

## Resistance Fundamentals

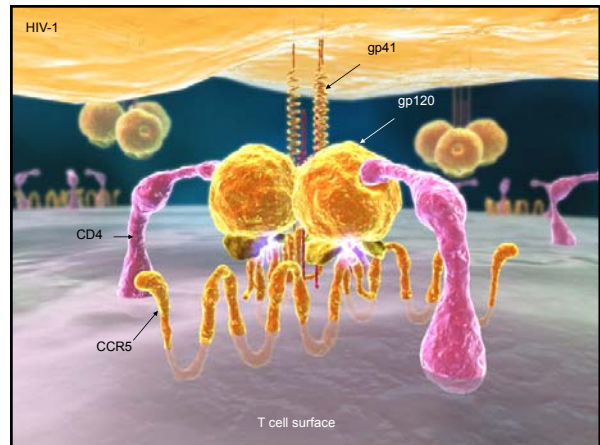
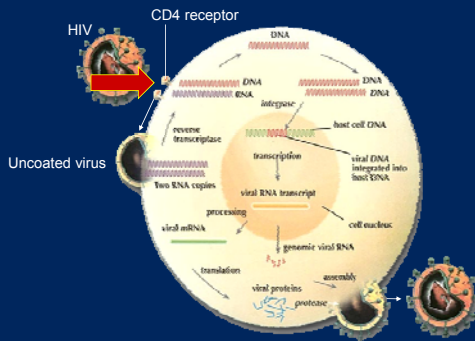
Nobel A. Bellosillo, MD  
Director, Medical Affairs  
Virco Labs, Inc

## Disclosures

- Financial Relationships
  - Gainfully employed by Virco Labs, Inc
    - ♦ manufacturer of virco®TYPE HIV-1
    - ♦ a Johnson and Johnson sister company of Tibotec Therapeutics, manufacturers of Prezista™ (darunavir), Intelence™ (etravirine)
- This presentation will include discussions on the following products of the above companies
  - Virco Labs, Inc
    - ♦ virco®TYPE HIV-1
  - Tibotec Therapeutics
    - ♦ mechanisms of action of and resistance to darunavir, etravirine

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## HIV Life Cycle

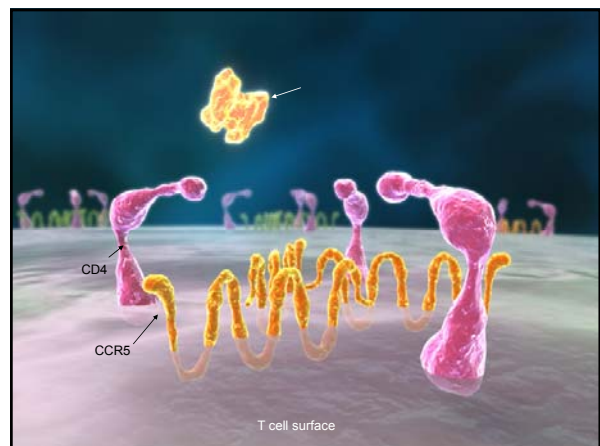


## Inhibition of Viral Attachment

Co-receptor antagonists  
CCR5 Inhibitor

- maraviroc

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## Mechanisms of Viral Escape

- Resistance
- Tropism 'switch'

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## CCR5 Inhibitor Associated Mutations

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## Maraviroc Resistance

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## HIV fusion Step 1: Attachment

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## Step 2: Coreceptor binding

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## Step 3: Fusion

### Insertion and 'zipping'

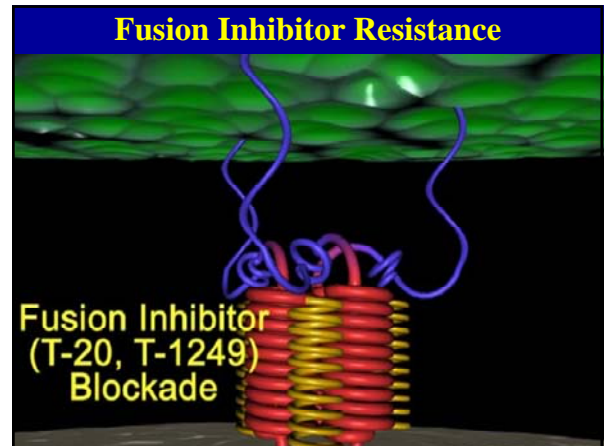
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## Inhibition of Viral Entry

