Supplementary Material

Structural basis of HIV-1 resistance to AZT by excision

Xiongying Tu, Kalyan Das, Qianwei Han, Joseph Bauman, Arthur D. Clark, Jr., Xiaorong Hou, Yulia V. Frenkel, Barbara L. Gaffney, Roger A. Jones, Paul L. Boyer, Stephen H. Hughes, Stefan G. Sarafianos, and Eddy Arnold

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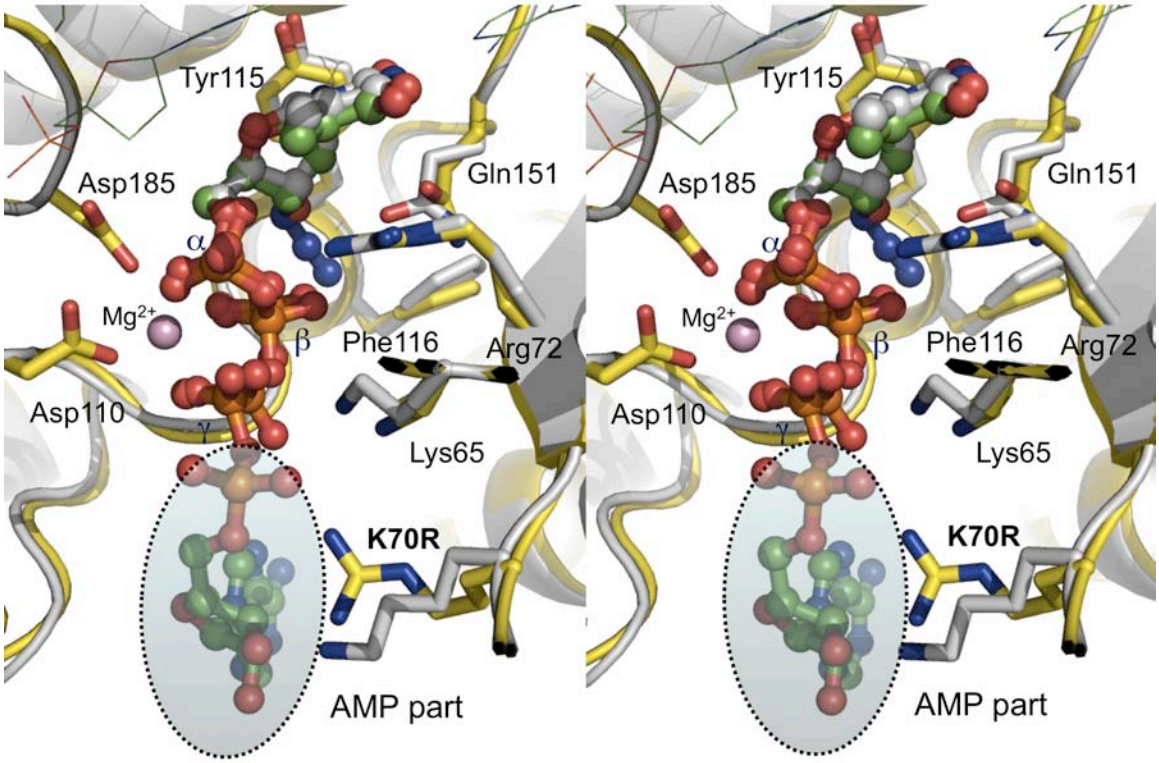

Figure S1. Stereo view of superposition of AZTr RT–dsDNA–AZTppppA excision product complex (yellow) and polymerization catalytic ternary complex wild-type RT–dsDNA–dTTP[4] (gray). The AZTppppA is shown as green C– and orange P– atoms.

