[c]	Naive	85	0	15
GSK[d]	Naive	88	0	12
TORO 1/2[e]	Experienced	62	4	34
ViroLogic[f]	Experienced	50	2	48

a Data on file
b Harrigan PR *et al*. 15th IAC 2004. Abstract MoPeB3117
c Moyle GJ *et al*. 15th IAC 2004. Abstract WePeB5725
d Demarest *et al*. ICAAC 2004. Abstract H-1136
e Whitcomb *et al*. CROI 2003. Abstract 557
f Huang *et al*. ICAAC 2002. Abstract 2040

Inhibition of Co-receptor-mediated Entry

- Promising interventional target
- CCR5 in humans
  - CCR5 Δ32 mutant associated with essentially normal immune function

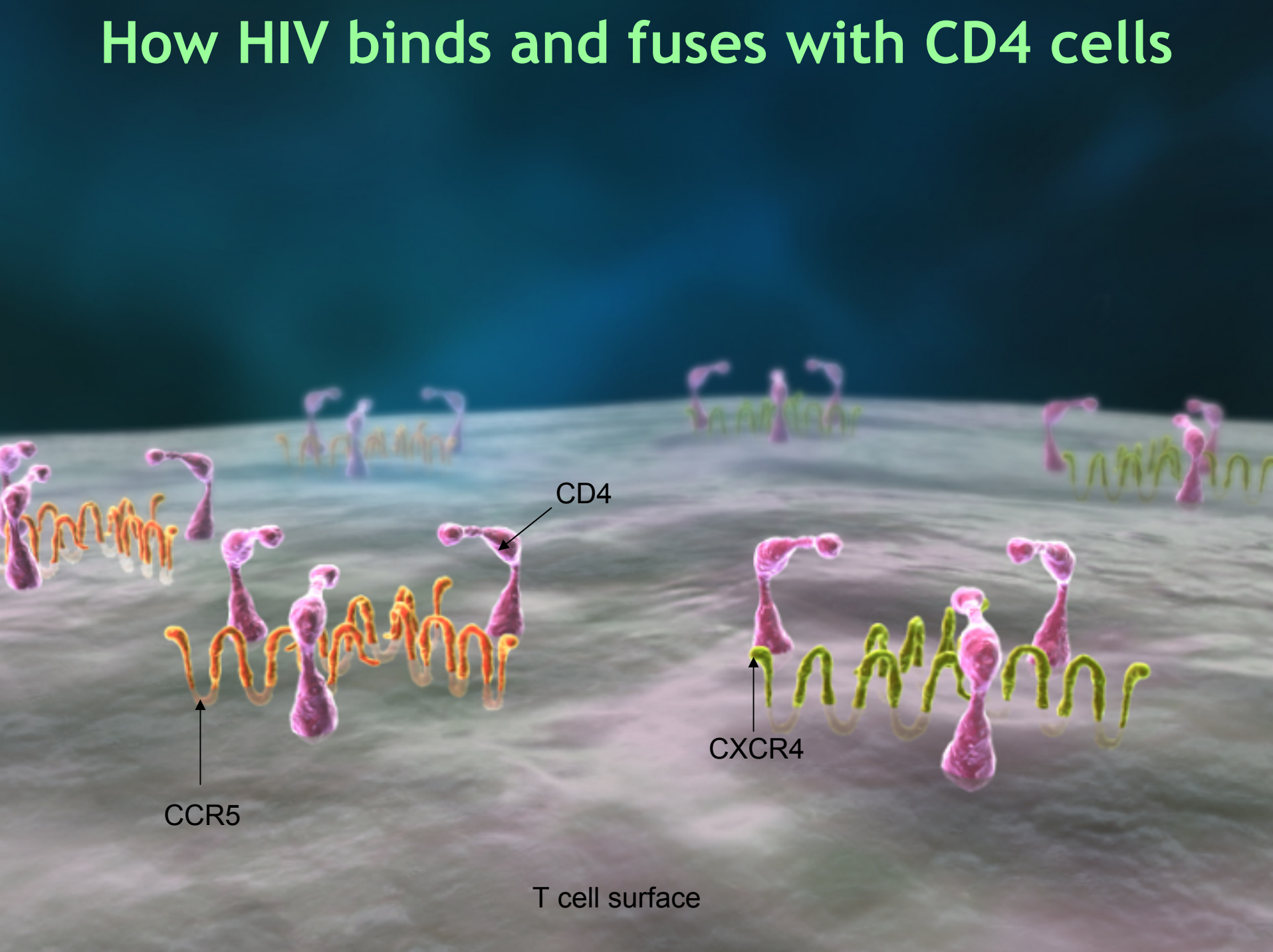
Key co-receptor for HIV, alternative is CXCR4

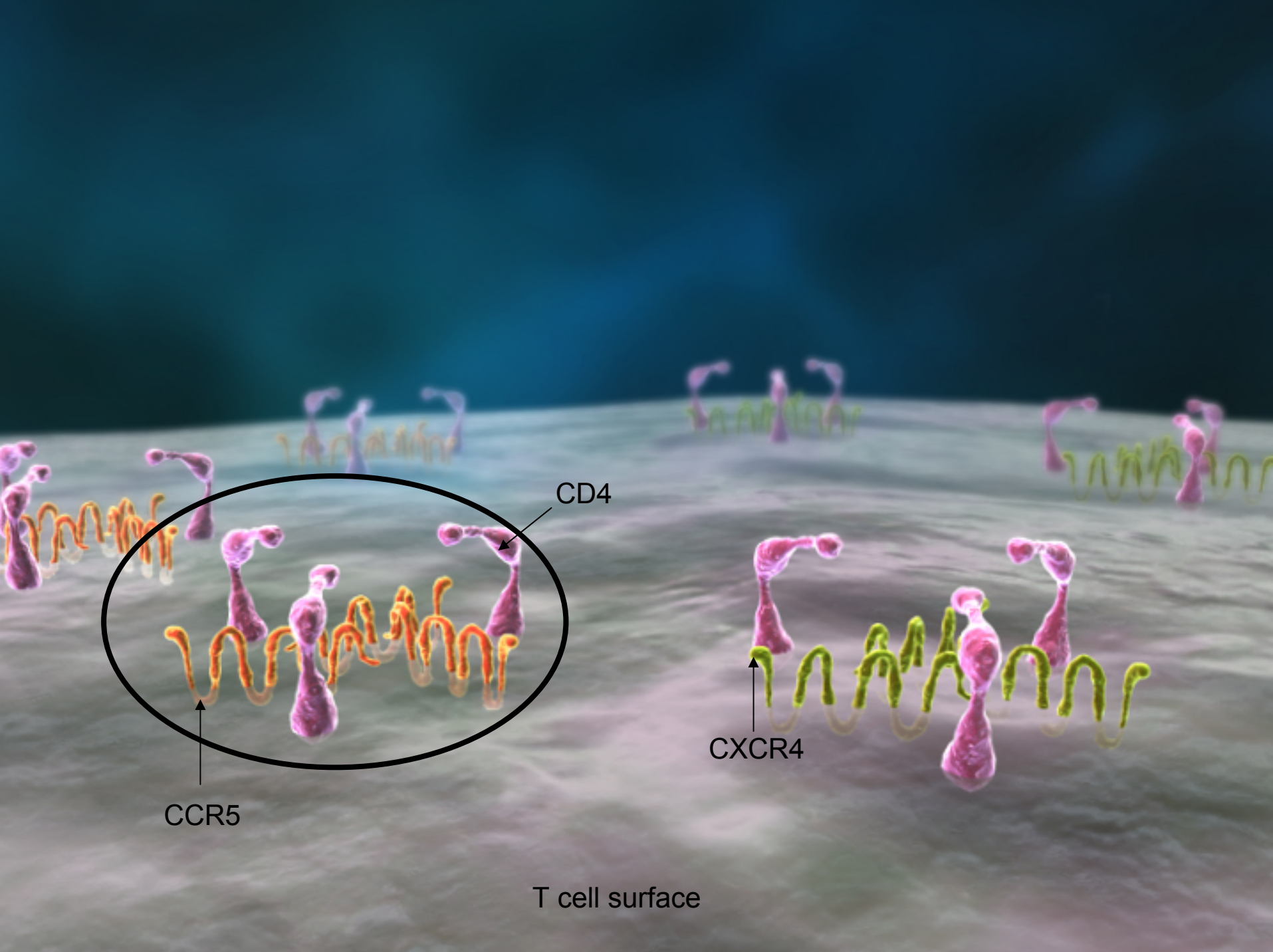


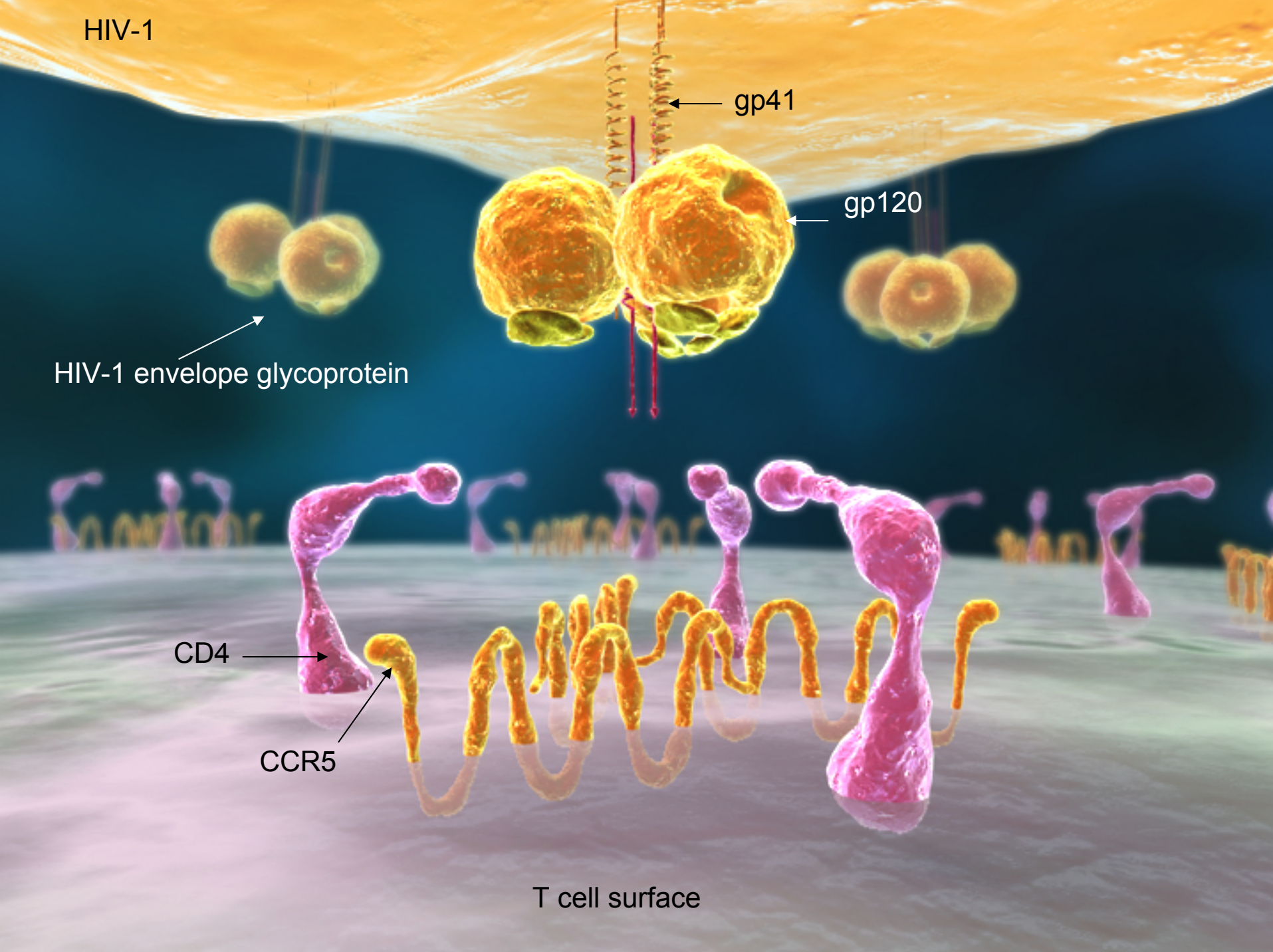
Lui R *et al*. Cell. 1996;86:367-7
Samson M *et al*. Nature. 1996;382:722-5
Dean M *et al*. Science. 1996;273:1856-62

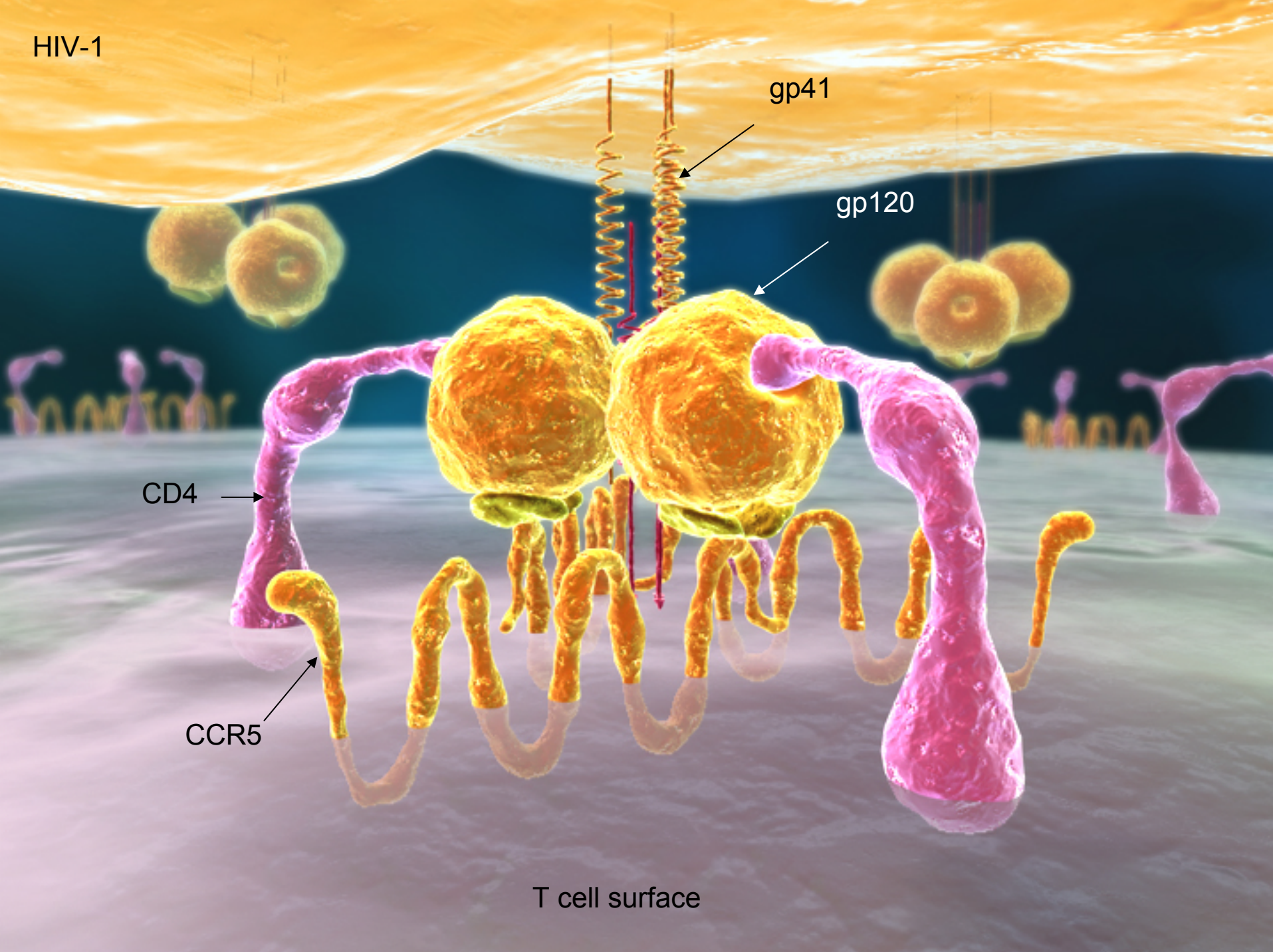
Huang Y *et al*. Nat Med. 1996;2:1240-3
Michael NL *et al*. Nat Med. 1997;3:1160-2
Eugen-Olsen J *et al*. AIDS. 1997;11:305-10