Fusion Inhibitors

- enfuvirtide

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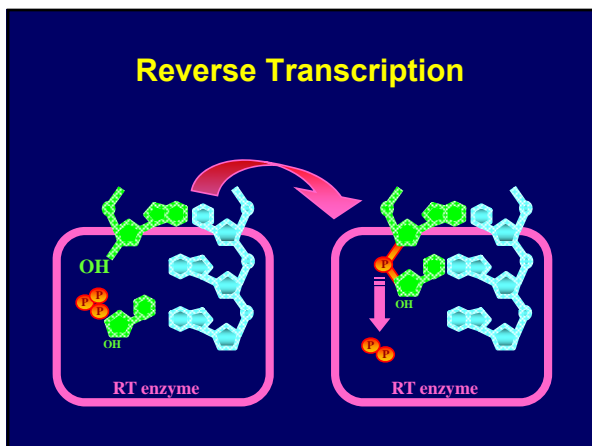
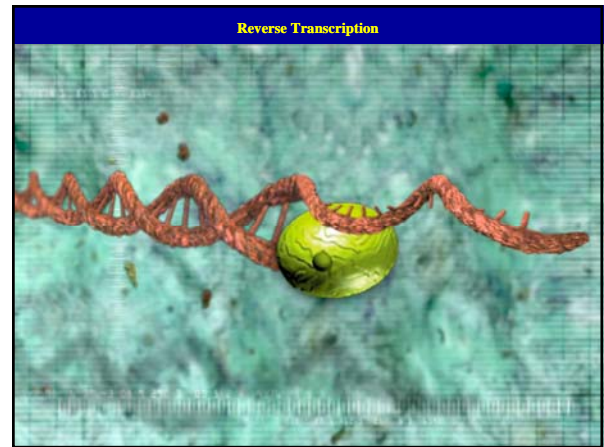
## Enfuvirtide Resistance

Substitutions in gp41  
Amino acids 36-45

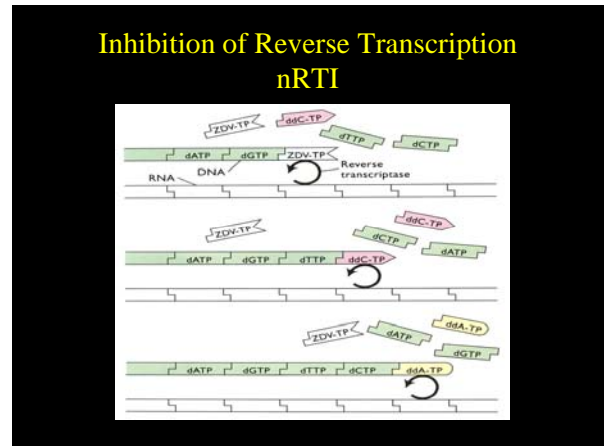
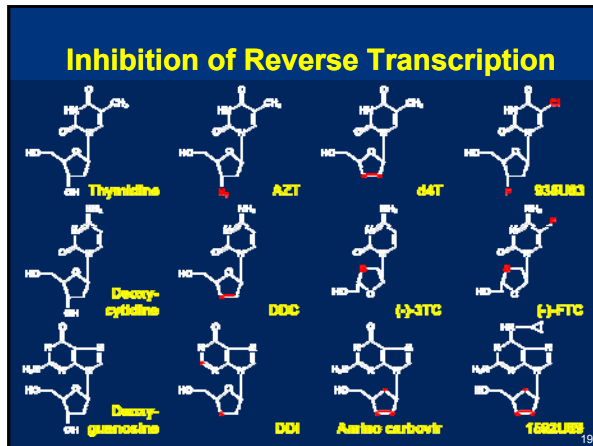
Fold Change from baseline  
in enfuvirtide susceptibility

