

Emergence of Atazanavir Resistance and Maintenance of Susceptibility to Other PIs is Associated with an I50L Substitution in HIV Protease

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SUMMARY

Atazanavir (ATV, BMS-232632) is a once daily protease inhibitor (PI) currently in late stage clinical development. Characterization of ATV-resistant viruses selected *in vitro* indicated that N88S, I84V and I50L substitutions may play an important role in ATV resistance and that multiple pathways to resistance are possible.¹ Analysis of a panel of 950 clinical isolates showed that ATV had a distinct resistance profile relative to other PIs.² In general, reductions in ATV susceptibility required several amino acid changes, were modest in degree and susceptibility was retained among isolates resistant to one or two of the currently approved PIs. There was a clear trend toward loss of susceptibility to ATV as isolates exhibited increasing levels of cross-resistance to multiple PIs. A genotypic characterization of this panel of isolates demonstrated a correlation between the accumulation of 5 or more changes at 14 key amino acids (L101V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, I84V and L90M) and reduced susceptibility to ATV.² Here, we confirm the identity of a unique I50L substitution as the signature change for ATV and show that isolates harboring the I50L substitution exhibit ATV-specific resistance and increased susceptibility to other PIs. This unique phenotypic pattern appears to be distinct from that observed in the presence of the I50V and 30N substitutions induced by amprenavir (APV) and nelfinavir (NFV), respectively.

APPROACH

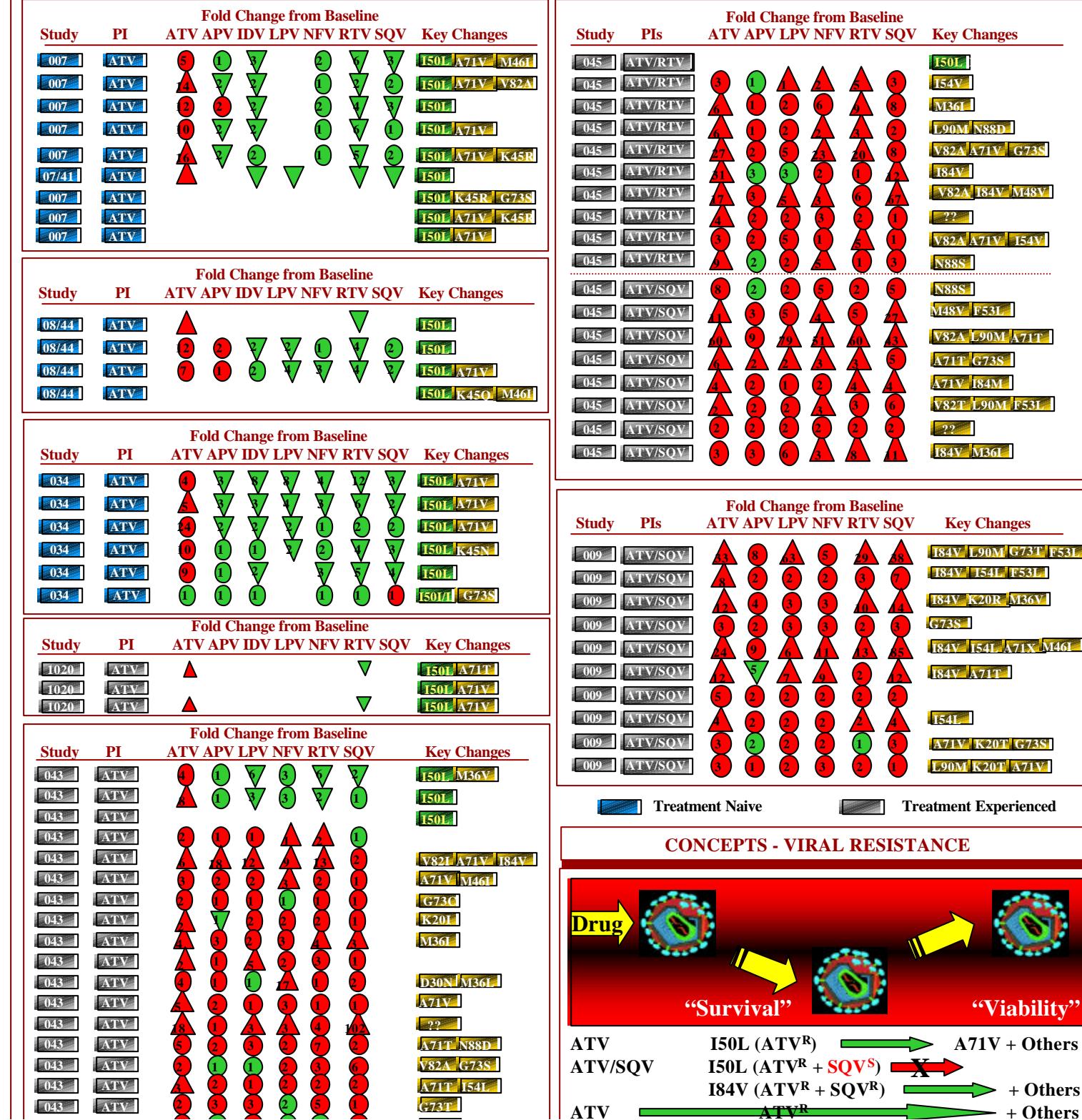
The emergence of ATV resistance was monitored in clinical studies AI424-007, -008/044, -009, -034, -043, -045 and ACTG P1020. The phenotype and/or genotype of 68 clinical isolates, designated as virologic failures on ATV containing regimens and who displayed reduced susceptibility to ATV, were determined for ATV, APV, indinavir (IDV), lopinavir (LPV), ritonavir (RTV) and saquinavir (SQV) and evaluated. Summary tables show the net fold change (FC) in susceptibility between baseline and on treatment isolates.