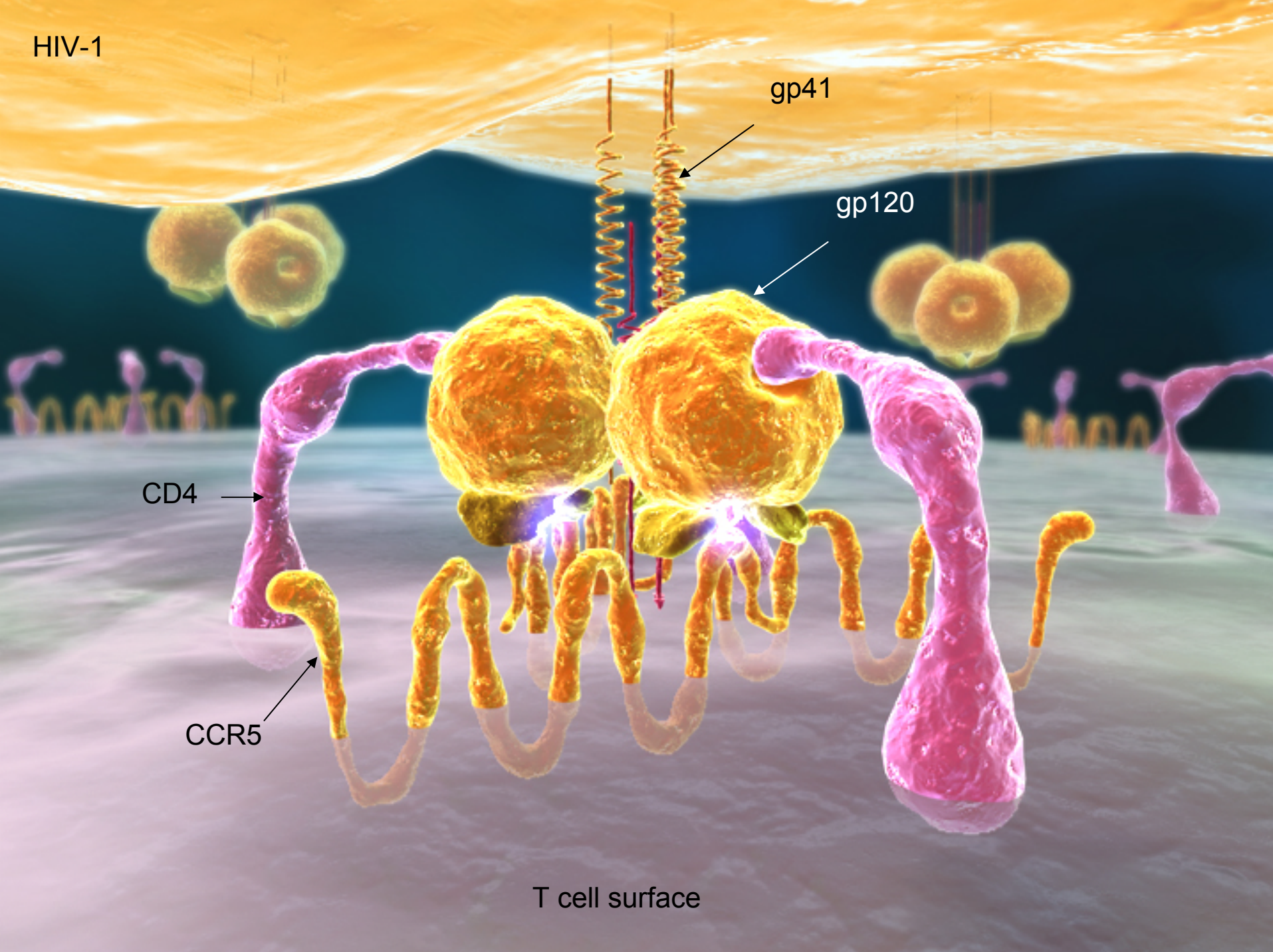
How HIV binds and fuses with CD4 cells

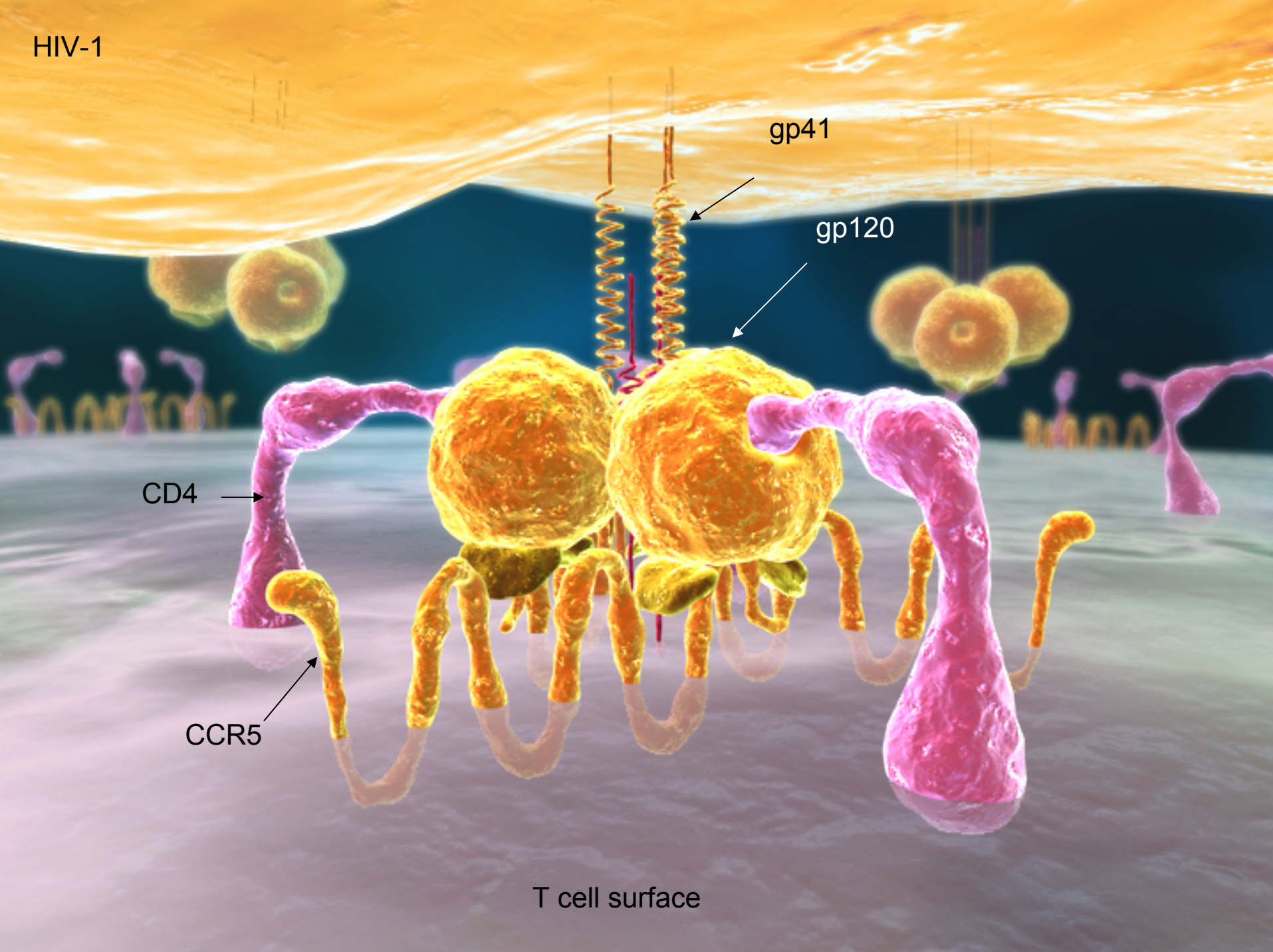


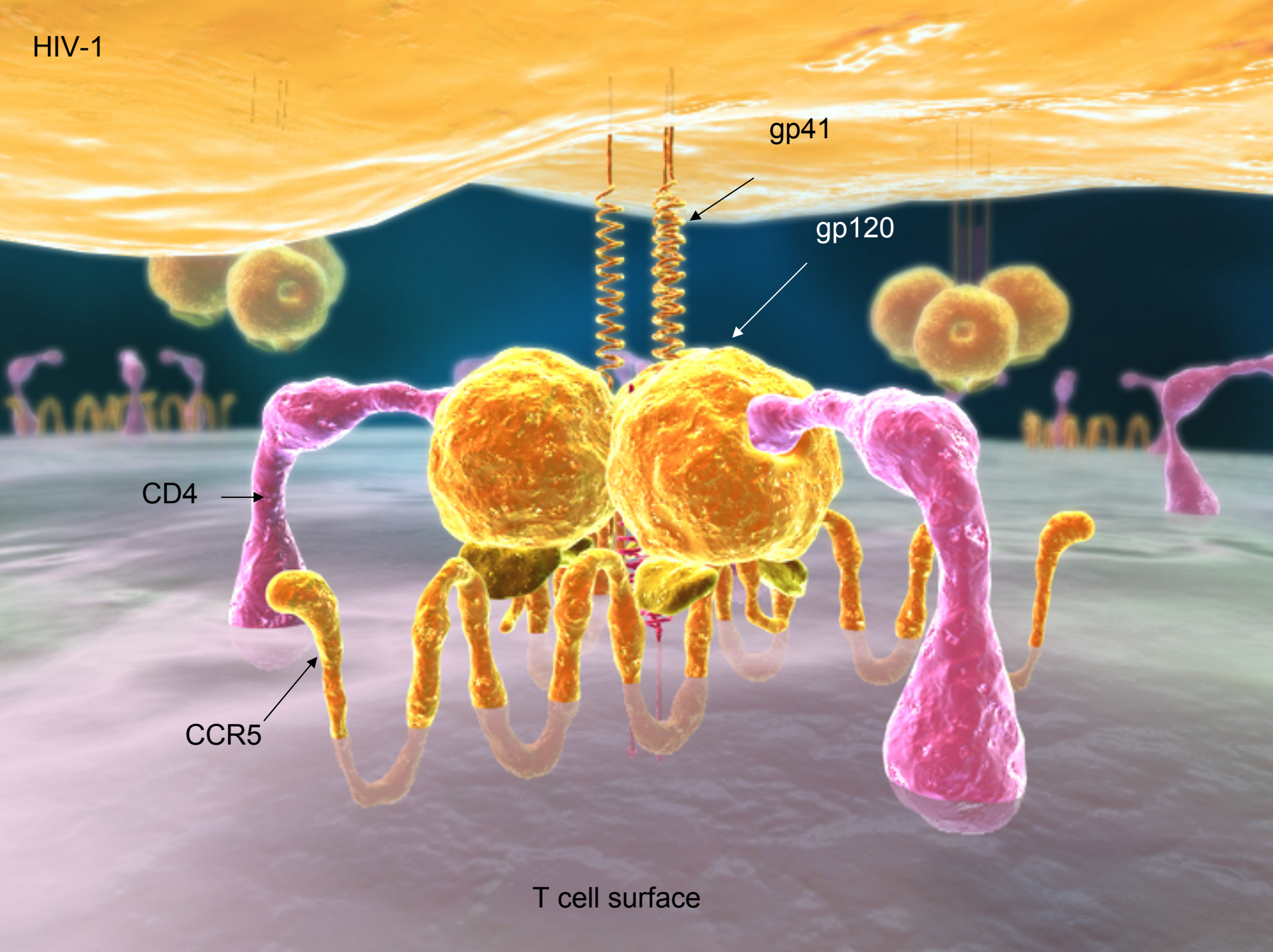

CD4
CCR5
CXCR4
T cell surface

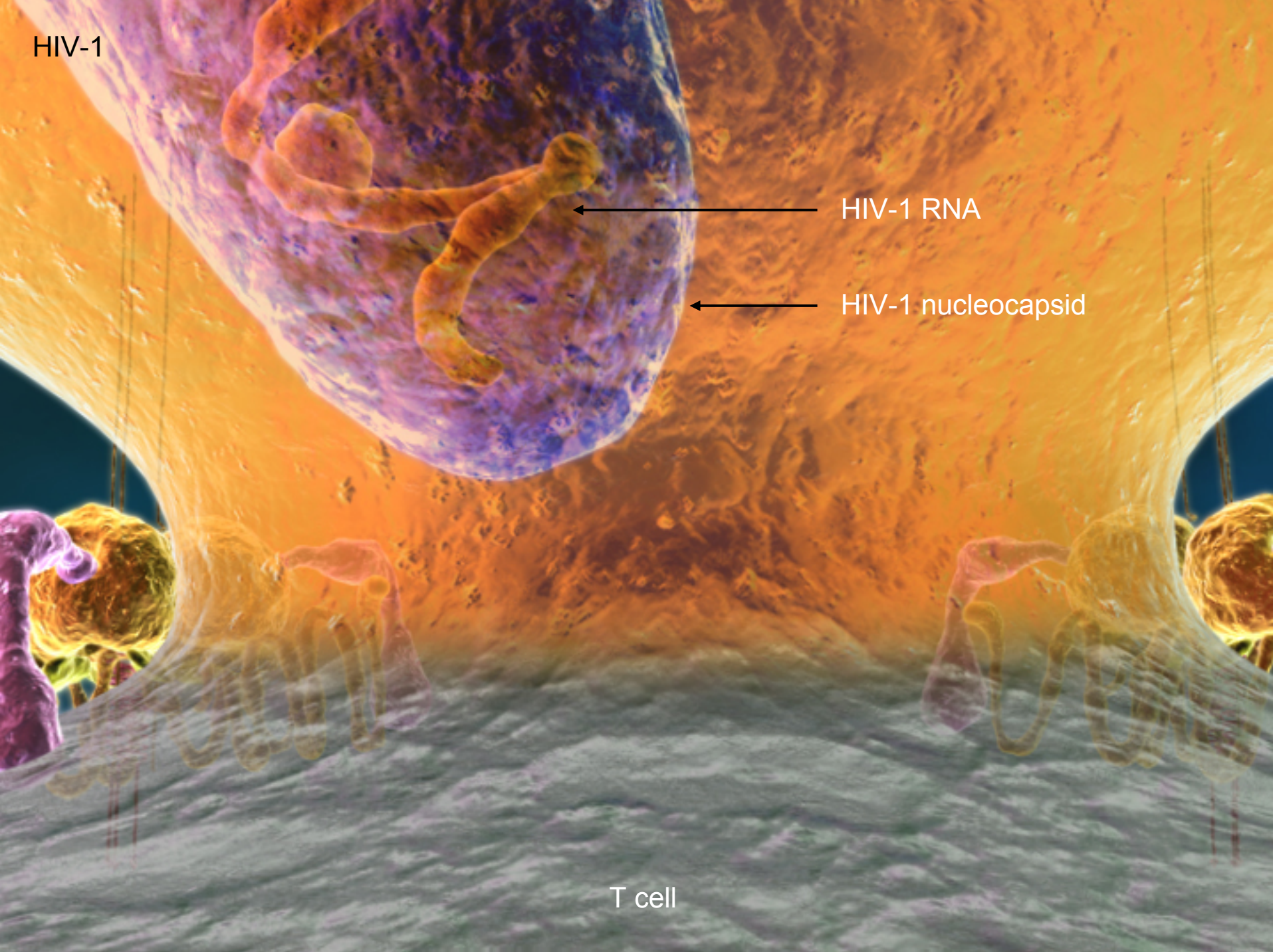

HIV-1
gp41
gp120
HIV-1 envelope glycoprotein
CD4
CCR5
T cell surface


HIV-1
gp41
gp120
CD4
CCR5
T cell surface

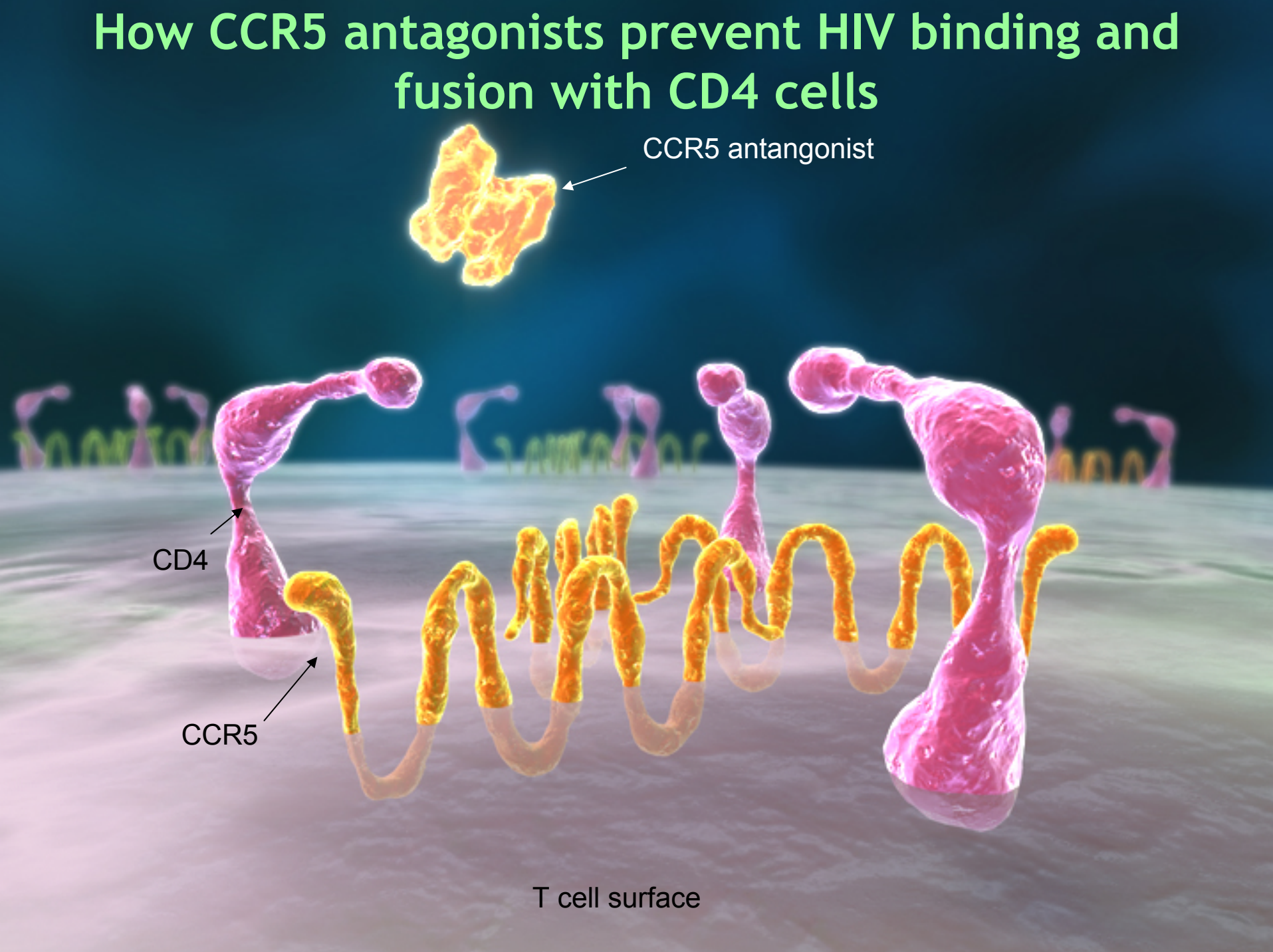

HIV-1
gp41
gp120
CD4
CCR5
T cell surface


HIV-1
gp41
gp120
CD4
CCR5
T cell surface

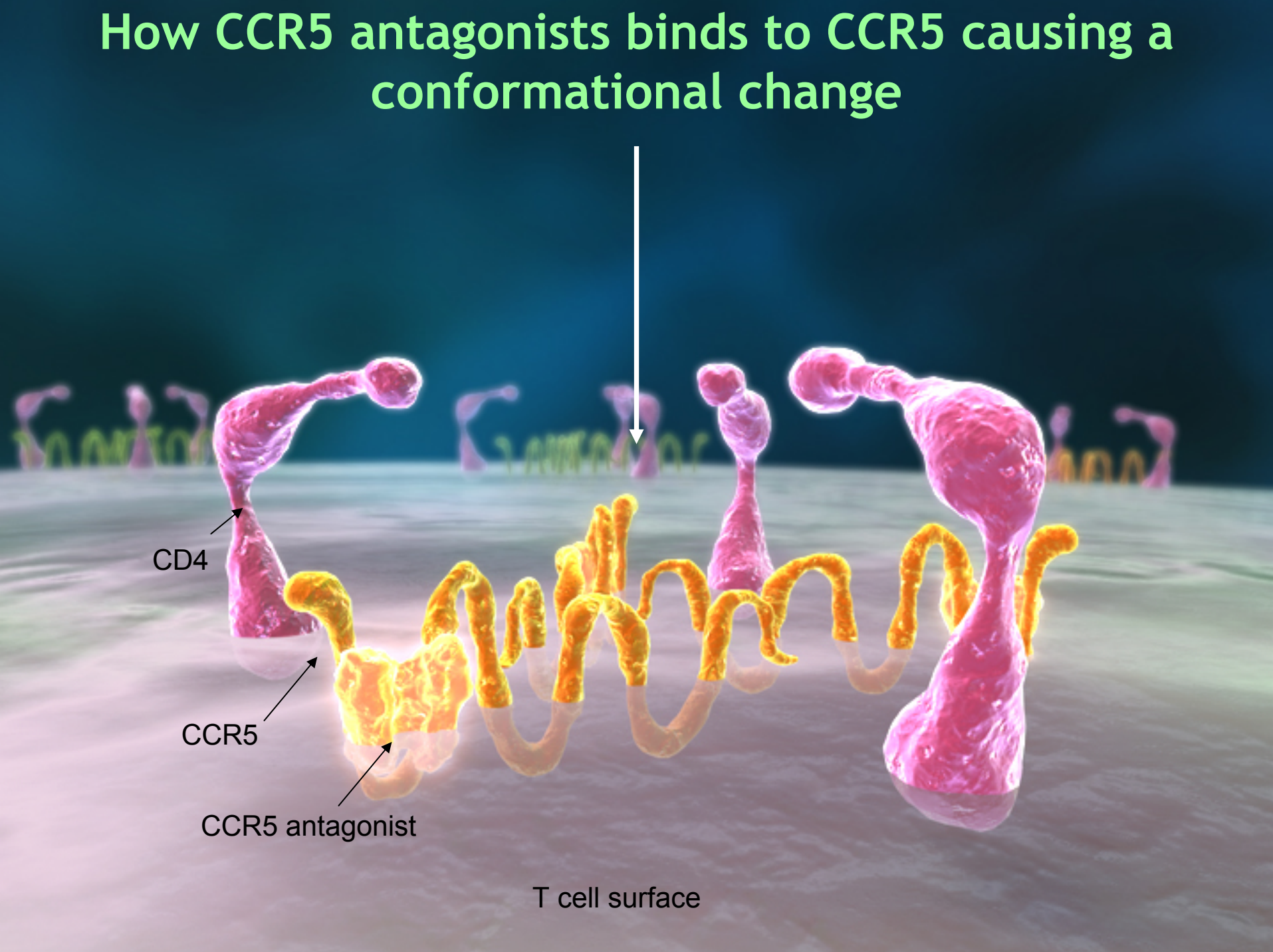

HIV-1
gp41
gp120
CD4
CCR5
T cell surface

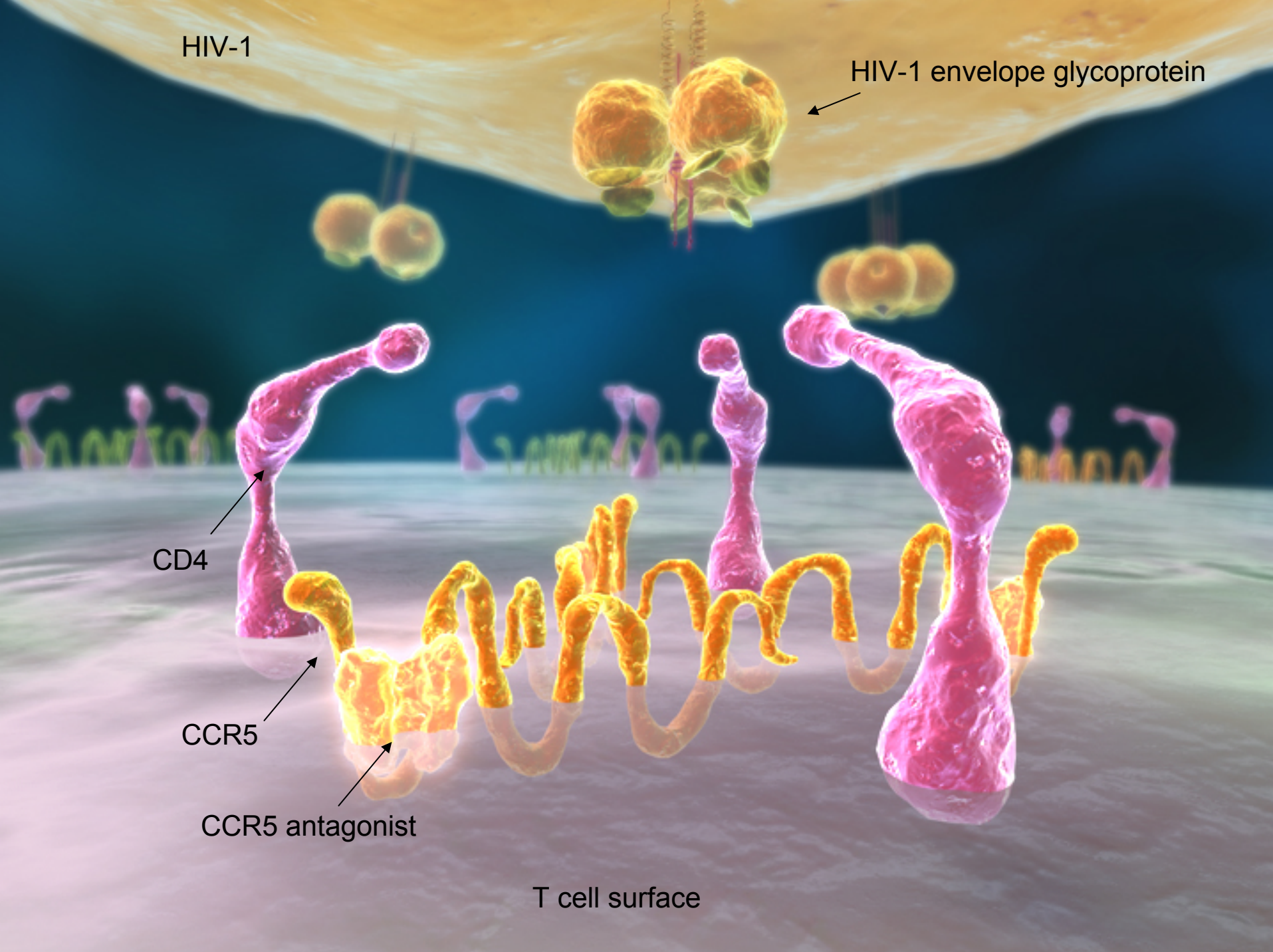

