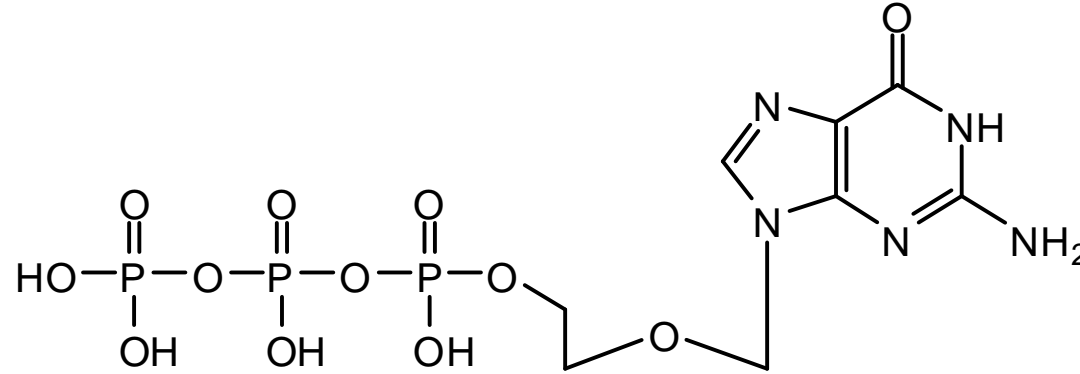


ACYCLOVIR (ACV)

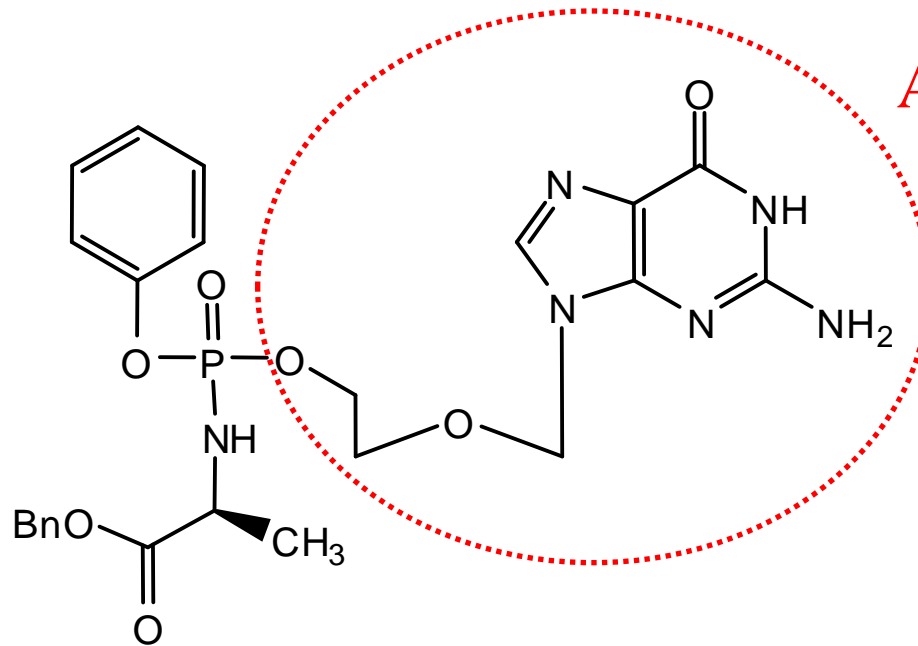
- Guanosine analogue; potent anti-HSV drug; requires activation by viral kinase
- ACV is activated into a HIV-1 RT Inhibitor by HHV-6 in infected human tissues. **Lisco et al. 2008**
- ACV selects for V75I, M184V and T69N in HIV-1 RT. **McMahon et al. 2008**