	N	Geometric Mean	Range
V38A	27	42	10-185
V38V/A	8	36	8-324
G36D	16	32	15-60
N43D	19	26	8-401
V38M	6	15	10-26
N43N/D	5	9	5-17

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- ## Inhibition of Reverse Transcription
- Nucleoside Reverse Transcriptase Inhibitors
- ZDV
  - ddI
  - ddC
  - 3TC
  - d4T
  - abacavir
  - FTC
- Nucleotide Reverse Transcriptase Inhibitors
- tenofovir
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### Effect of nRTI-associated mutations

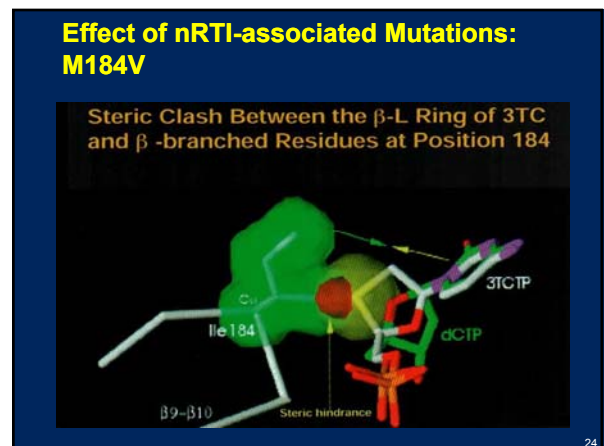
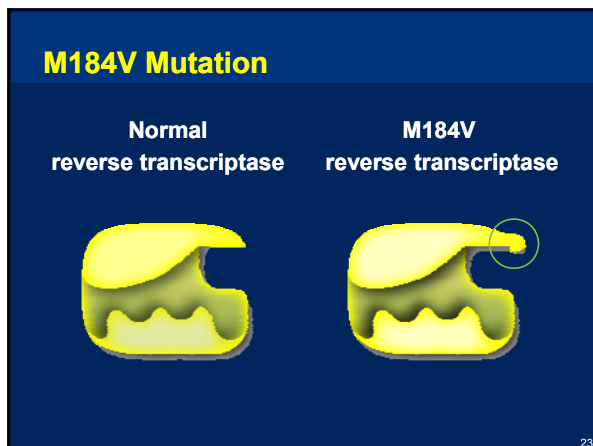
**"INTERFERENCE"**  
PREVENT NUCLEOSIDE ANALOGUE INCORPORATION

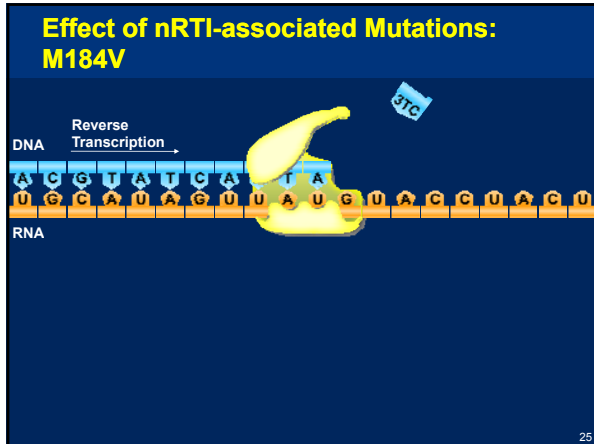
**"PLUCKERS"**  
PROMOTE NUCLEOSIDE ANALOGUE REMOVAL

### Effect of nRTI-associated mutations

PREVENT NUCLEOSIDE ANALOGUE INCORPORATION

- \*M184I/V  
Selected by: 3TC, FTC, ABC, (ddI)  
Confers resistance to: 3TC, FTC, (ABC)
- \*K65R  
Selected by: TDF, (ABC, ddI)  
Confers Resistance to: TDF, ddI, 3TC, FTC (ABC)
- \*L74V  
Selected by: ddI, ABC  
Confers Resistance to: ddI, (ABC)