HIV-1
HIV-1 RNA
HIV-1 nucleocapsid
T cell

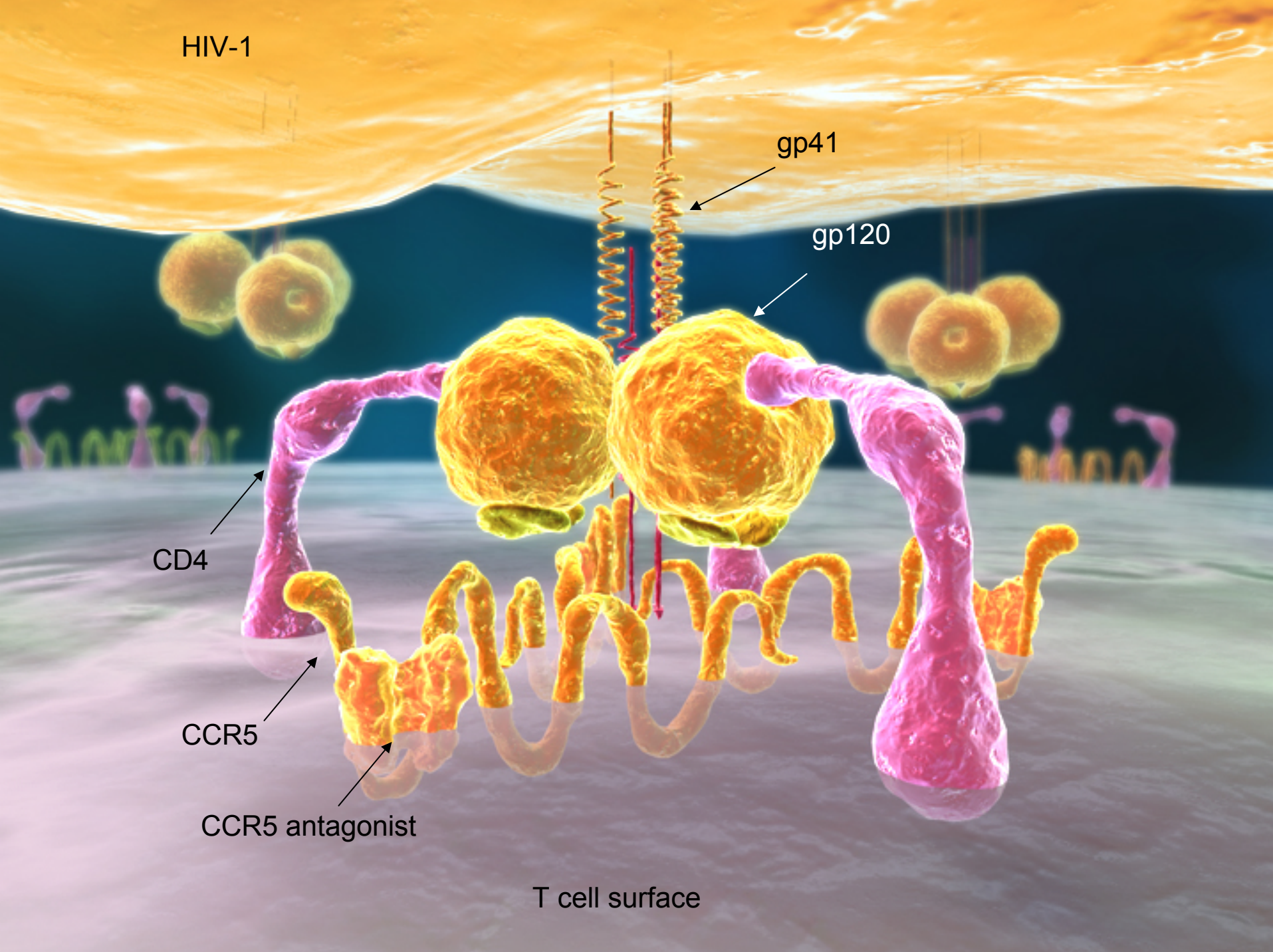
How CCR5 antagonists prevent HIV binding and fusion with CD4 cells



How CCR5 antagonists binds to CCR5 causing a conformational change




HIV-1
HIV-1 envelope glycoprotein
CD4
CCR5
CCR5 antagonist
T cell surface


HIV-1
gp41
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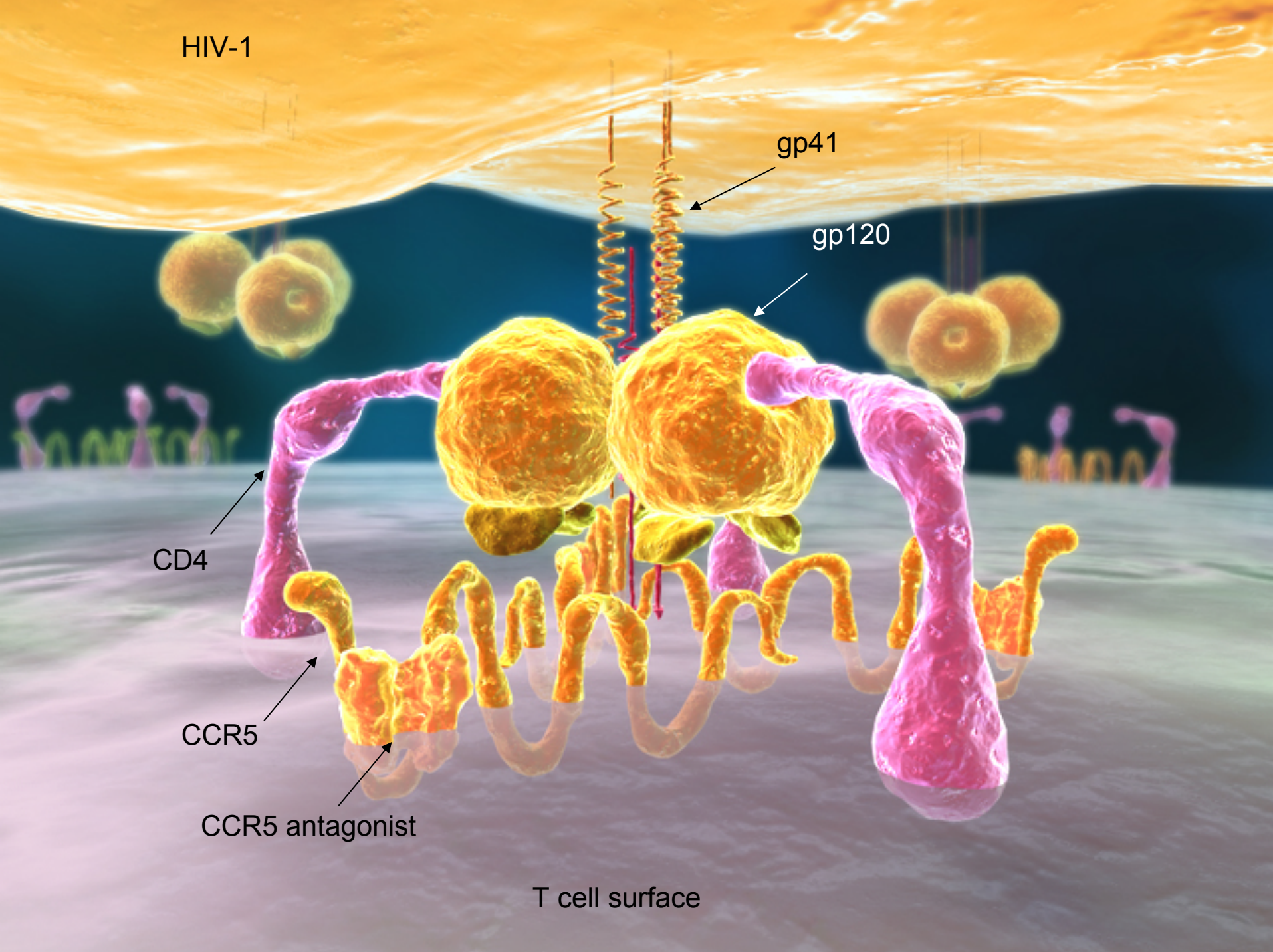
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CD4
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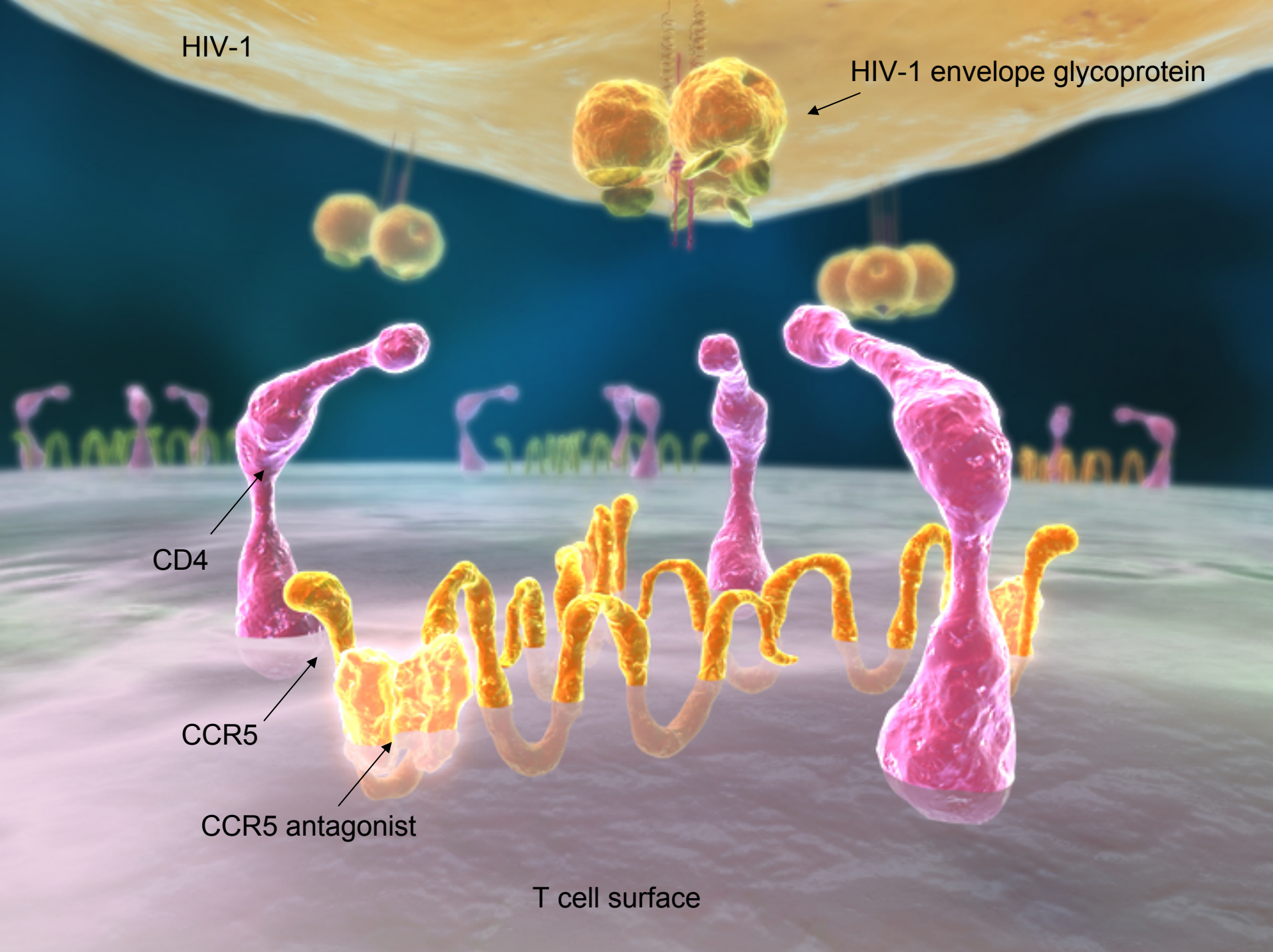
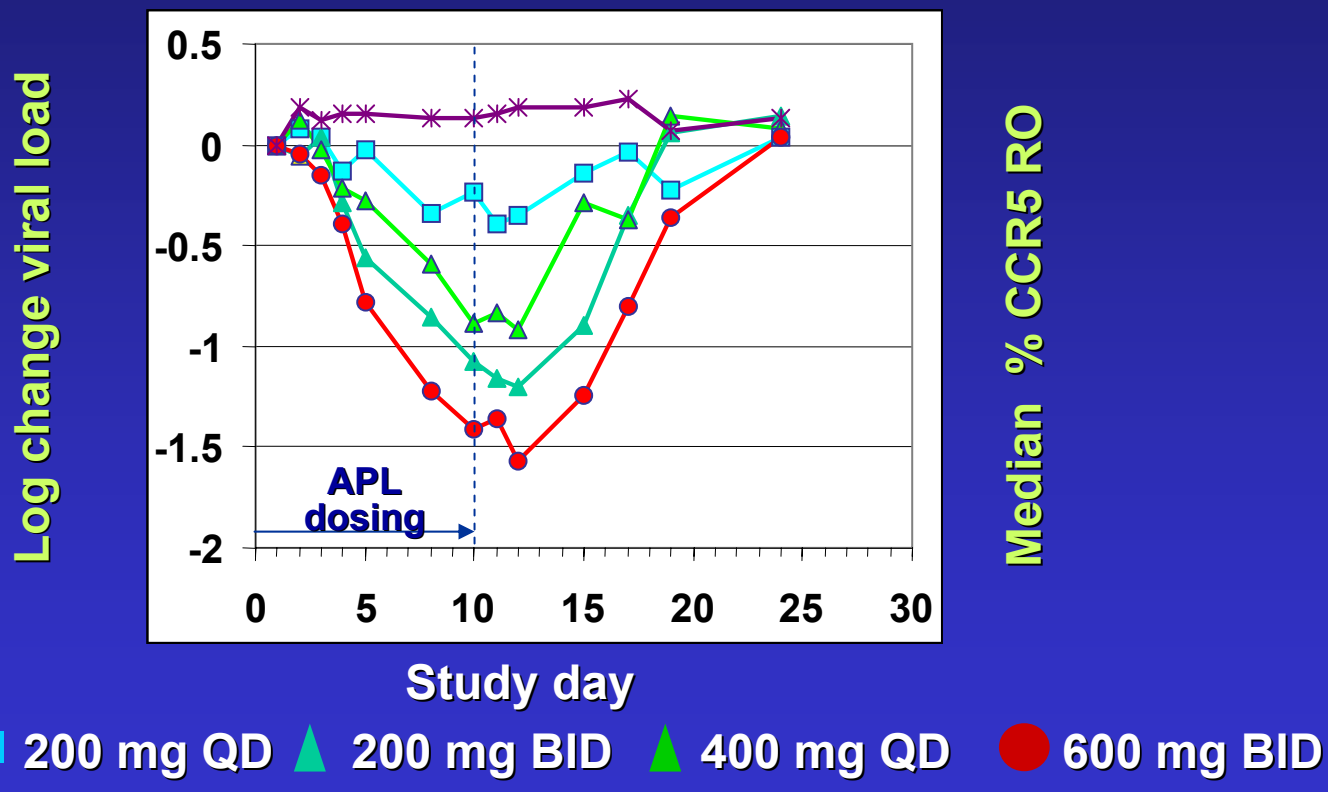