CONCLUSIONS

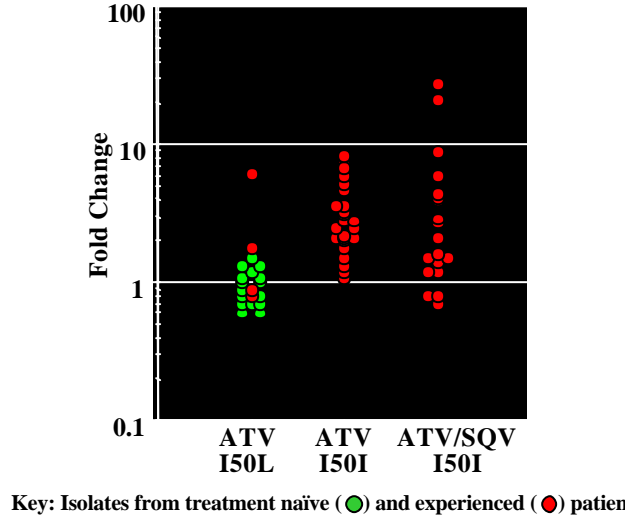
- Emergence of ATV^R observed in ~ 6% of treated patients and ~20% of all treatment failures from ATV containing regimens
- 26 isolates had a unique I50L substitution
 - Susceptible at baseline (FC <2) with ≤3 key substitutions
 - Developed ATV specific resistance
 - Baseline or increased susceptibility to other PIs
 - Potential to re-sensitize resistant isolates
- 42 isolates without I50L substitution
 - Includes all 18 from subjects treated with ATV/SQV combination
 - Decreased susceptibility at baseline (FC >2) with >3 key substitutions
 - Multiple changes, including primary and secondary PI resistance substitutions observed for other PIs
 - Develop high level cross-resistance to other PIs

Net Fold Change in Susceptibility From Baseline of Individual Isolates in ATV Clinical Trials

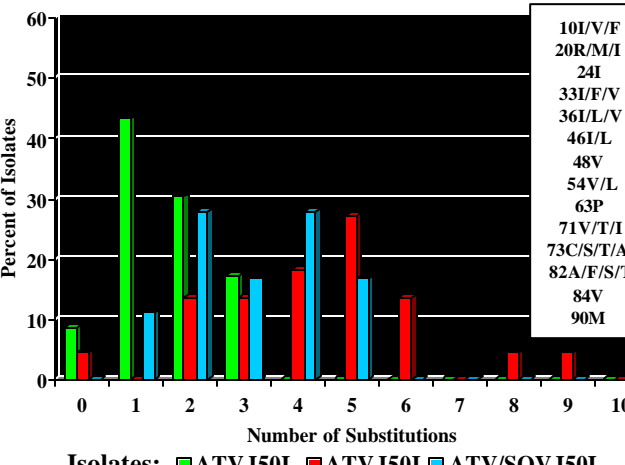
● = Fold increase in susceptibility ▼ = Fold increase to FC <0.4 ● = Fold decrease in susceptibility ▲ = Fold decrease to FC >10
 Key Changes - Emerging substitutions at amino acid 50 and/or primary and secondary sites correlated with PI resistance