### Effect of nRTI-Associated Mutations

**INCREASED NUCLEOSIDE ANALOGUE REMOVAL**

41L, 67N, 70R, 210W, 215Y/F, 219Q/E

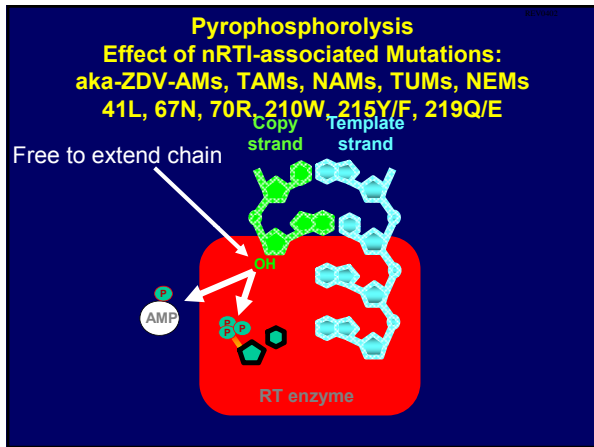
Selected by: AZT, d4T

≥3 NAMS = AZT, d4T

≥3 NAMS + 184V = abacavir

Modifications for: TDF, ddl

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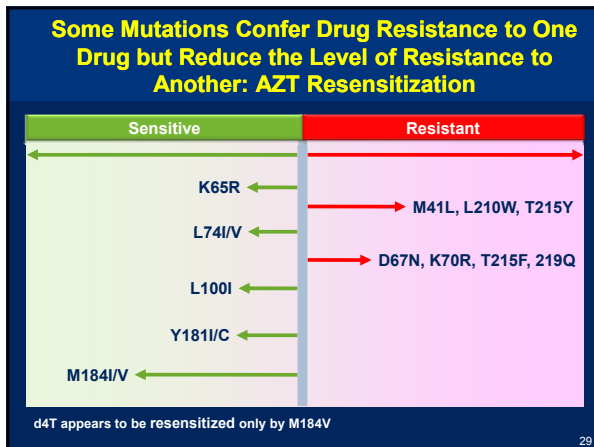
### Typical Mutational Patterns of ≥3 Nucleoside Analog Mutations (NAMS)

	NAMs 1			NAMs 2		
	41 / 210 Pathway			70 / 219 Pathway		
3 NAMS:	M41L L210W	T215Y	11%*	D67N K70R K219Q/E/N		12%*
≥ 4 NAMS:	M41L L210W	D67N T215Y	7%*	D67N K70R T215F K219Q/E/N		8%*

\* Integrated Studies 902 + 907 database (n=333)

<sup>1</sup>Yahi et al., J. Clin. Micro. (1999) and Hanna et al., J. Inf. Diseases (2000)

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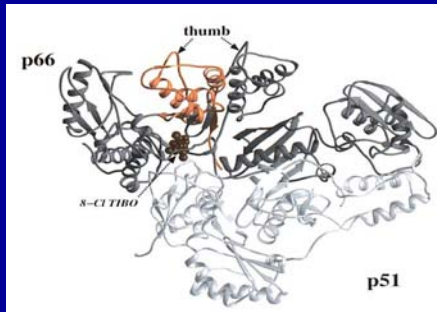
### Inhibition of Reverse Transcription

1st generation Non-Nucleoside Reverse Transcriptase Inhibitors

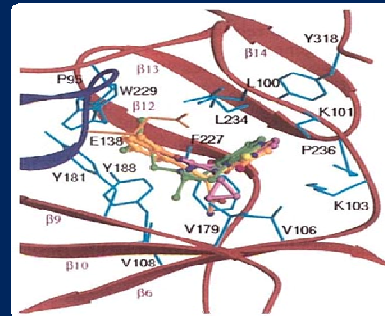
- nevirapine
- delavirdine
- efavirenz

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## Inhibition of Reverse Transcription

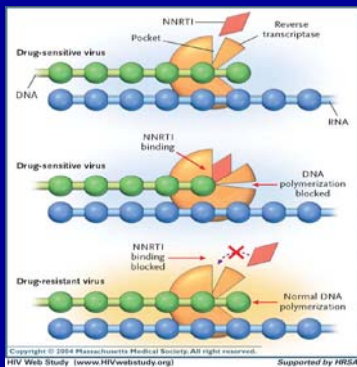


## Effect of NNRTI-associated Mutations K103N, Y181C, or Y188L



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## Inhibition of Reverse Transcription