HIV-1
HIV-1 envelope glycoprotein
CD4
CCR5
CCR5 antagonist
T cell surface

CCR5 Receptor Occupancy (RO) in HIV+ Subjects After 10 Days' Repeat Dosing of Aplaviroc

Potential relationship to sustained antiviral activity

Viral load response



Sparks S, *et al*. 12th CROI 2005; abstract 77

APLAVIROC

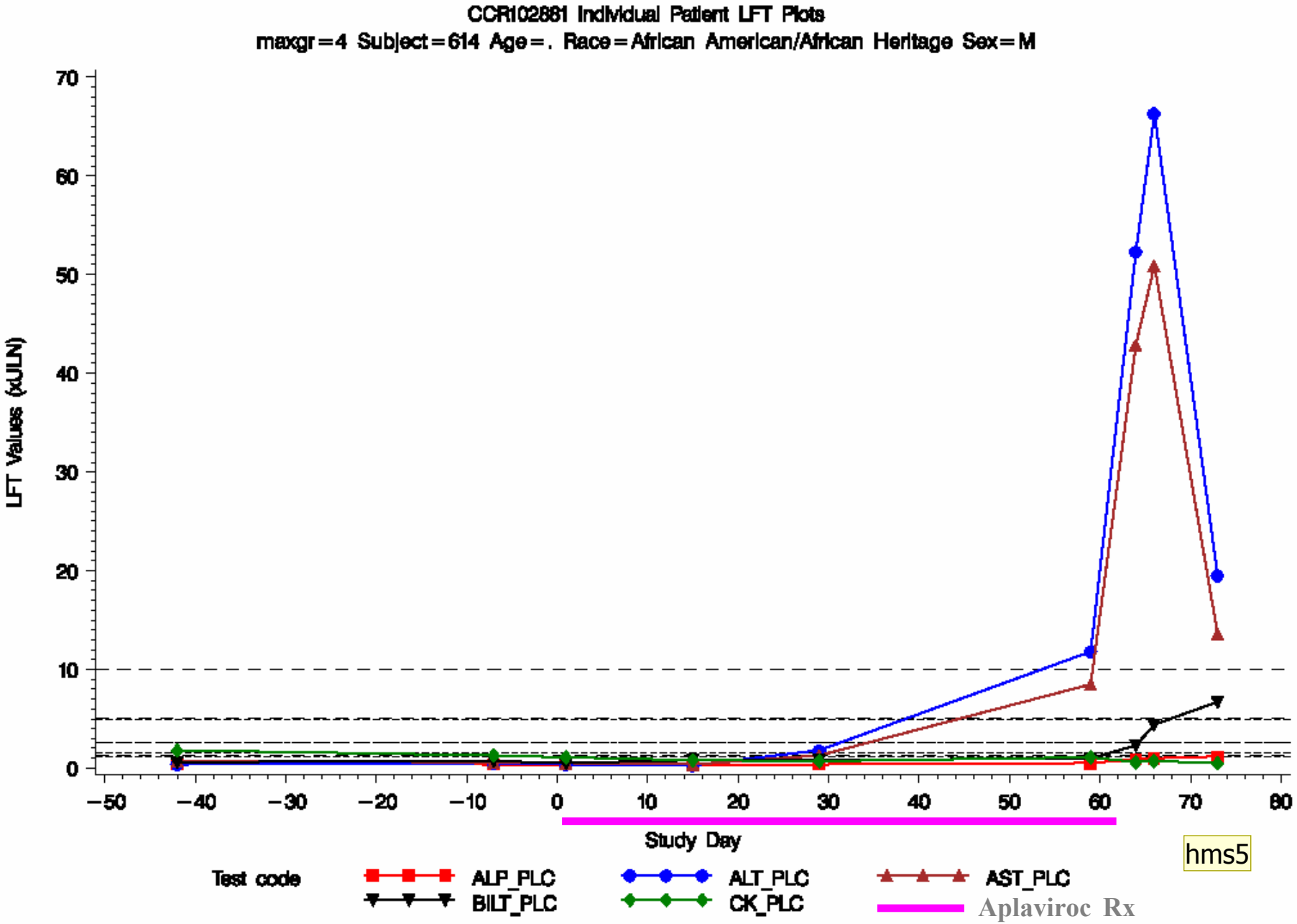
- Potent antiviral activity in low to subnanomolar range
- Active against multiple clades
- Prolonged and substantial CCR5 occupancy
- Aplaviroc was not antagonistic to currently approved NRTIs, NNRTIs, PIs, and T20

Hepatotoxicity of Aplaviroc:Index Case

- 39 year old black male
- No previous medical history of note and no history of recent travel
- HIV from sexual contact
- CDC class A
- Baseline CD4 cell count 283
- No alcohol or substance abuse
- No hepatic disease
- Negative serology for HBV, HCV at baseline

Hepatotoxicity of Aplaviroc:Index Case

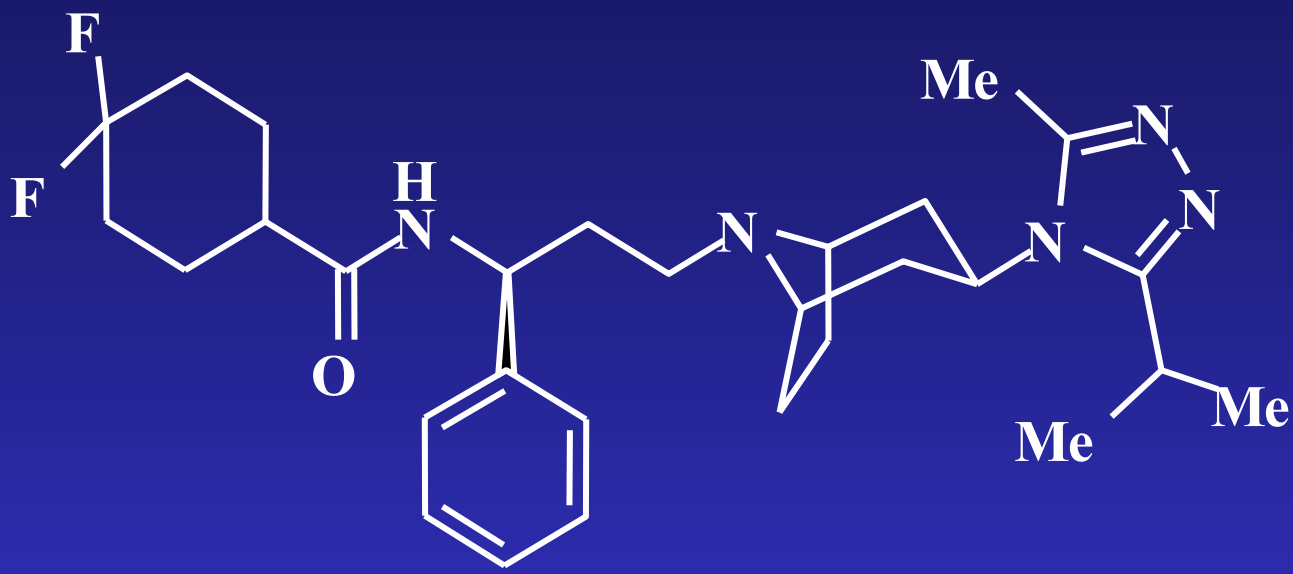
- Started Aplaviroc 800 mg BID + Combivir June 21 2005 Normal LFTs at baseline.
- 59 days later (19 Aug 2005) developed G4 hepatic cytolysis considered life threatening :
  - ALT 52 x ULN (rose to max x 66)
  - AST 43 x ULN (rose to max x 51)
  - Bilirubin rose ~7 x ULN
- Small rise ALP, INR 1.25, hepatic function preserved.
- Treatment discontinued on Aug 22 2005


CCR102881 Individual Patient LFT Plots
maxgr=4 Subject=614 Age=. Race=African American/African Heritage Sex=M
LFT Values (xULN)
70
60
50
40
30
20
10
0
−50
−40
−30
−20
−10
0
10
20
30
40
50
60
70
80
Study Day
Test code
ALP_PLC
BILT_PLC
ALT_PLC
CK_PLC
AST_PLC
Aplaviroc Rx
hms5

hms5 check dates of Rx

hms45351; 27/09/2005

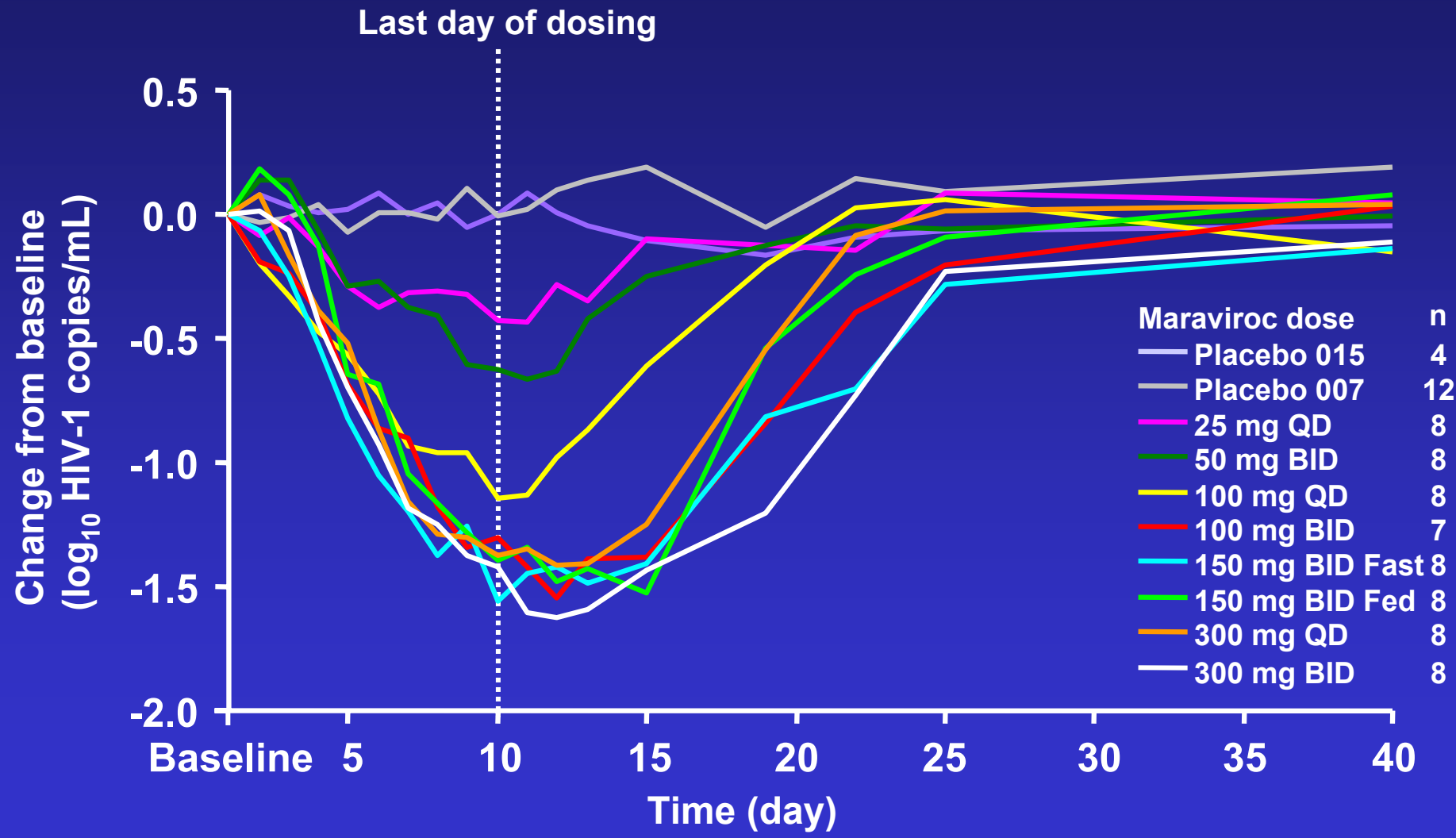
Maraviroc (UK-427,857) Pre-clinical Profile



- Selective, reversible binding to the CCR5 receptor
- ~ 2 nM antiviral IC_{90} (primary isolates in PBMCs)
- Excellent cross-clade potency against primary CCR5-tropic isolates
- Active vs. current class-resistant HIV but not CXCR4-using virus

Dorr P *et al*. 10th CROI 2003. Oral Presentation 12
Macartney *et al*. 43rd ICAAC 2003. Poster H-875

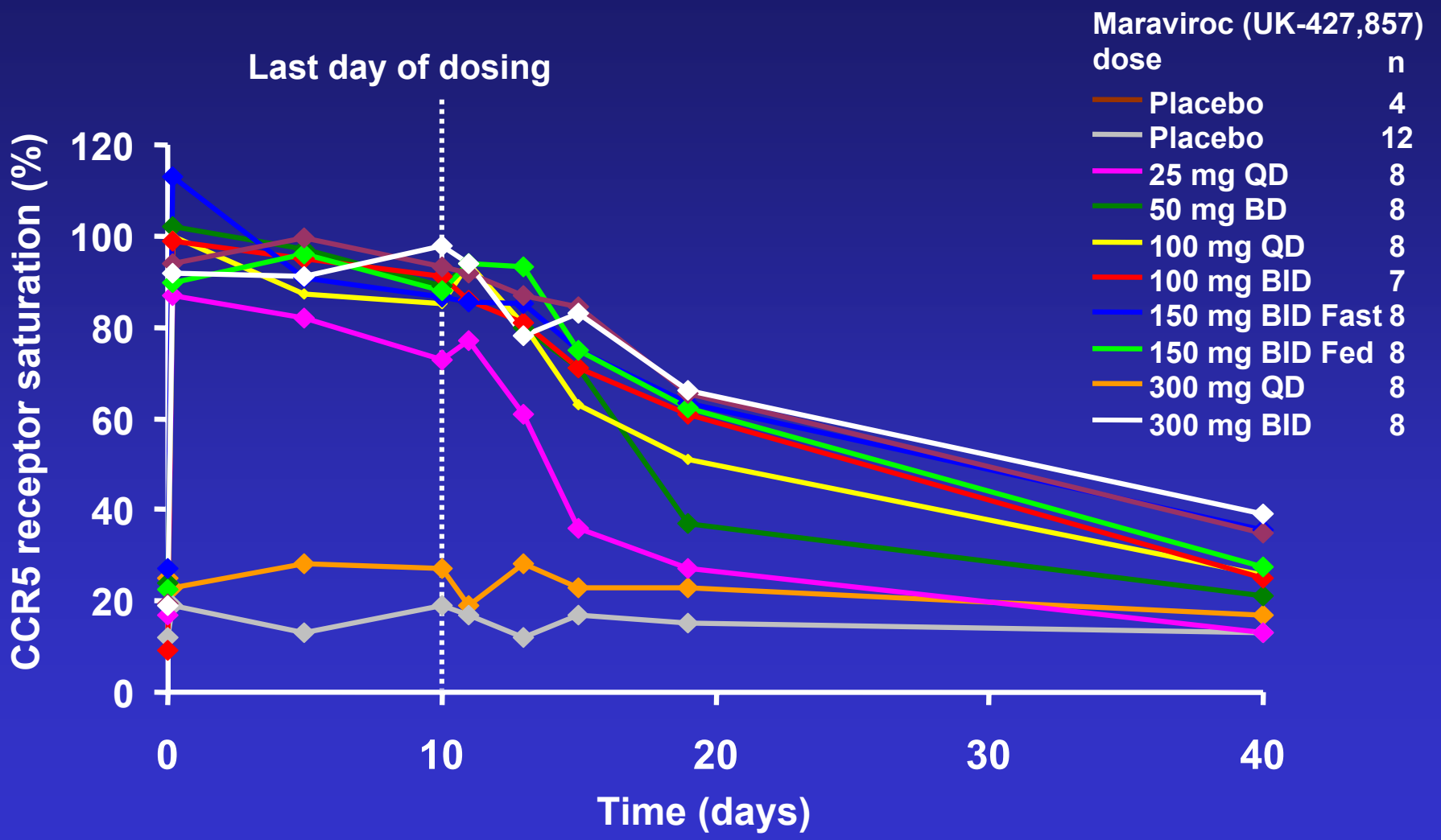
Maraviroc (UK-427,857) Efficacy Results: Mean Reduction in Viral Load over Time