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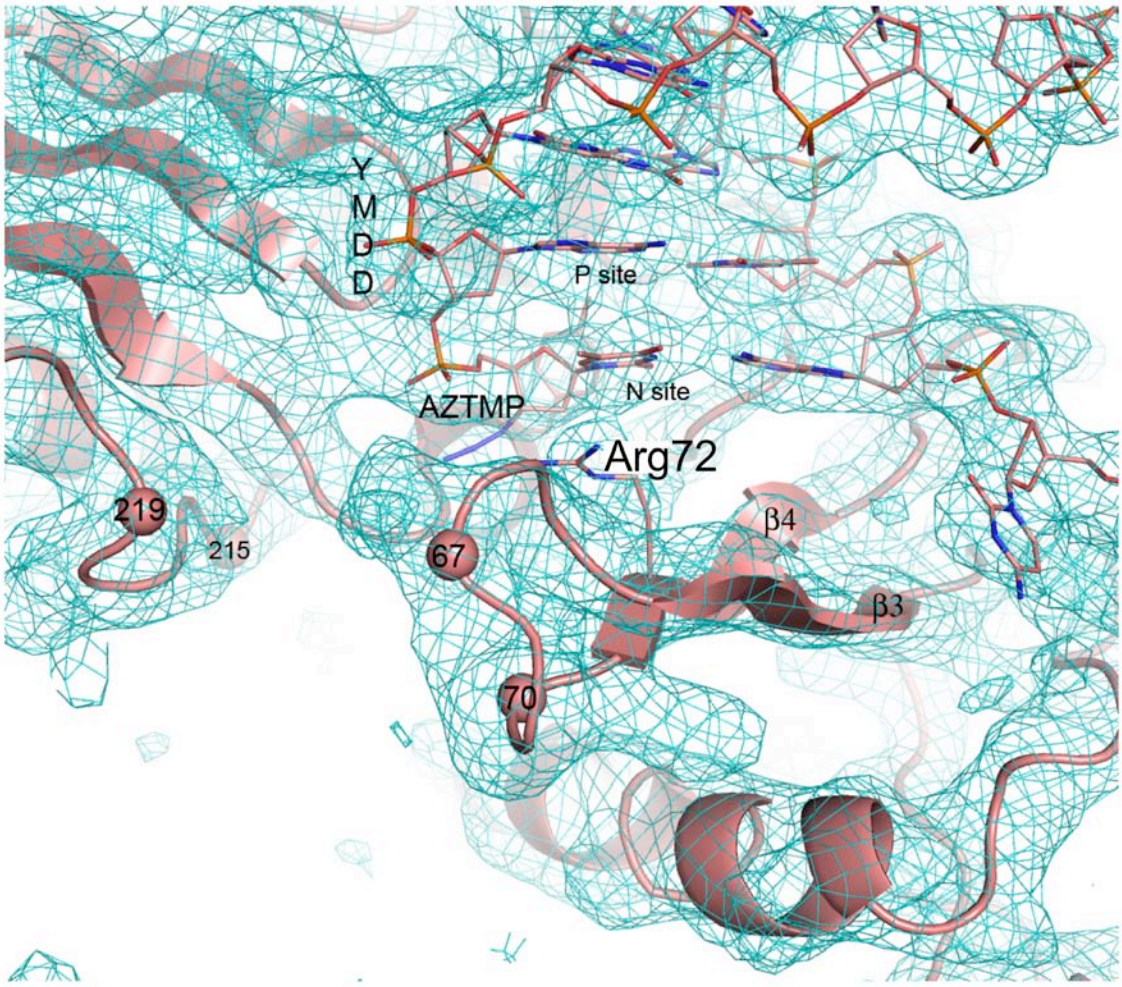

Figure S2. 2(|Fo|-|Fc|) Fourier map (contoured at 1.4σ) of the AZTr HIV-1 RT–dsDNA–AZTMP (N-site) complex at 3.7 Å resolution clearly shows that the 3- 4 segment of p66 fingers subdomain has a closed conformation when the incorporated AZTMP occupies N-site.