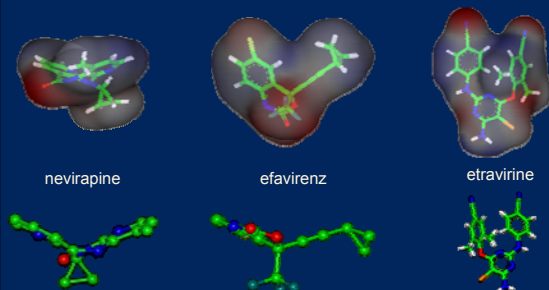
## Inhibition of Reverse Transcription

2nd generation  
 Non-Nucleoside Reverse Transcriptase Inhibitor

- etravirine

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## NNRTI Structures



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## Etravirine Resistance

### ETR weighted genotypic scores

ETR (IAM)	Weight factor			Prevalence* (%)	ETR (IAM)	Weight factor			Prevalence* (%)
	TGT (n=17)	MGR (n=38)				TGT (n=17)	MGR (n=38)		
V90I	1	1		6.53	Y181C	2.5	4		32.32
A98G	1			8.51	V181F		1		0.07
L100I	2.5	4		6.40	V181I	3	4		1.40
K101R	1	2		8.51	V181V		4		0.88
K101H	1	1		2.19	Y188L		2		0.45
K101P	2.5	4		2.61	V189I		1		3.81
V106A		2		2.12	G190A	1			23.23
V106I	1.5			4.28	G190E		1		0.47
V106M		1		1.08	G190Q		3		0.49
E138A	1.5	3		2.52	G190S	1.5			0.72
E138G				0.73	G190T		1		0
E138K		2		0.39	R221Y		1		9.58
E138Q		1		1.13	R228M		1		3.32
V179D	1	1		2.12	M230L	2.5	3		1.06
V179E		3		1.53	K238N		3		0.88
V179F	1.5	1		0.68	K238T		1		3.23
V179L		2		0.49					
V179M		1		0.16					
V179T	1			0.81					

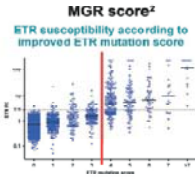
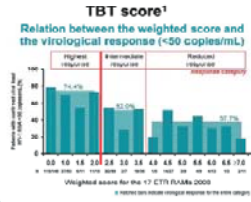
\*The prevalence was determined in the panel of 4,249 HIV-1 clinical isolates

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## Etravirine Resistance

### Methods (cont'd)

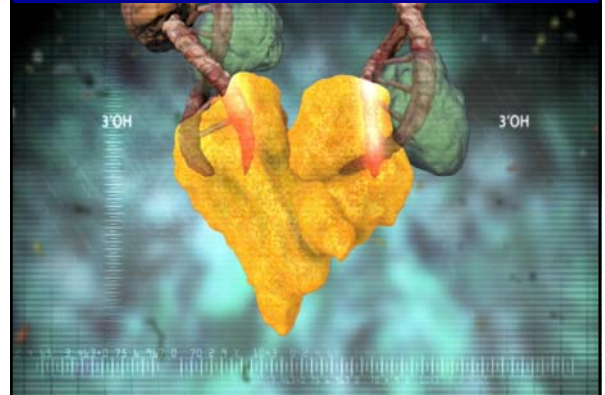
- A single cut-off was used to categorise samples as 'sensitive' or with reduced susceptibility ('resistant'). These cut-offs were set at '2' for the Tibotec algorithm and '3' for the Monogram algorithm



1. Vingerhoets J, et al. *Antivir Ther* 2006;13(Suppl. 3): A20  
2. Benhamida J, et al. *Antivir Ther* 2008;13(Suppl. 3): A142