Study 1007/1015

Fätkenheuer G *et al*.15th IAC 2004. Abstract TuPeB4489

CCR5 Receptor Occupancy over Time

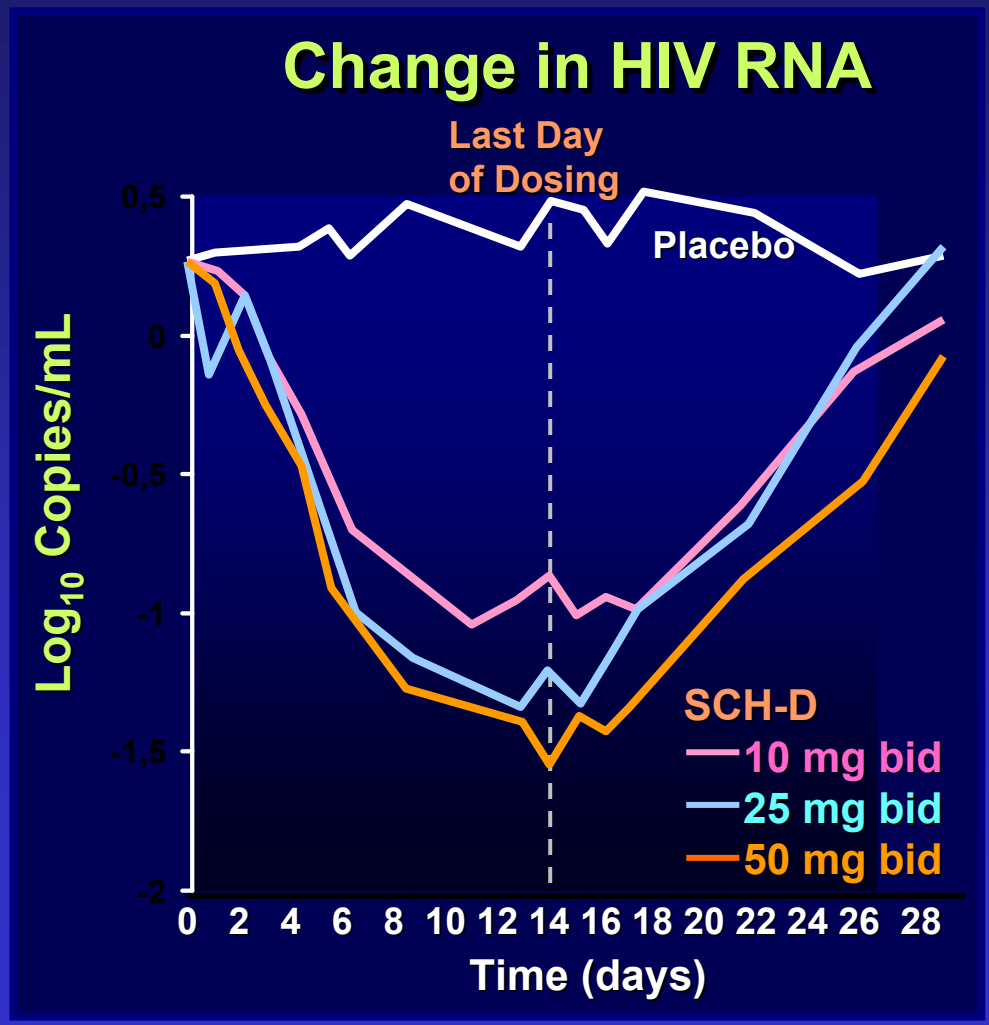


Study 1007/1015

Fätkenheuer G *et al*.15th IAC 2004. Abstract TuPeB4489

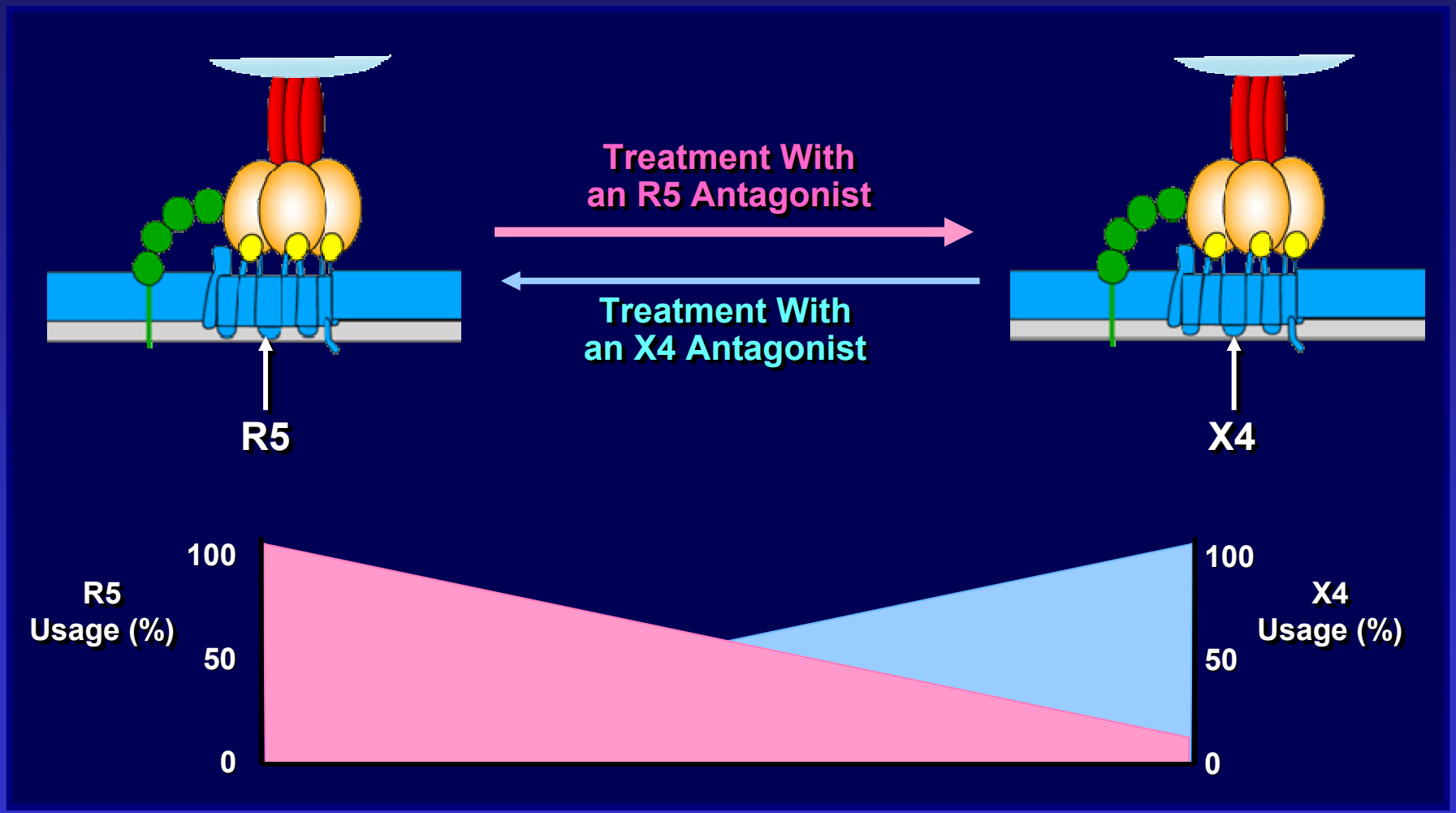
CCR5 Co-Receptor Antagonist: Phase 1 Study With SCH-D

- Randomized, blinded, sequential dose-escalation
  - N=48
- Dose-related decrease in HIV RNA
- No treatment limiting adverse events reported
  - No QTc prolongation was reported



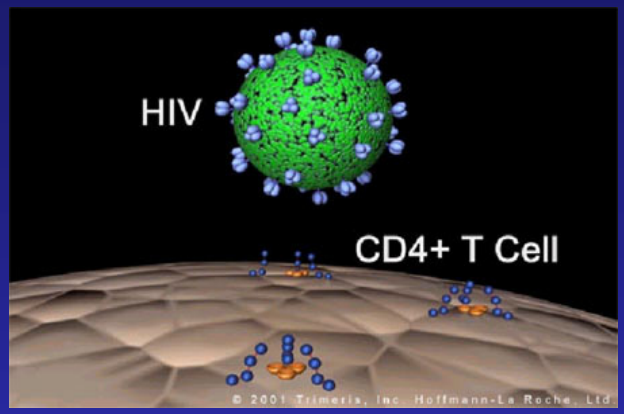
Schurmann D, et al. 11th CROI. San Francisco, 2004. Abstract 140LB.

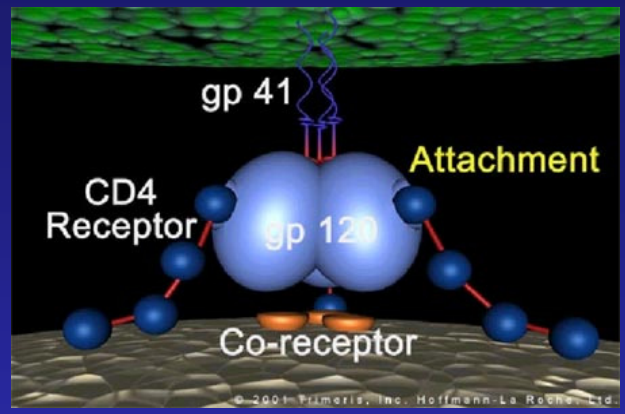
Reversible X4 and R5 Selection After Coreceptor Antagonist Use

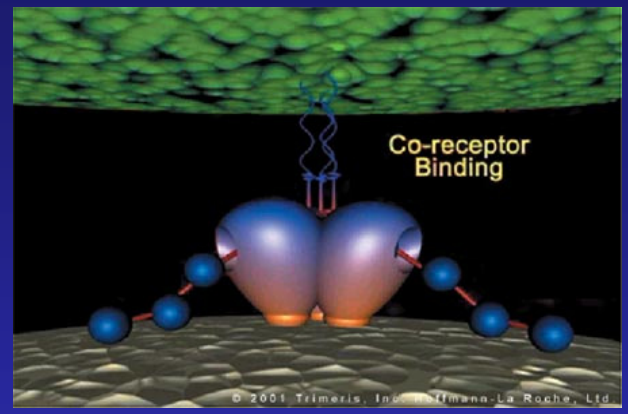


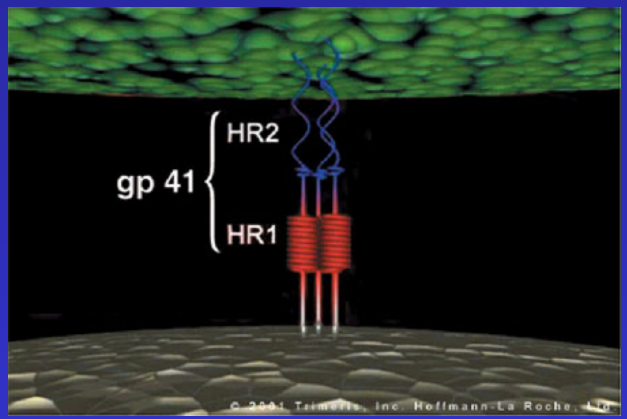
Moore JP, et al. *PNAS.* 2003;100:10598-10602.

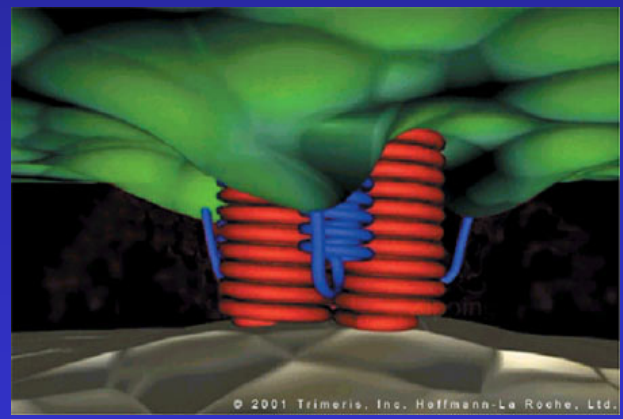
HIV fusion inhibition

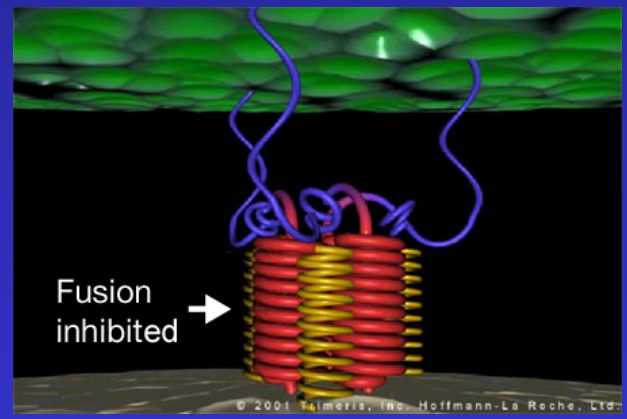




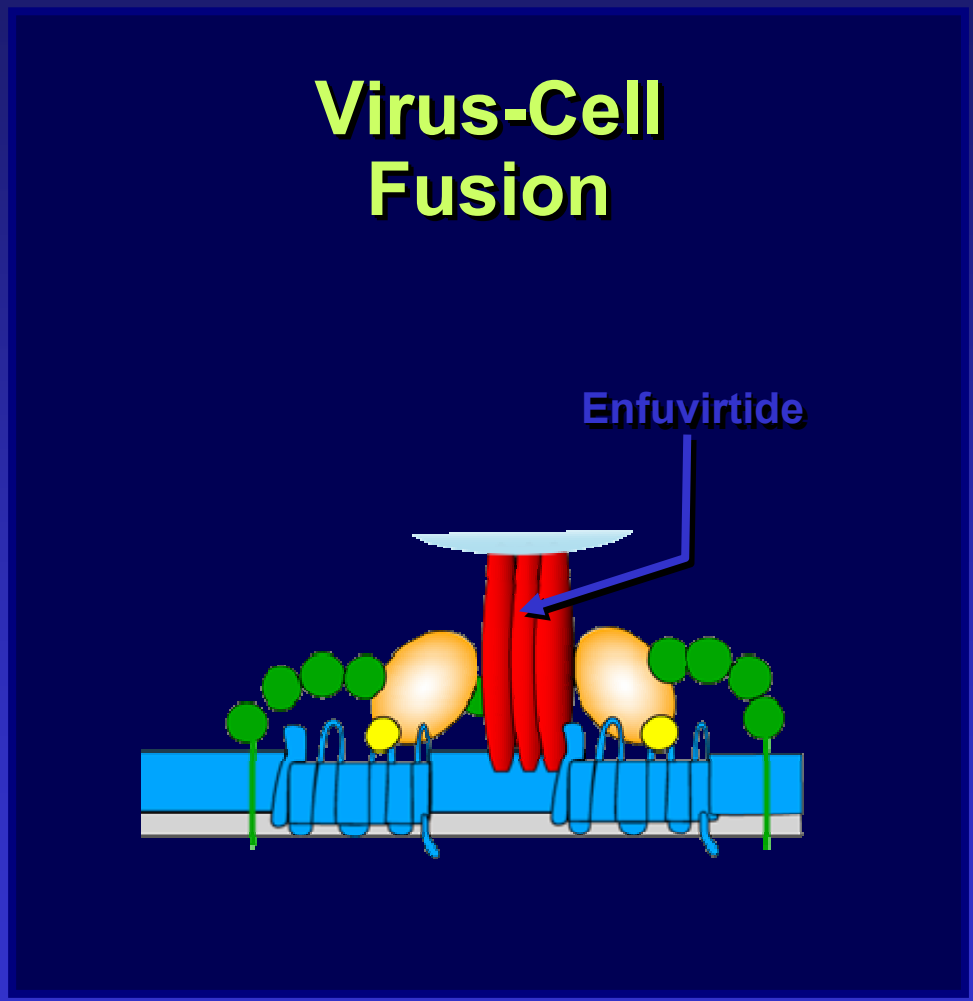






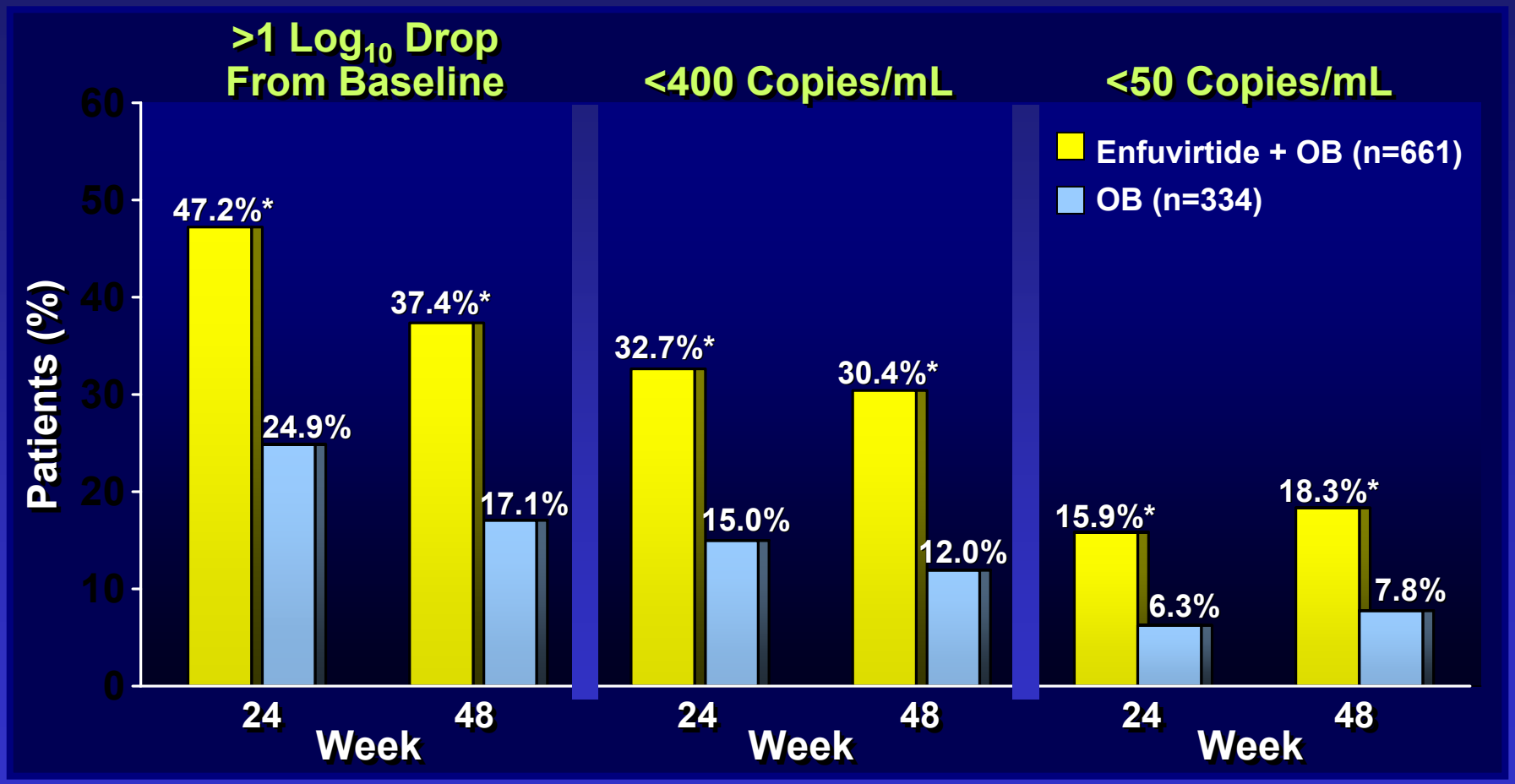


HIV Attachment and Fusion Targets for Inhibition



Moore JP, et al. *PNAS.* 2003;100:10598-10602.