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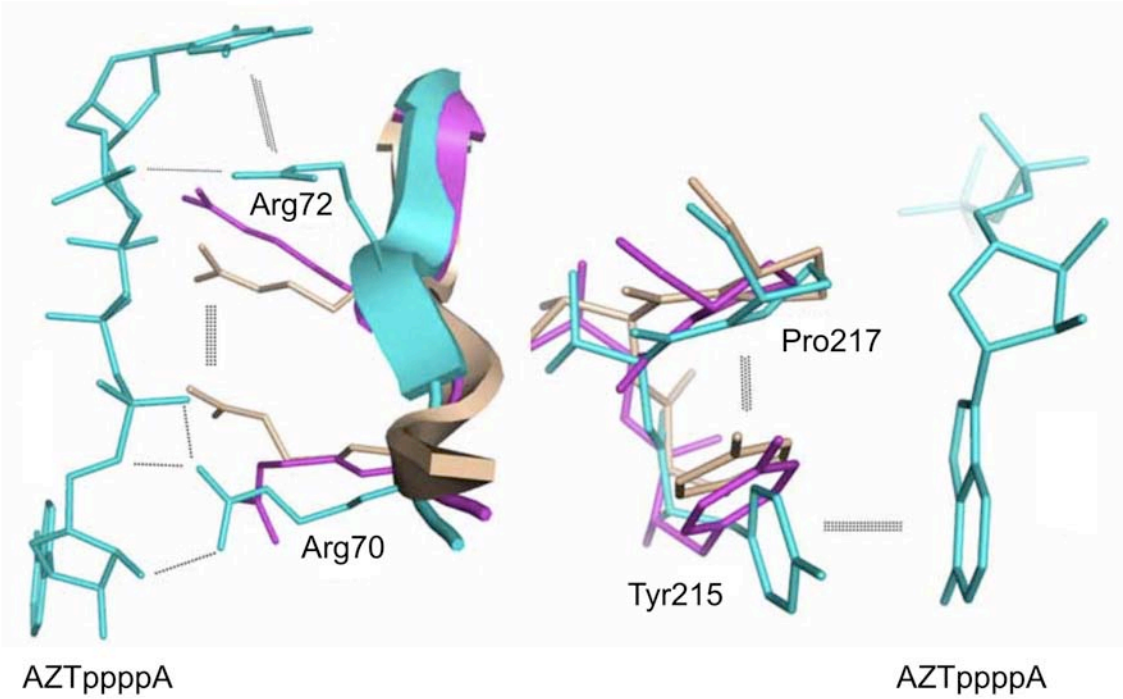

a b

Figure S3. Side-chain conformations of the primary resistance mutations change during the process of ATP-mediated excision. (a) Arg70 positions the ATP of AZTppppA (Superposition is based on residue 55-80 of the p66 fingers subdomain). (b) Tyr215 creates a binding cleft (superposition is based on the residues 107 to 115 and 151 to 215 of the p66 palm subdomain). AZTr apoRT, AZTr RT–dsDNA-AZTMP (P-site) complex, and AZTr RT–dsDNA–AZTppppA excision product complex are colored magenta, wheat, and cyan, respectively.

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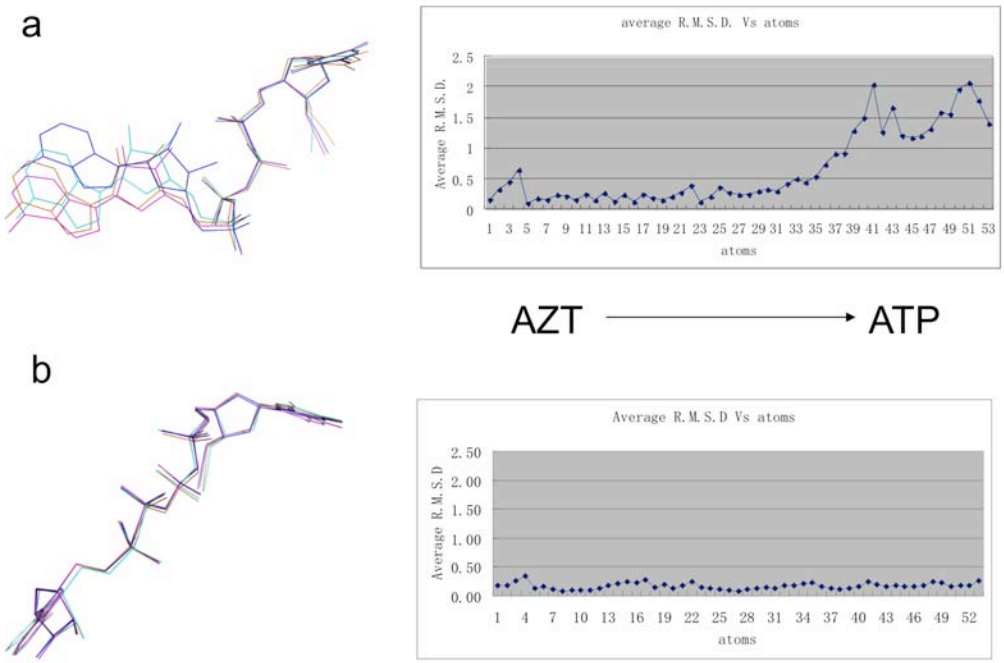

