

# Hypersusceptibility to protease inhibitors associated with mutated proteases at codons 30 and 88 in treated patients

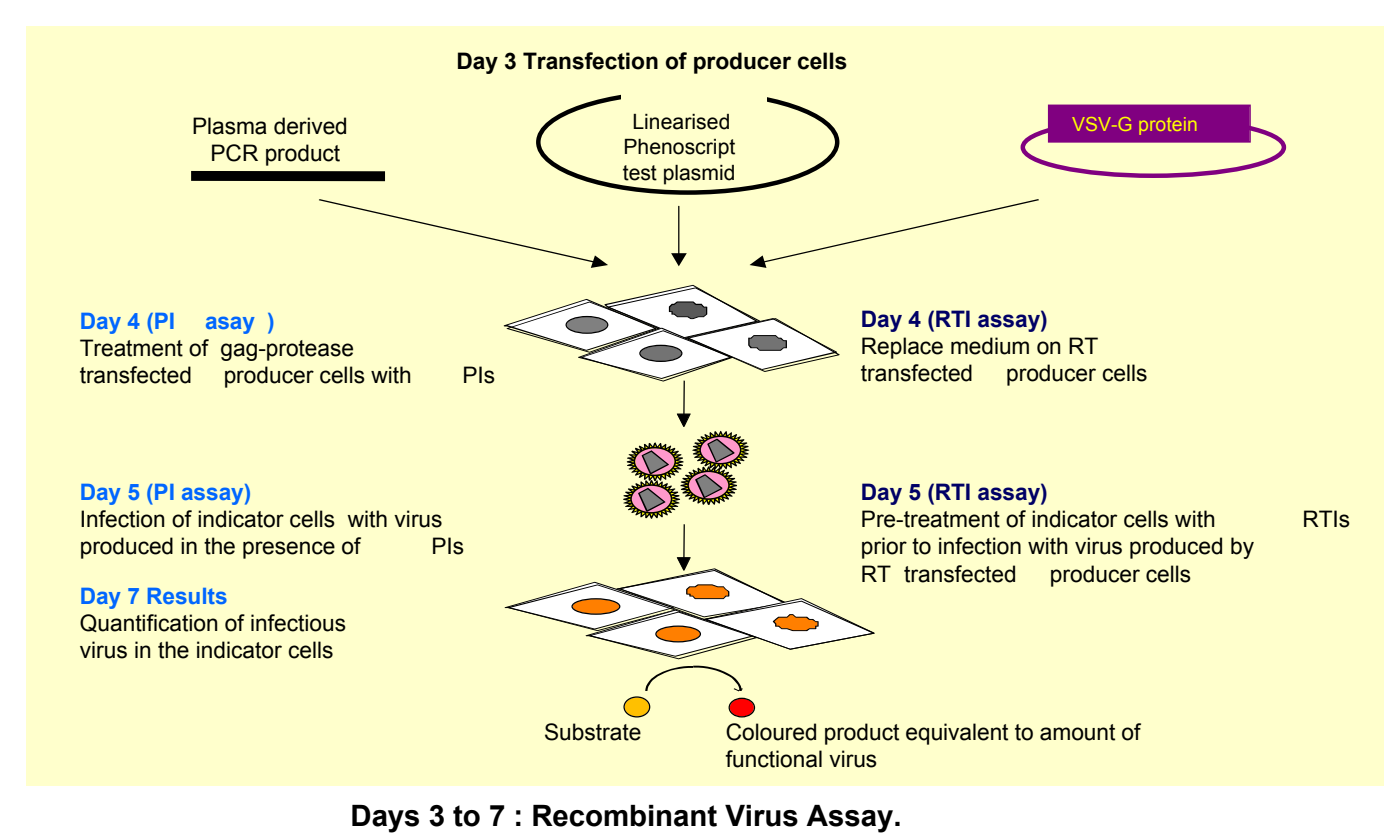
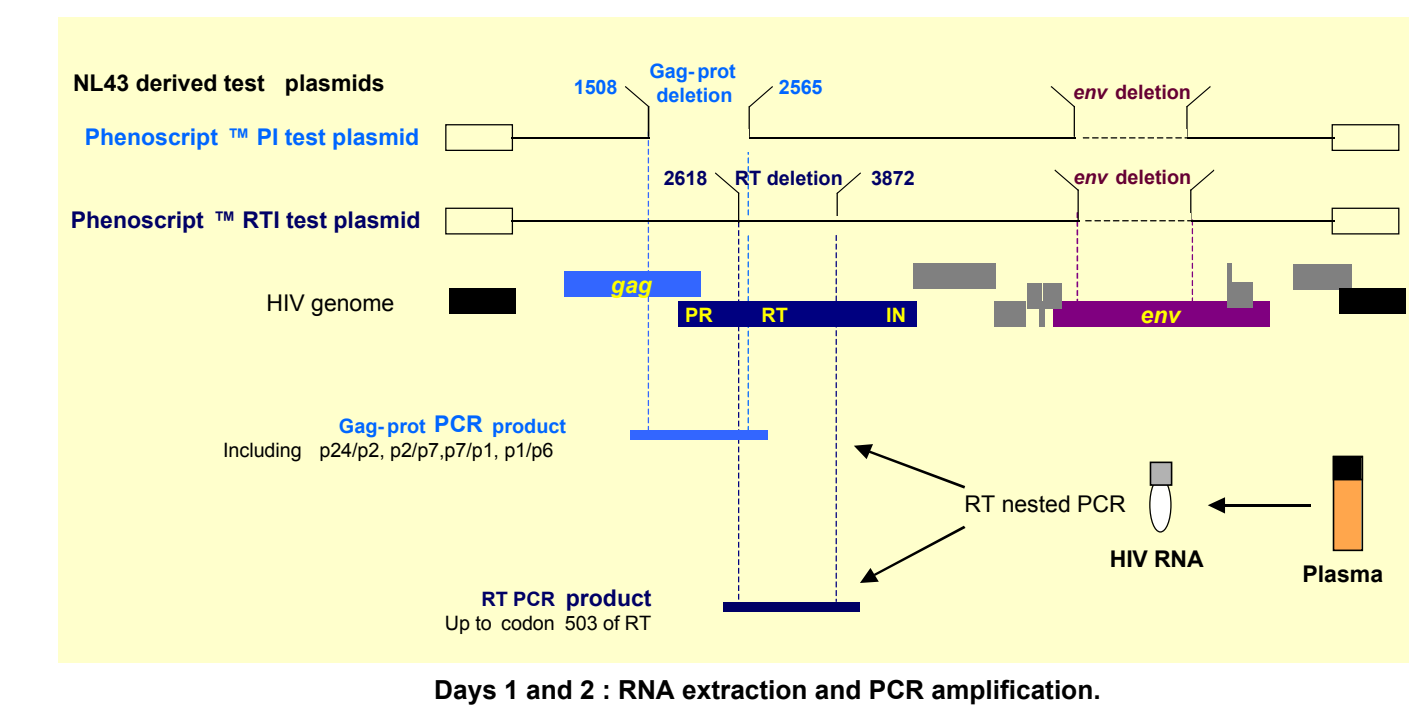
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## INTRODUCTION