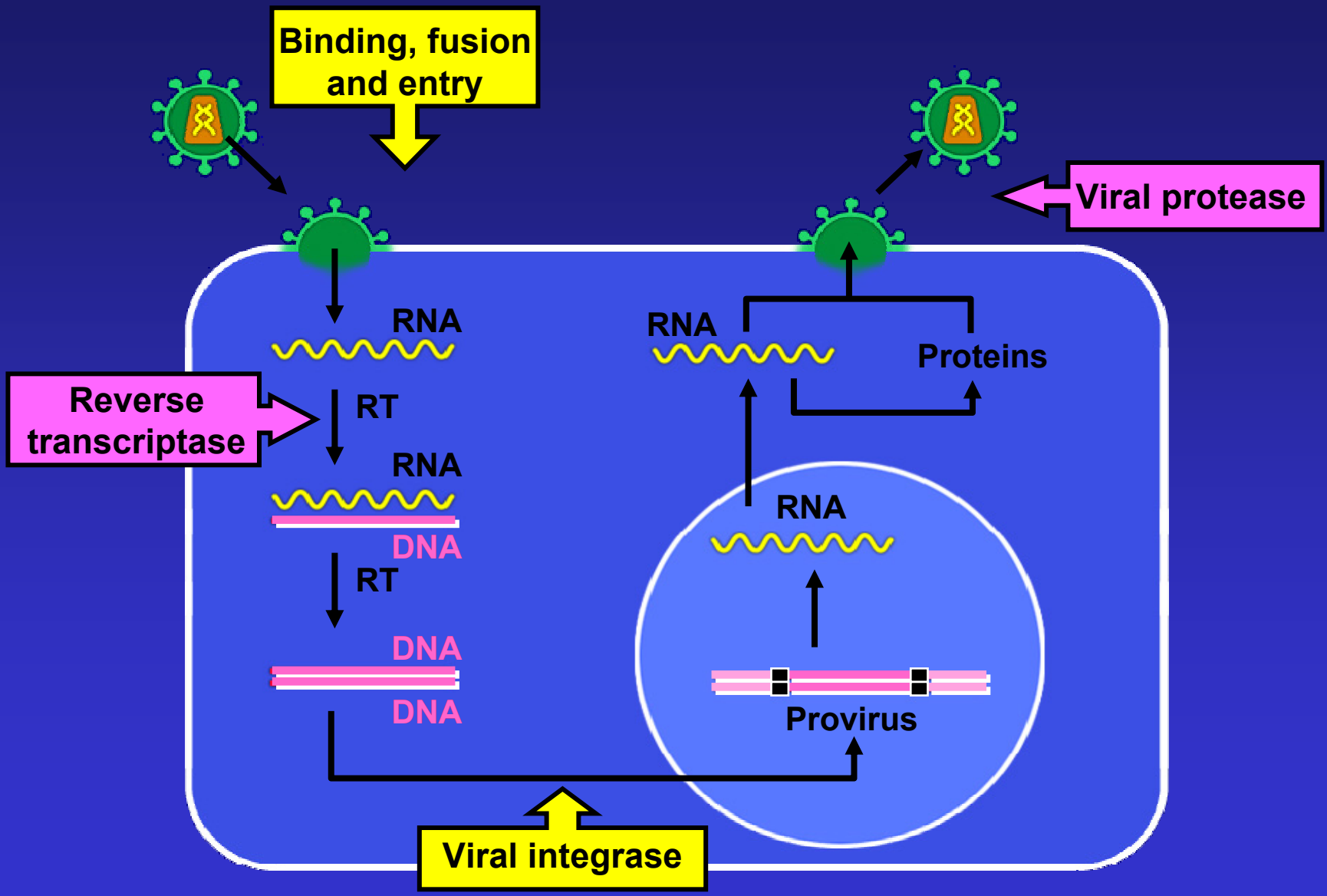
TORO 1 and 2: Durability of Response to Enfuvirtide Through 48 Weeks



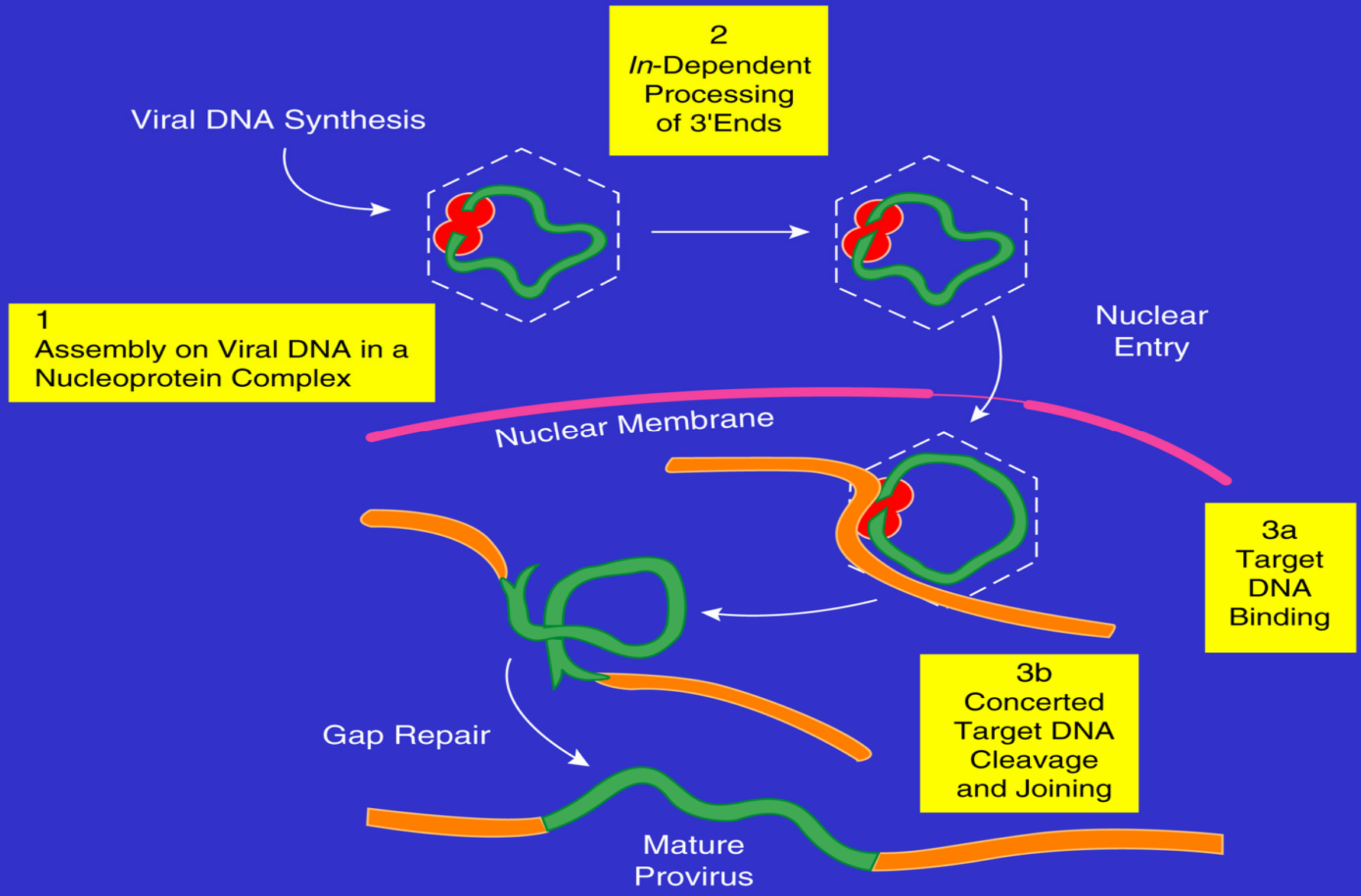
ITT: discontinuation or virologic failure=failure.
OB=optimized background regimen.
P<0.001 versus OB.

Trottier B, et al. 43rd ICAAC. Chicago, 2003. Abstract H-835.

New targets


Binding, fusion and entry
Viral protease
RNA
Reverse transcriptase
RT
RNA
DNA
RT
DNA
DNA
RNA
Proteins
RNA
Provirus
Viral integrase

HIV Integrase Mechanism



Investigational Drugs 2005: Other Mechanisms

- GAG processing inhibitors
- budding inhibitors
- DC-SIGN inhibitors
- defensins
- si RNAs
- regulatory protein (e.g., NEF, VIF, TAT) inhibitors
- uncoating inhibitors
- RNAase H inhibitors
- zinc finger (DNA complex) inhibitors
- capsid protein polymerization inhibitors
- assembly inhibitors

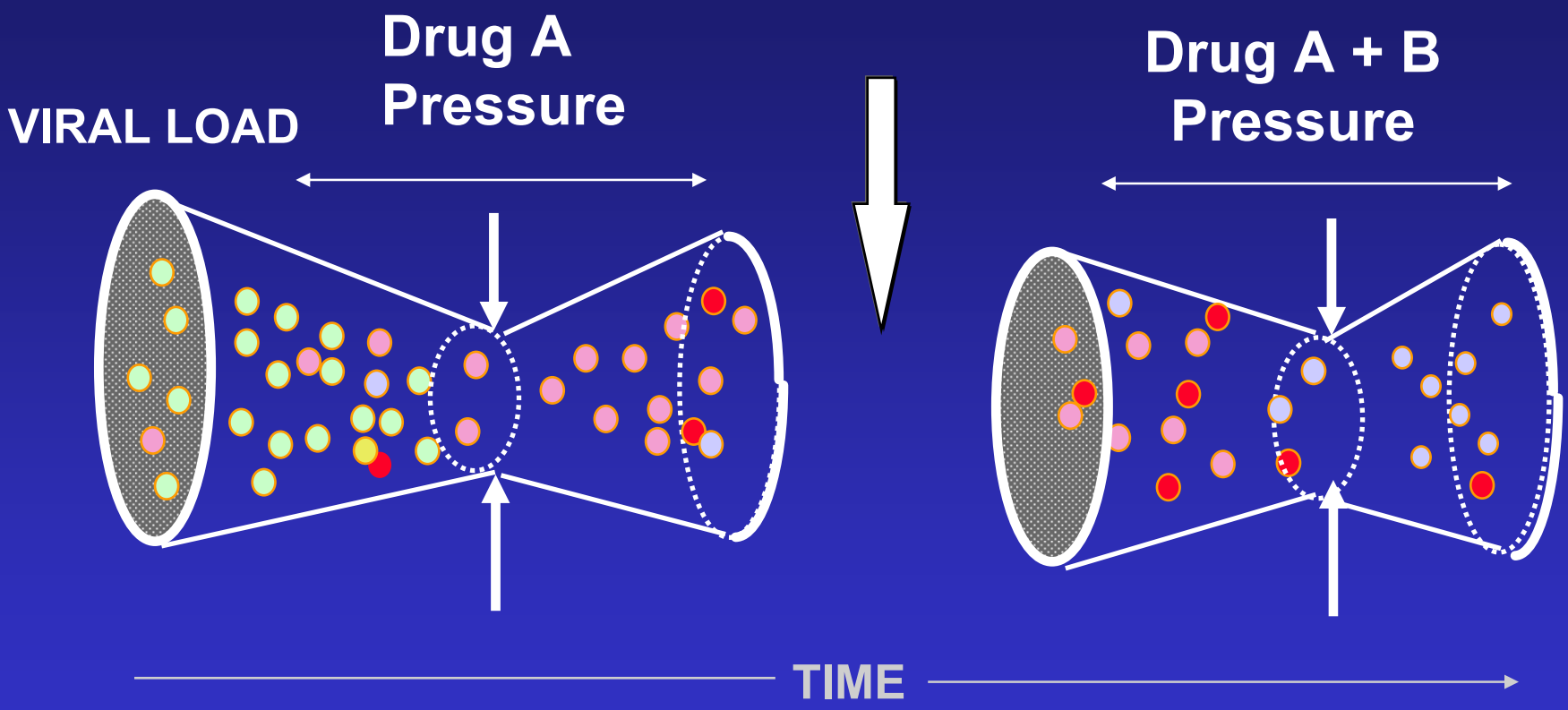
Why are new drugs needed ?

- **Resistance is a major factor limiting drug efficacy**
- **Resistance is a major factor contributing to treatment failure**
- **Resistance and cross-resistance patterns are major factors determining drug-sequencing strategies**

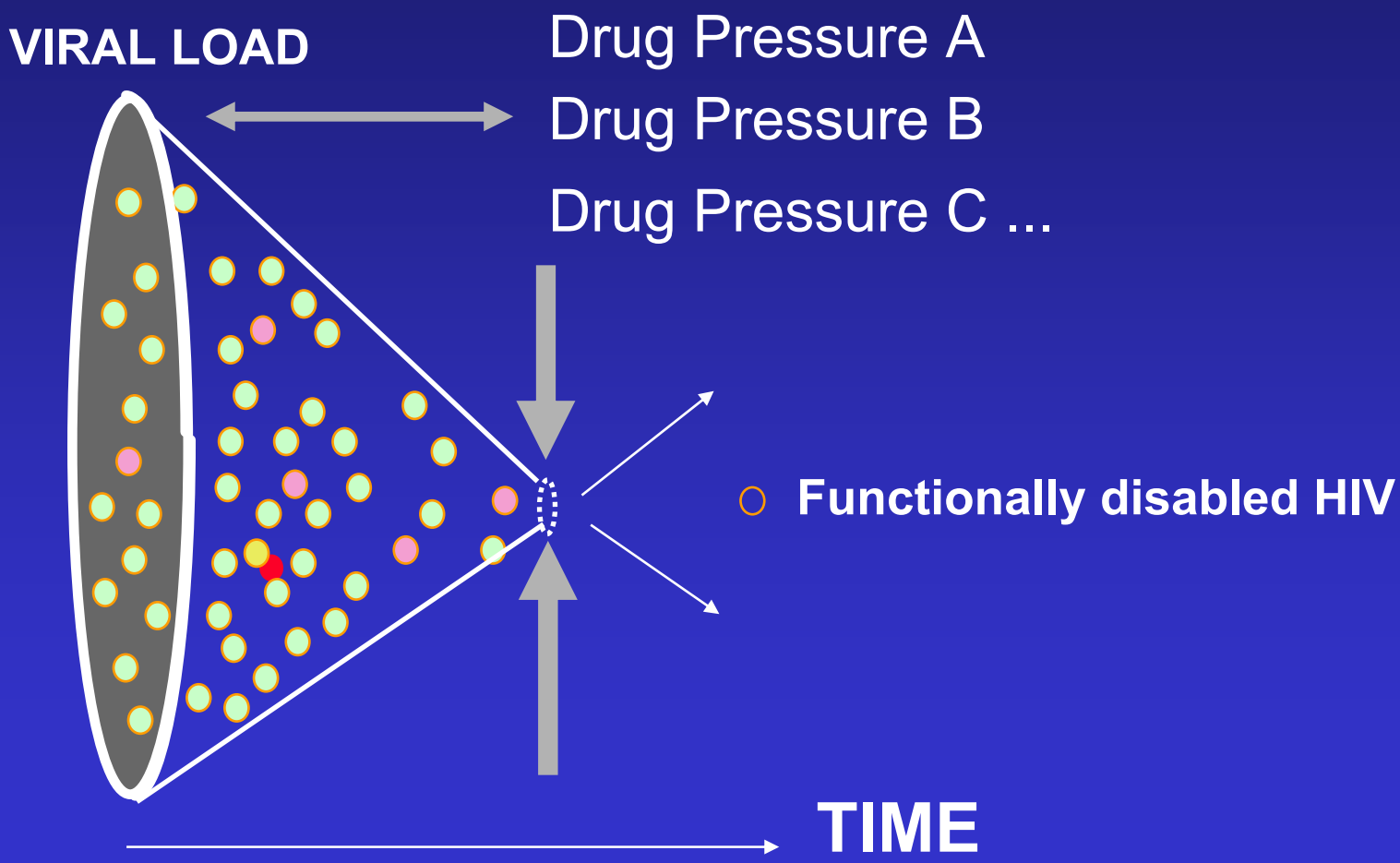
Drug Resistance: A Predetermined Agenda in the Absence of Drugs

- An estimated 20 billion mutations occur every day in an HIV-infected person
- The naturally occurring HIV population contains many genetic variants to comprise a quasi-species
- All possible drug-resistant variants are sure to occur on a daily basis
- They generally exist as minority sub-populations