Figure S4. Superposition of the four copies of AZTppppA in the asymmetric unit of (a) the wild-type excision-product ternary complex crystal and (b) the AZTr excision-product ternary complex crystal. There is significant variation in the positions of atom as we move from AZT towards the AMP part of AZTppppA in the wild-type RT complex, whereas, the positions of the atoms of AZTppppA superimpose in AZTr RT complex structure.

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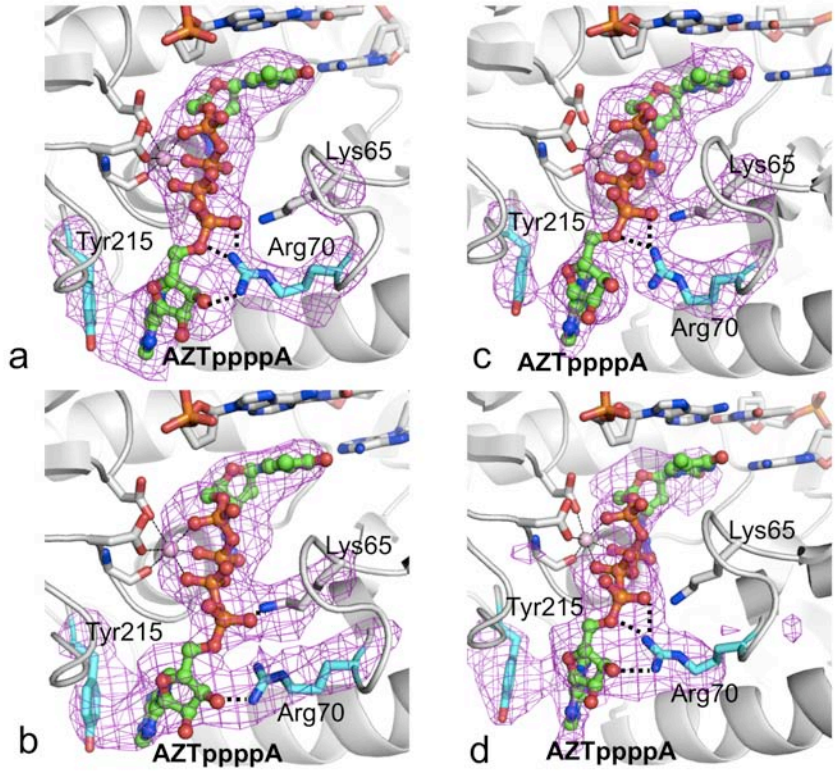

Figure S5. Simulated-annealed difference omit maps (3.0) of AZTppppA in the four independent AZTr excision product complexes. Comparison of four independent complexes in the asymmetric unit reveals the variations in the interactions of Lys65, Arg72, and the ATP part of AZTppppA. The carbon atoms of AZTppppA are colored green; the C-atoms of Arg70 and Tyr215 are colored cyan; the carbon atoms of other residues are colored gray.

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