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## CRYSTAL STRUCTURES OF HIV-1 REVERSE TRANSCRIPTASE MUTATED AT CODONS 100, 106 AND 108 SHOW NEVIRAPINE RESISTANCE IS MEDIATED VIA PERTURBATION OF INTERACTIONS WITH TYR181 OR TYR188

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**BACKGROUND:** First generation non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs) such as nevirapine lose potency in the presence of a range of mutations whilst second generation compounds such as UC-781 show much greater resilience. Mutations at L100I, V106A and V108I give resistance to various NNRTIs and this is greater in the case of nevirapine compared with UC-781. We have undertaken crystallographic structure determination of these reverse transcriptase (RT) mutants as NNRTI complexes to understand the molecular basis for nevirapine resistance and the greater resilience of second generation inhibitors.

**METHODS:** HIV-1 RT mutants (L100I, V106A and V108I) were crystallised as complexes with NNRTIs such as nevirapine and UC-781. X-ray data were collected to a maximum resolution of 2.4Å. Structures were determined by molecular replacement and refined with CNS. Co-ordinates of mutant RTs were overlapped with corresponding complexes of wild-type RTs to assess changes in the inhibitor position and interactions with the protein.

**RESULTS:** Six refined mutant HIV-1 RT crystal structures were determined. It was observed that nevirapine and UC-781 rearrange within the NNRTI site of L100I and V106A with smaller movement in the V108I RT mutant. This gives rise to significant perturbations in the interactions of nevirapine with the aromatic side chains of Y181 and Y188 for each mutant.

**CONCLUSIONS:** For all three mutants nevirapine resistance appears to be induced indirectly via perturbation of the inhibitor's interactions with either Y181 and/or Y188. This mechanism could provide a general explanation of why second generation compounds, which are less dependent on aromatic ring stacking with Y181 and Y188 than nevirapine, are more resilient to a range of mutations in the NNRTI binding site.

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