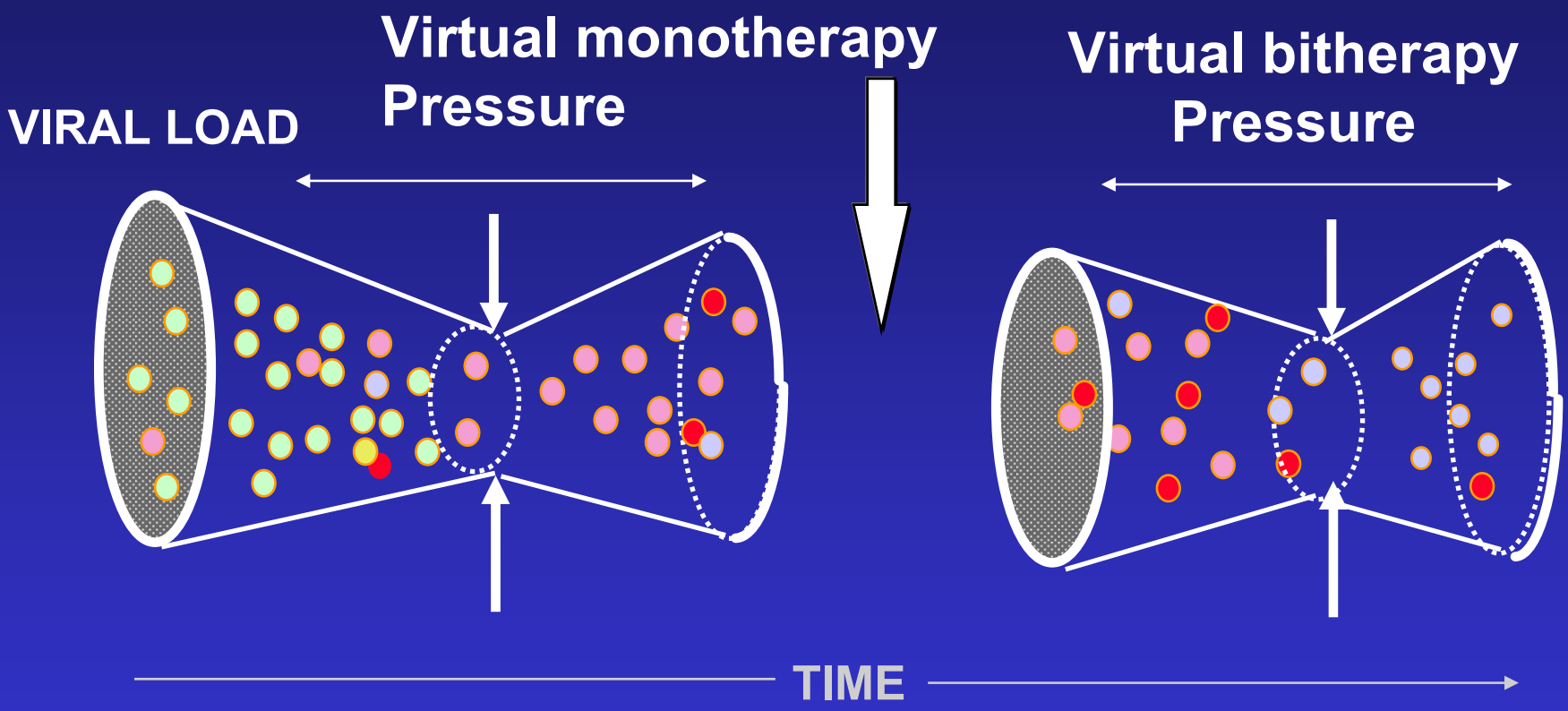
Drug Resistance: Selection Pressure(s)



(Combined) Use of Working Anti-HIV Drugs



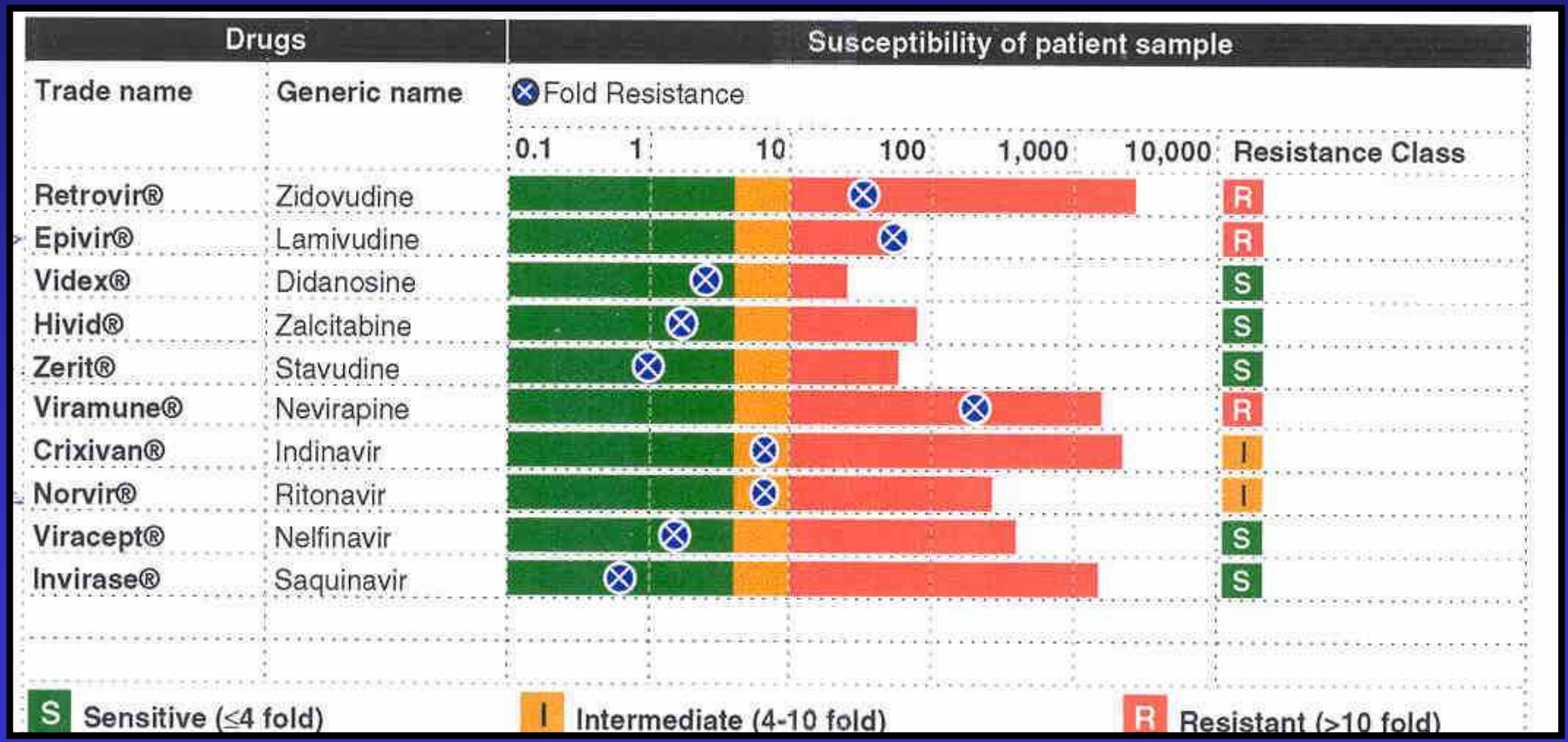
Drug Resistance: Selection Pressure(s)



Resistance

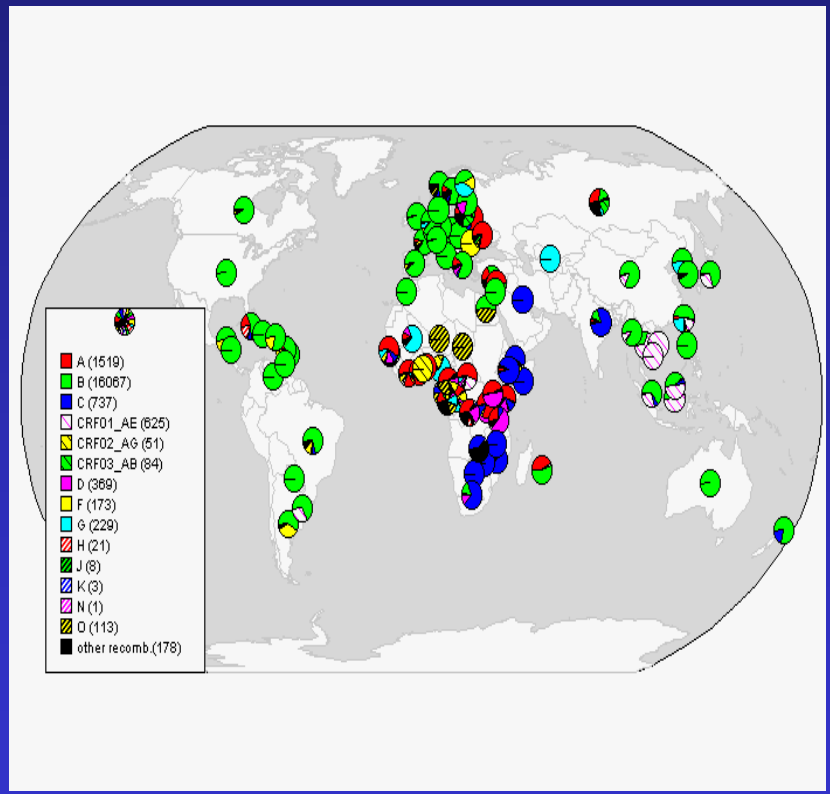
- **HIV-1 drug resistance is firmly established in the HIV-1 infected population**
  - as a result of treatment
  - to a much lesser extent as a result of transmission **of resistance** (active prevalence monitoring)
- **We can measure HIV-1 drug resistance**
  - by looking for changes known to be associated with resistance in the genotype (GT)
- **Loss of HIV-1 drug susceptibility is associated with treatment failure**

Antivirogram®



HIV Sub-types

- Most patients who have benefited from HAART are infected with HIV-1 B subtypes.
- However, most HIV infected people worlwide live in areas where subtypes other than B are most prevalent.



HIV Sub types

- Availability of HAART to developing countries is increasing.
- An increasing number of HIV-1 positive immigrants are being treated with HAART in the industrialised world.
- Data on the clinical response to therapy for non-B HIV-1 infections are thus becoming of great practical importance, in order to identify potential subtype specific differences in the response to therapy and development of resistance.

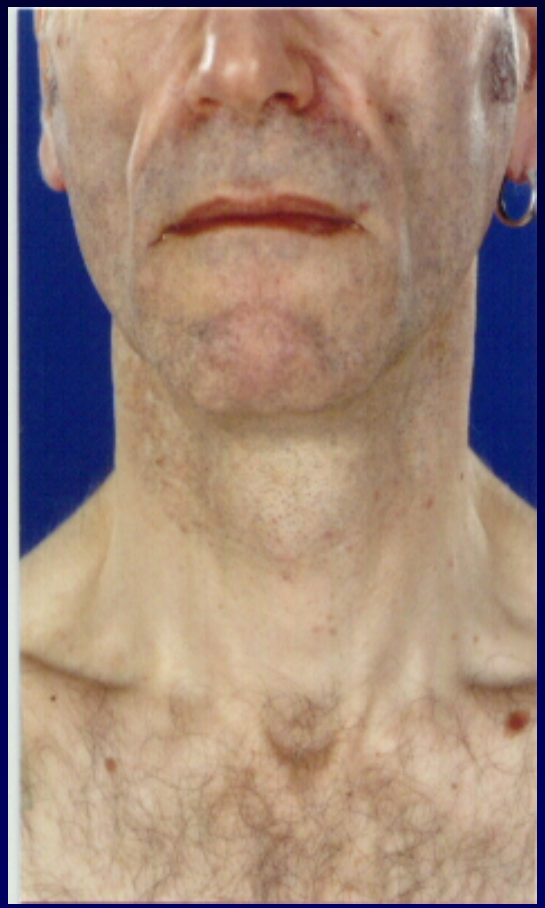
Types of Metabolic Toxicity

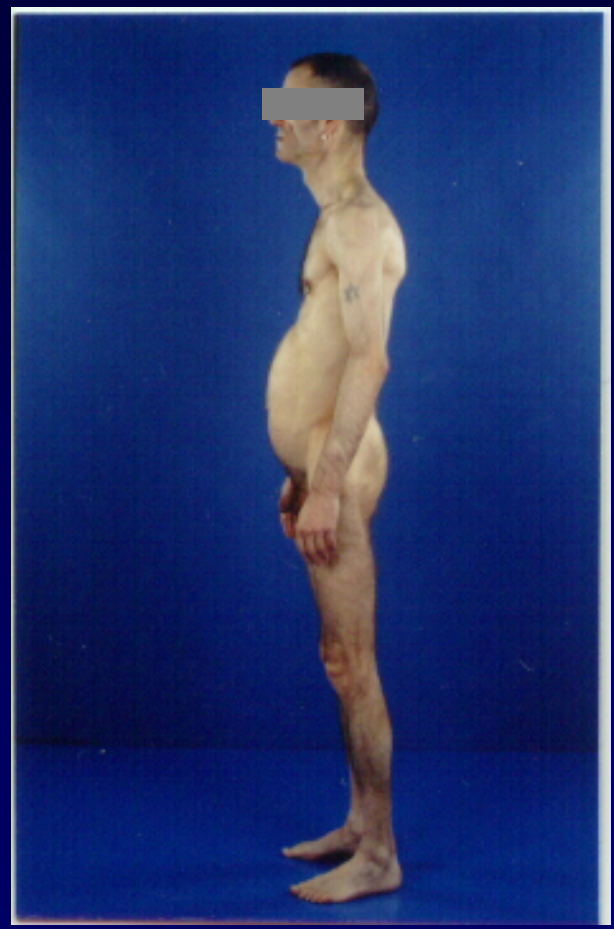
- lipid and glucose metabolism
- adipose tissue distribution

Lipodystrophy syndrome(s)

- Lactic acidemia/acidosis
- Disorders of bone mineralisation (?)

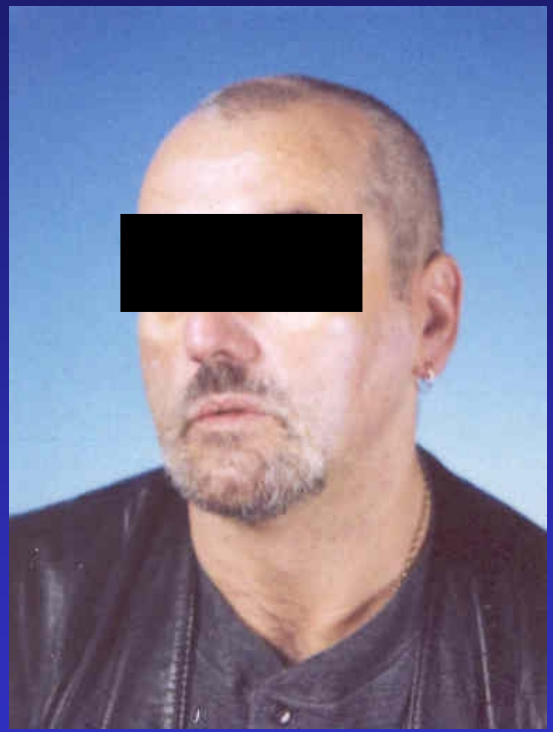
Peripheral lipoatrophy / fat wasting

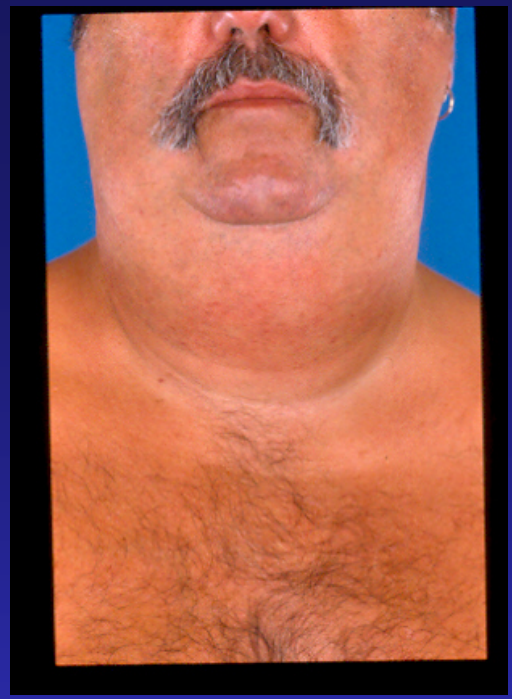


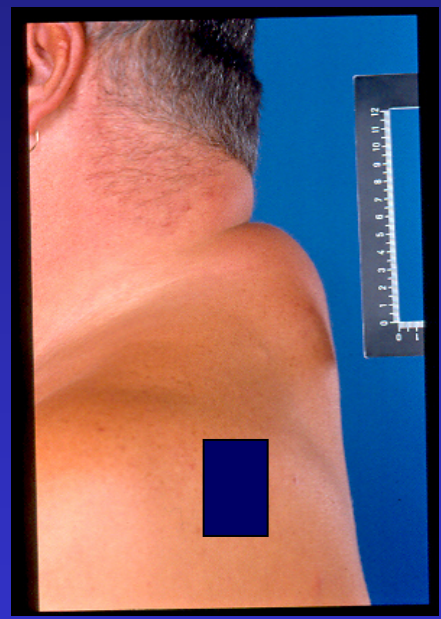


central fat accumulation

Fat accumulation







1997

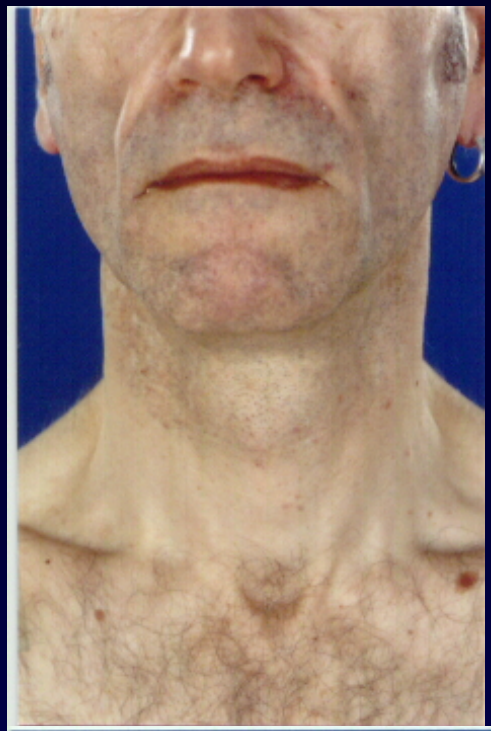
2001

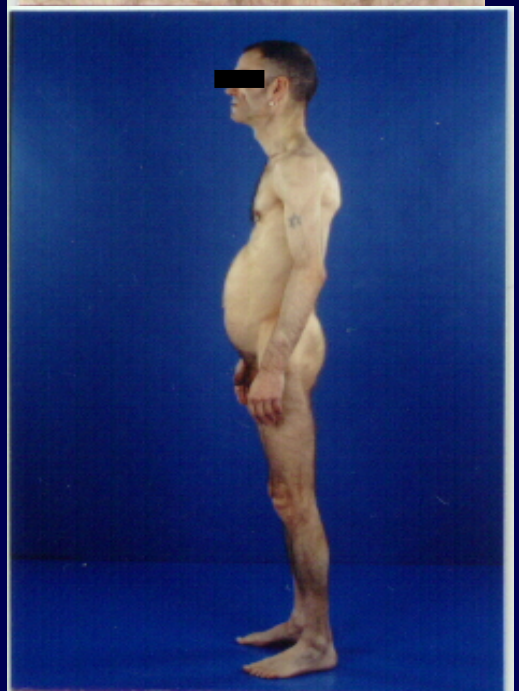
Is it common?