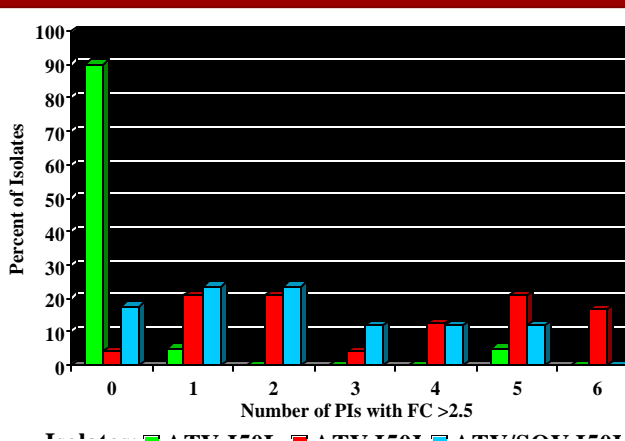
ATV Susceptibilities of Isolates at Baseline



ATV Key Substitutions at Baseline



Presence of PI Resistance at Baseline



Impact of I50L Substitution

Study ID	Treatment	Susceptibility (Fold Change)				
		ATV	APV	IDV	NFV	RTV
810024-clone 1	24	7.6	1.4	2.3	>142	0.8
810024-clone 2	24	22	0.1	0.1	6	0.1

Subject ID	Amino Acid Substitutions					
	10F, 13V, 23I, 30N, 37S, 41K, 62V, 63P, 70R, 71T, 88D, 93L					
810024-1						
810024-2	I50L					

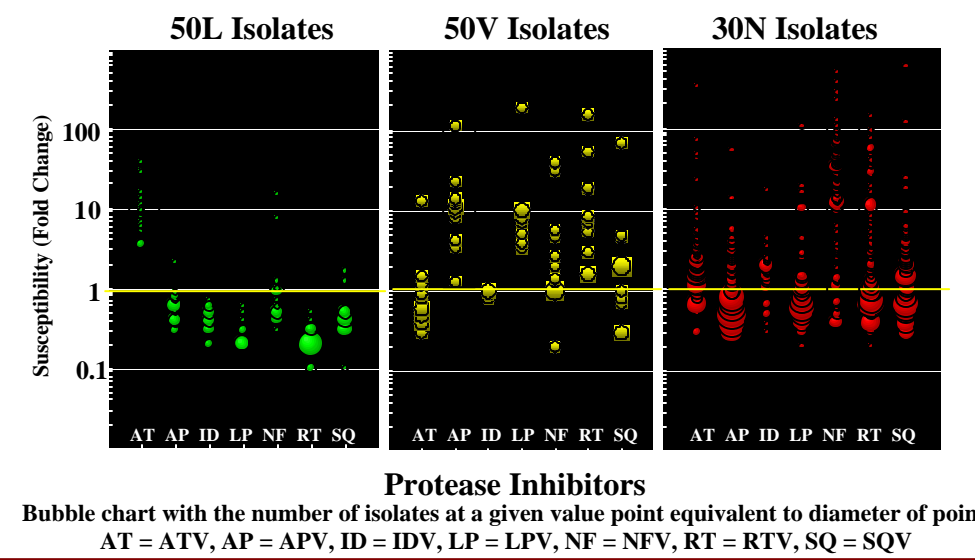
Key: Red = FC ≥ 2.5, Green = FC ≤ 0.4

Impact of I50L and A71V Substitutions in Recombinant Clones

Virus	Susceptibility (Fold Change)						
	ATV	NFV	IDV	RTV	APV	SOV	LPV
LAI							
I50L	5.4	0.2	0.1	0.1	0.2	0.4	0.2
A71V	2.4	1.1	0.6	0.5	0.7	0.9	0.6
I50L/A71V	10	0.3	0.3	0.2	0.2	0.07	0.3
NL4-3							
I50L	2.1	0.1	0.1	0.1	0.1	0.1	0.1
A71V	1.6	1.3	1.0	0.7	0.3	0.7	1.1
I50L/A71V	5.7	0.3	0.3	0.2	0.2	0.1	0.06
RF							
I50L	3.1	0.1	0.1	0.3	0.3	0.4	0.1
A71V	0.9	1.4	1.2	2.4	0.6	0.8	1.4
I50L/A71V	5.7	0.2	0.1	0.2	0.3	0.2	0.2

Key: Red = FC ≥ 2.5, Green = FC ≤ 0.4

PI Susceptibility Profiles of Resistant Isolates



References:
 1. Gong et al., Antimicrob Agents Chemother 44:2319-2326