Cross-resistance is a hallmark of HIV-1 resistance to protease inhibitors (PI). Some protease mutations, however, promote a lesser degree of cross-resistance, while others, e.g., N88S, have been described as able to induce hypersusceptibility to some PIs. We have examined the extent of hypersusceptibility to PIs in patients having failed PI treatment, using resistance phenotype data from the Narval ANRS 088 trial

## METHODS

The ANRS 088 (NARVAL) trial compared the viral load response after three months on a combination therapy chosen with or without the assistance of a genotypic or a phenotypic drug sensitivity test (reference). Genotyping was conducted using the Trugene (VisGen) sequence analysis system. Phenotyping was carried out using a single cycle recombinant virus assay as described below. Results are presented as a Resistance Index (RI) calculated by dividing the IC<sub>50</sub> (RTIs) or IC<sub>90</sub> (PIs) of the drug for the test virus by that for the NL43 wild-type control tested in parallel.



## RESULTS

Figure 1 : cross-resistance induced by mutations at codons 30 and 88

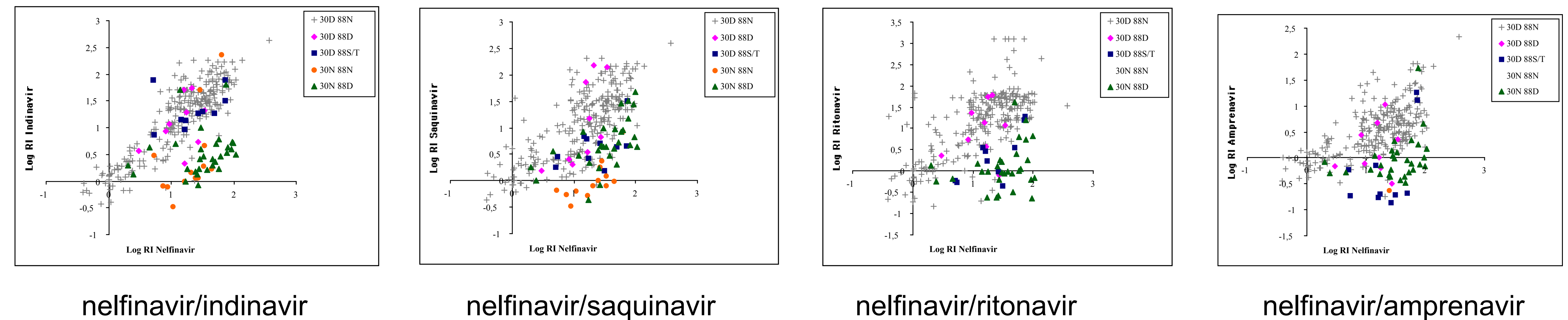


Table 1 : Incidence of hypersusceptibility to amprenavir and ritonavir in samples carrying mutations at codons 30 and 88 of the protease.

	30D 88N	30D 88D	30D 88S/T	30N 88N	30N 88D
N	258	9	10	13	29
Median APV RI	3.3	1.0	<b>0.2</b>	0.7	0.8
% APV RI<0.5	2.3	11.1	<b>60.0</b>	23.1	20.7
Median RTV RI	20.2	12.1	2.3	<b>0.49</b>	0.98
% RTV RI<0.5	3.1	0	10.0	<b>53.8</b>	13.8
Median NFV RI	17.9	16.6	22.0	24.7	32.8
Median N° of mutations in the protease*	5	4	3.5	2	3
Median reduction in viral load at M3	-0.708	-0.232	-1.842	-1.973	-1.622

\* Mutations at positions 10, 20, 36, 46, 48, 54, 71, 73, 77, 82, 84 and 90 were counted.

## CONCLUSIONS

Mutations at codons 30 and 88 in the protease are associated with a distinctive PI cross-resistance profile.

Hypersusceptibility (HS) to amprenavir and ritonavir is a frequent feature of viruses with mutations at codons 30 and/or 88.

While HS to amprenavir is mostly promoted by mutations N88S/T, HS to ritonavir is mainly associated with genotypes bearing D30N in the absence of codon 88 mutation.