Lipodystrophy syndrome

- Δ body appearance: 24 - 89%
- Dyslipidemia: 25 - 55%
- Glucose intolerance: 25 - 65%
- Diabetes mellitus: 0.7 - 6.7%

Overall Incidence: ~50%





The potential "slippery slope" of fat maldistribution

Change in body appearance

self-esteem ↓

shame ↑

social isolation ↑

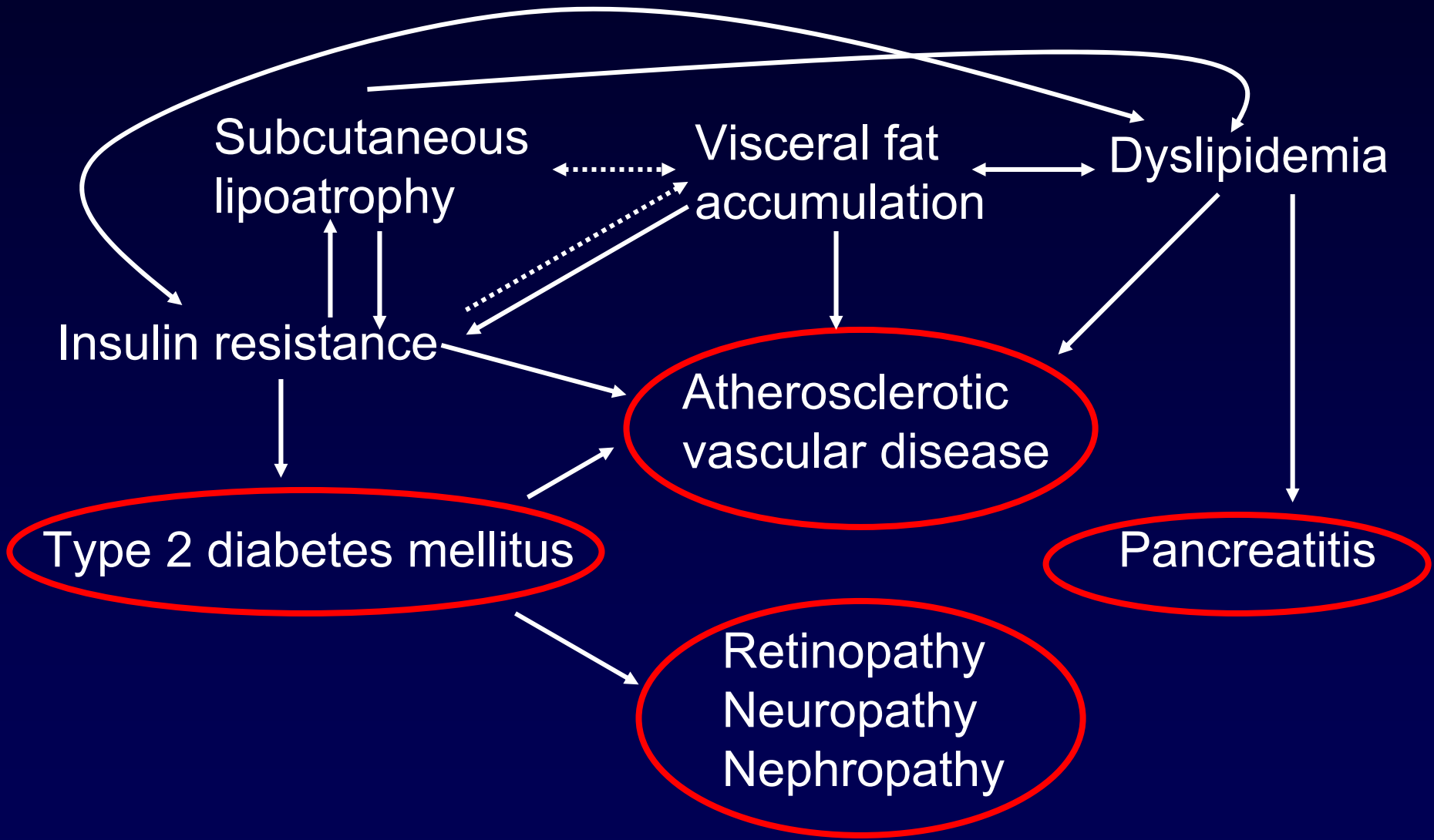
adherence to Rx ↓

emergence of resistance ↑

loss of viral control ↑

treatment failure ↑

Potential relationships and health risks in ART-associated metabolic syndrome



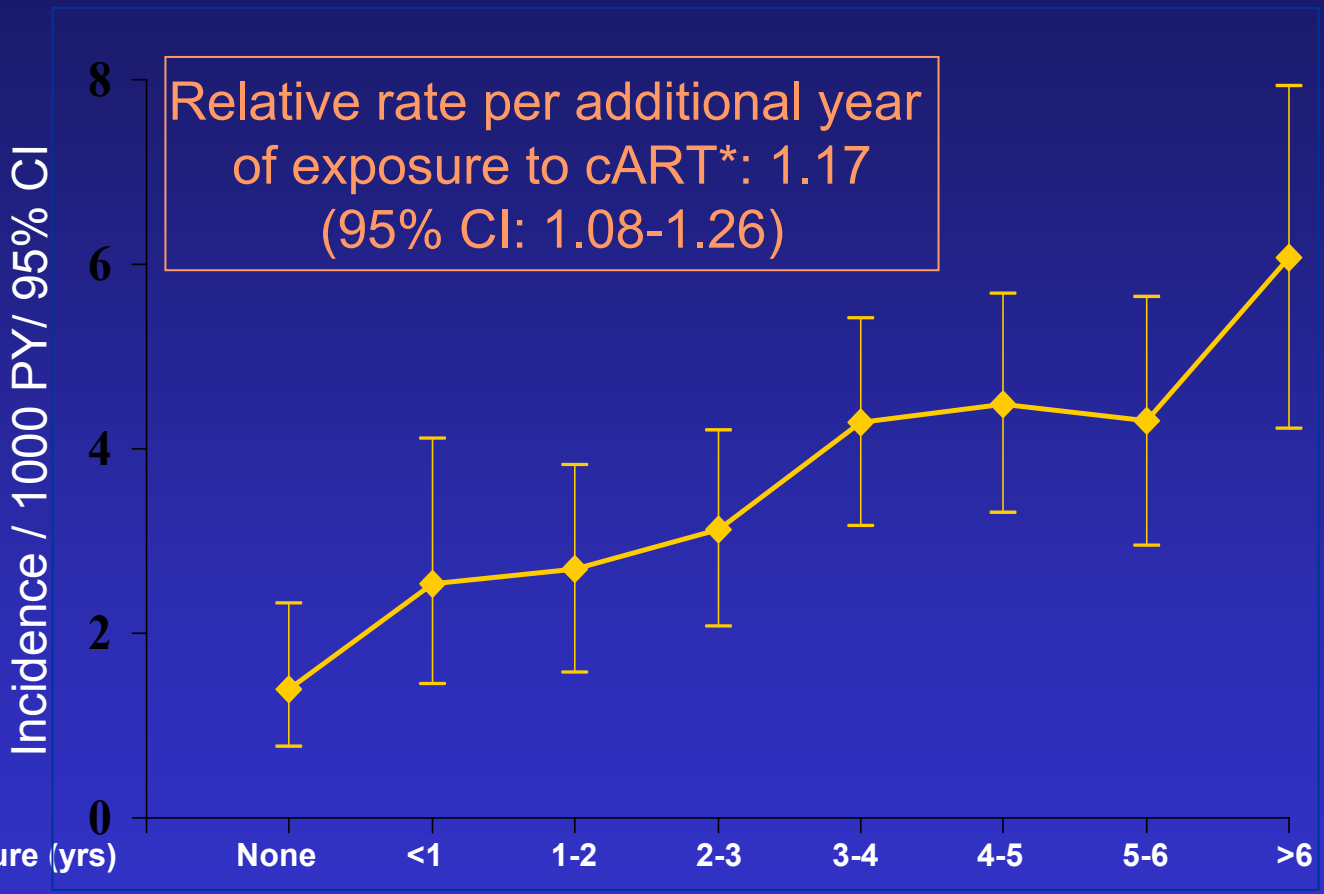
Adapted from C. Wanke et al. CID 2002;34:248-59.

HIV infection and Cardiovascular Risk

- Are patients with HIV infection at increased risk for arteriosclerosis ?

- If so, to what extent is the excess risk attributable to :
  - HIV infection per se (inflammation)
  - Lipid abnormalities due to therapy
  - Other drug effects (insulin resistance)
  - Consequence of fat redistribution

Incidence of myocardial infarction according to cART exposure in D:A:D

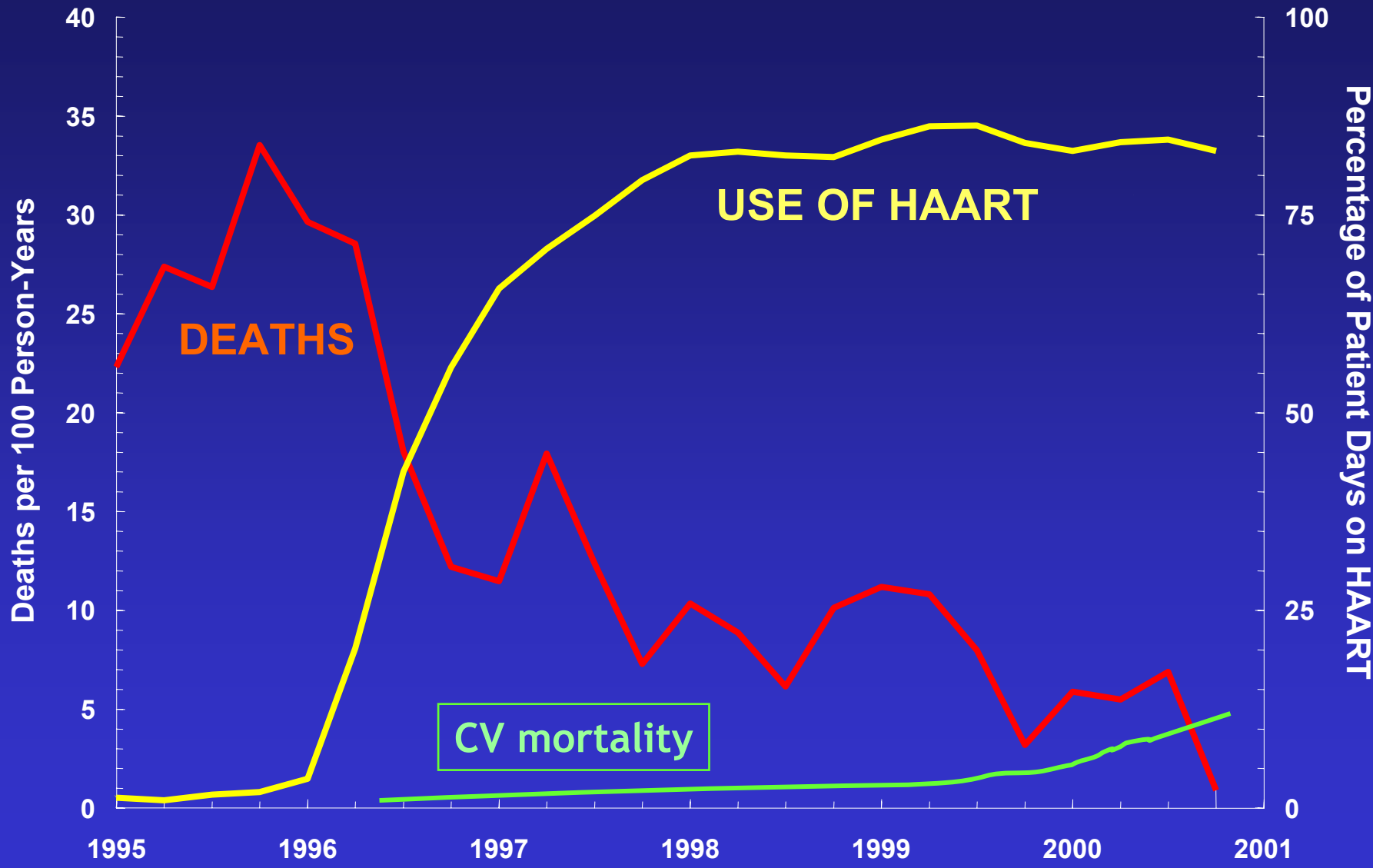


# MI	14	16	22	34	56	55	39	41	277
PYFU	10,103	6,324	8,165	10,846	13,060	12,254	9,073	6,751	76,577

*: Adjusted for conventional risk factors not influenced by cART

El-Sadr *et al*, CROI 2005 (#N-186

Mortality vs. HAART Utilization



Managing Dyslipidemia and CV Risk in HIV patients

- Obtain fasting lipids prior to starting therapy
- Consider and assess other risk factors
  - Hypertension
  - Smoking
  - Family history
  - Diet
  - Menopause
  - Assess insulin sensitivity ?
- Consider aspirin therapy in patients with other CV risk factors
- Select initial ARV with these factors in mind
- Repeat lipids at 3-6 months

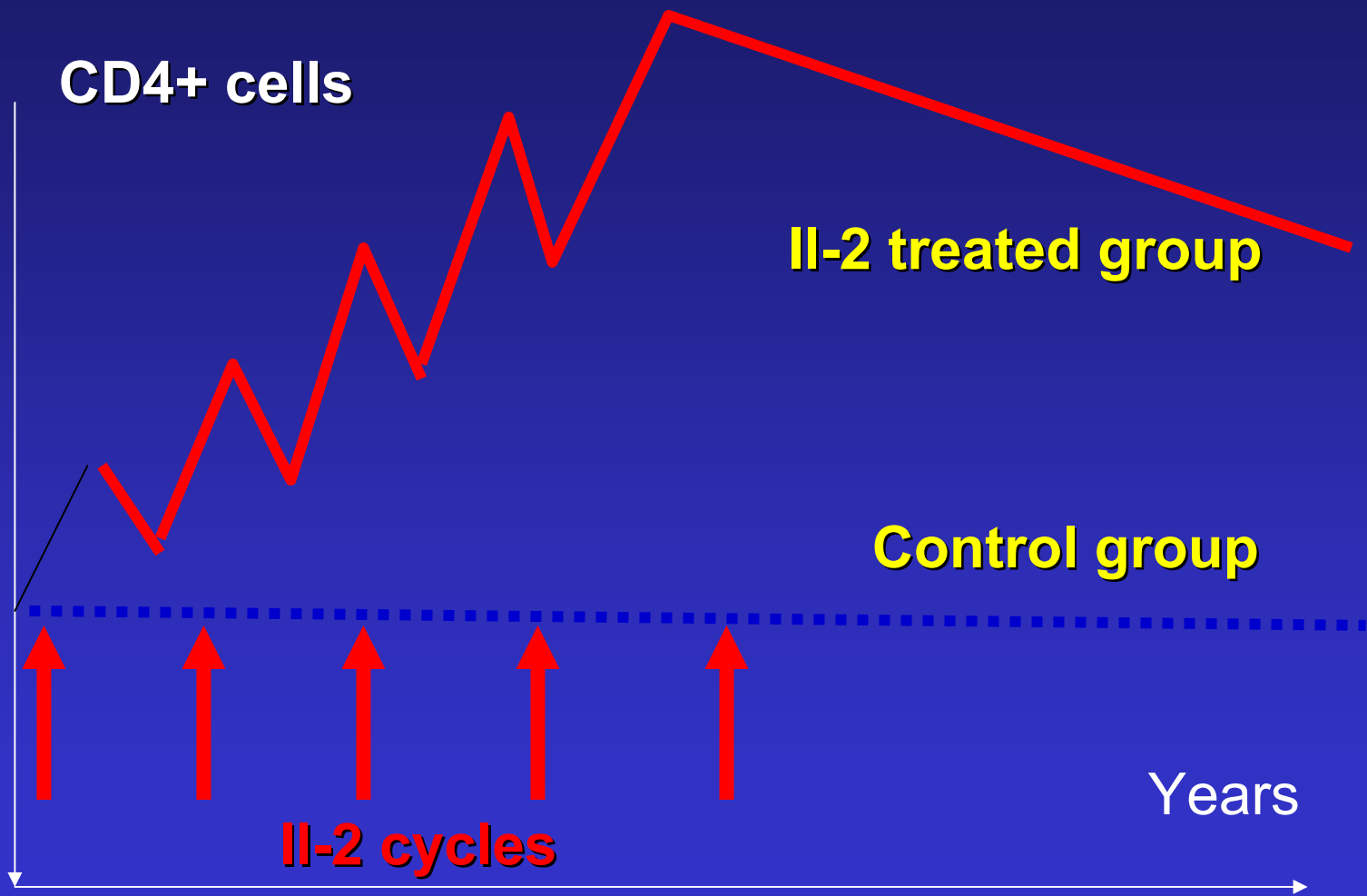
Ongoing strategic trials

SMART
Drug Conservation
or Virologic suppression?

Stop or defer AR therapy until CD4+ cell count declines to below 250 cells/mm3; then treat to increase CD4+cell count > 350 cells/mm3, then use episodic AR treatment based on CD4+cell count.

Use AR treatment to maintain viral load as low as possible irrespective of CD4+ cell count by changing AR treatment when the viral load is not suppressed.

Interleukin-2



What about cure…?

…well, it’s not taboo anymore…

…we could discuss that at the 2015 SBIMC/BVIKM autumn symposium.

Thank you for your attention.