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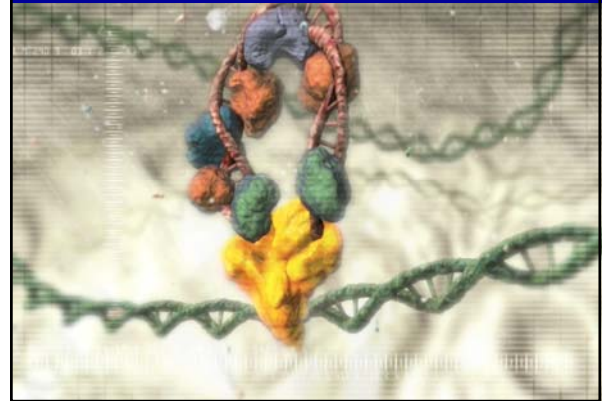
## Integration



## Integration



## Integration

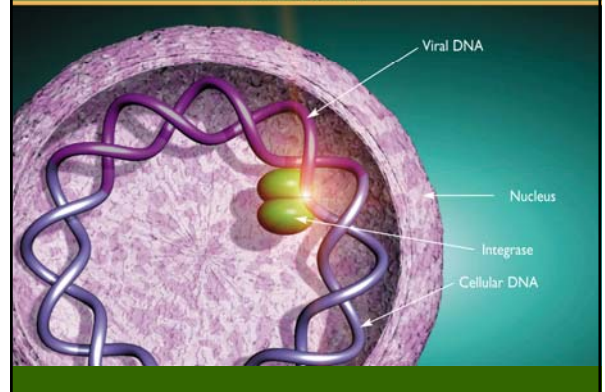


## Inhibition of Integration

- raltegravir

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## STEP 4 INTEGRATION

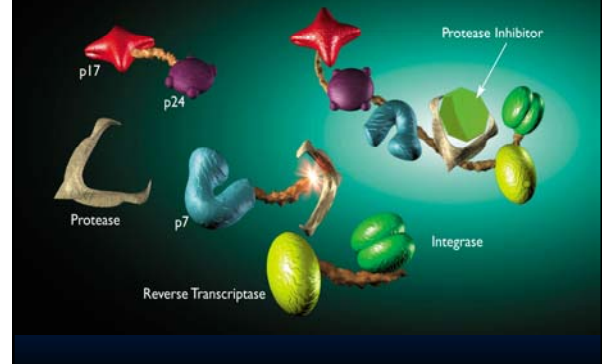


## Raltegravir Resistance BENCHMRK 1 & 2 Conclusions to Date

- Three pathways defined by primary mutations at 143, 148, and 155
- Secondary mutations lead to higher resistance  
If not present at VF, evolves at later time
- Q148 pathway is preferred  
Virus population can switch N155 to Q148  
Q148 mutants lead to greater resistance

2008 ICAAC-IDSA Abstract H-898

## STEP 7 CLEAVAGE



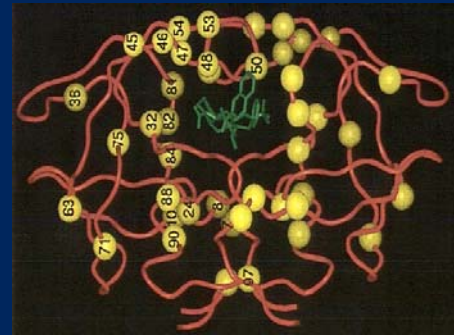
## Inhibition of Cleavage

### Protease Inhibitors

- saquinavir
- ritonavir
- indinavir
- nelfinavir
- fos-amprenavir
- lopinavir/ritonavir
- atazanavir
- tipranavir
- darunavir

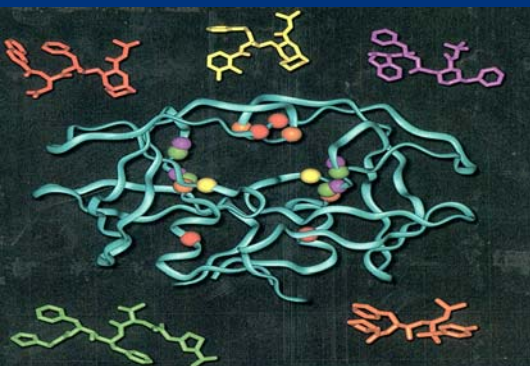
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## Effect of PI-associated Mutations



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## Overcoming PI resistance



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