ACV monophosphorylated prodrug CF2648

Acyclovir triphosphate – active form



CF2648

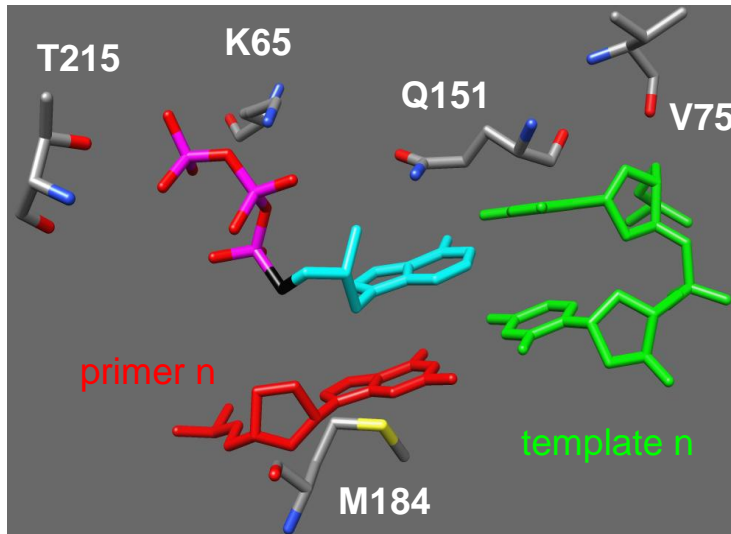


Acyclovir
prodrug

Inhibitory Activity of CF2648 against HIV-1 in MT-4 Cells

	Wild-Type (WT)	CF2648 Selected (V75I)	Fold increase
$EC_{50} \pm SE (\mu M)^a$	3.4 ± 2.8	51 ± 2.3	15

Possible Effects of V75I



1. NRTI Binding, e.g. M184V
2. NRTI Incorporation, e.g. Q151M
3. NRTI Excision, e.g. T215Y

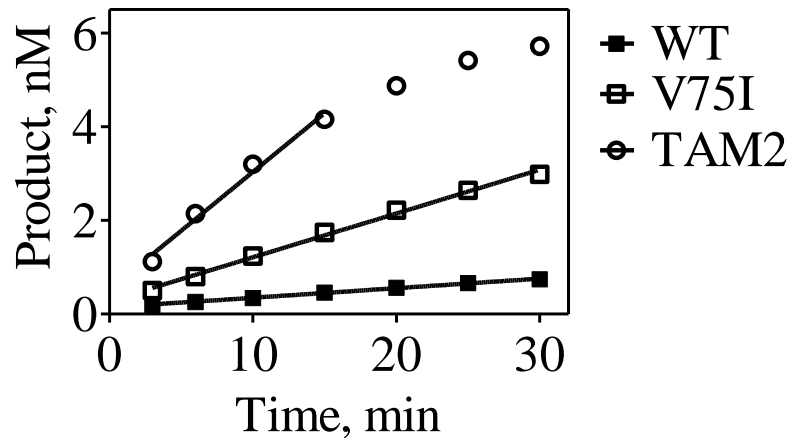
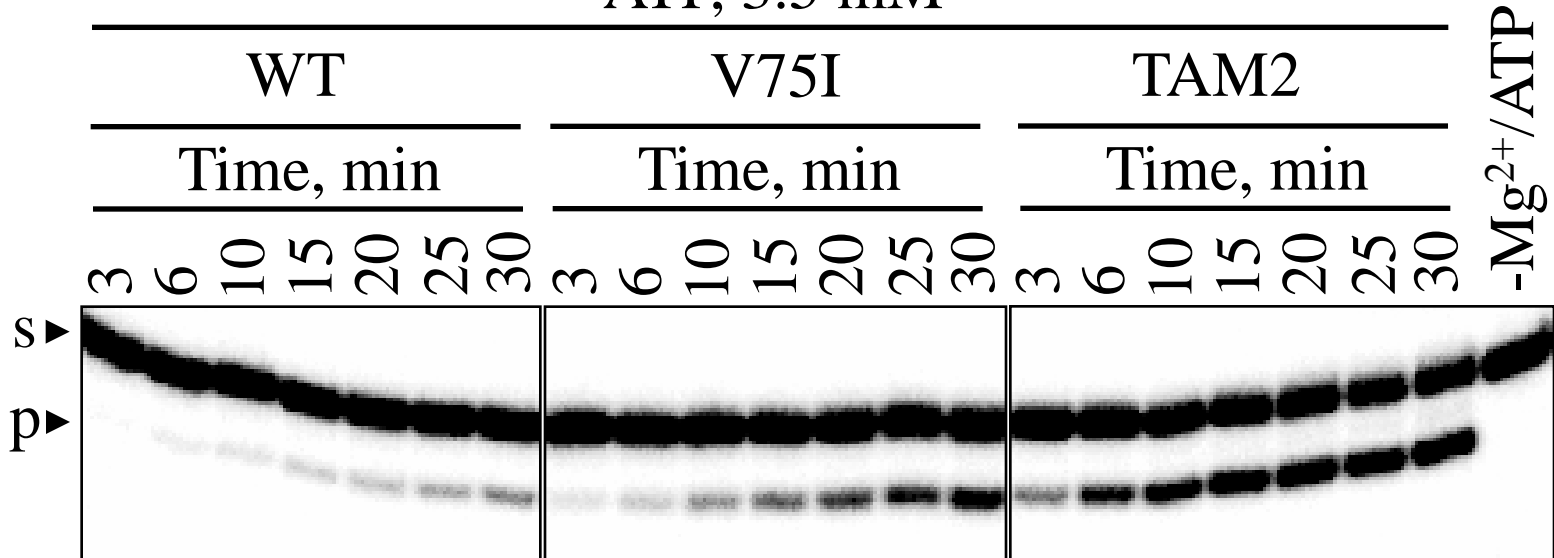
V75I effect on nucleotide incorporation

Enzyme	Substrate						SEL	RES
	dGTP			ACV-TP				
	k_{pol} sec ⁻¹	K_d μM	k_{pol}/K_d	k_{pol} sec ⁻¹	K_d μM	k_{pol}/K_d		
WT	66 ±3. 0	1.3 ±0.1 6	51	14 ±0.3 9	2.2 ±0.1 8	6.4	8.0	1.0
V75I	114 ±2. 9	3.7 ±0.1 8	31	1.5 ±0.0 7	3.8 ±0.4 3	0.40	78	9.8

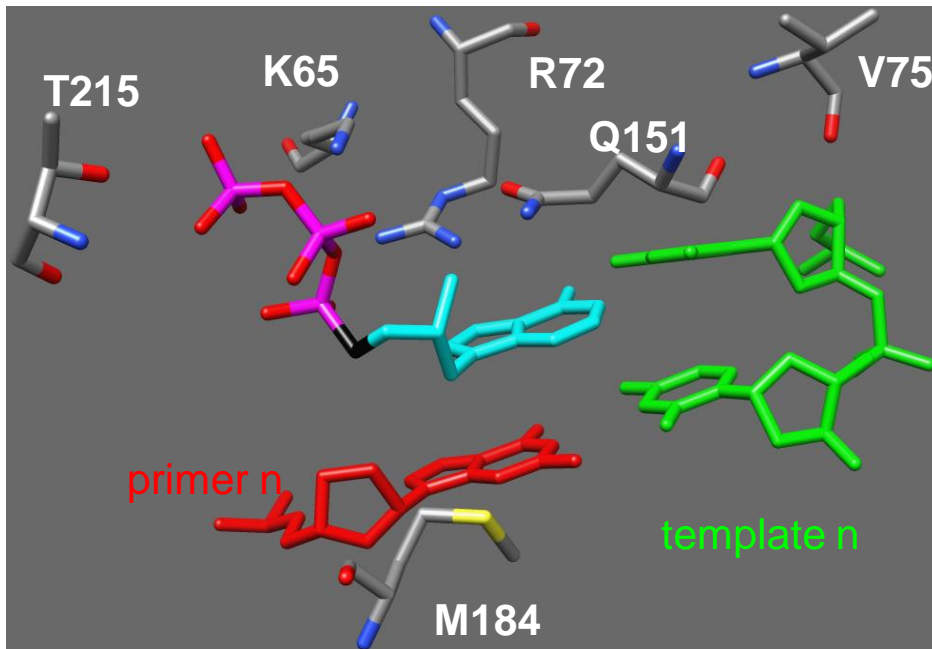
V75I effect on ATP-dependent excision

Substrate: ACV-MP terminated primer / template

ATP, 3.5 mM



Conclusions



V75I discriminates against ACV at the level of incorporation.

This effect is mediated indirectly, perhaps through Q151 or R72, or the base at template position n+1.

Diminished DEC formation, and increased efficiency of excision in the presence of TAMs suggest that ACV is vulnerable to both major NRTI resistance pathways.

Acknowledgments

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