

## Quick Reference Guide to Antiretrovirals

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### Guide to Antiretroviral Agents

#### Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Nucleotide RTIs (NtRTIs)

Generic	Brand	Dose	Comments and Common Side Effects
Abacavir (ABC)	<i>Ziagen</i>	300 mg 2x/d	About 4% hypersensitivity reaction: fever, malaise, possible rash, GI, respiratory. Resolves within 2 days after discontinuation. DO NOT RECHALLENGE. Also: rash alone without hypersensitivity.
Didanosine (ddI)	<i>Videx EC</i>	400-mg capsule 1x/d on empty stomach (>60 kg body weight)	Peripheral neuropathy in 15%, rare pancreatitis; avoid alcohol. OK to take at same time as other antiretrovirals that can be taken on an empty stomach. Older chewable tablet formulation has additional restrictions.
Lamivudine (3TC)	<i>EpiVir</i>	150 mg 2x/d	Generally well tolerated. Active against HBV.
Stavudine (d4T)	<i>Zerit</i>	40 mg 2x/d (>60 kg body weight)	Peripheral neuropathy (1%-4% in early studies; 24% in expanded access patients with CD4+ counts <50).
Zalcitabine (ddC)	<i>Hivid</i>	0.375-0.75 mg 3x/d	Peripheral neuropathy in 17%-31% of trial participants; oral ulcers. Used rarely due to toxicity, inconvenient dosing, and questions regarding efficacy.
Zidovudine (ZDV, AZT)	<i>Retrovir</i>	300 mg 2x/d	Initial nausea, headache, fatigue, anemia, neutropenia, neuropathy, myopathy.
ZDV + 3TC	<i>Combivir</i>	1 tablet 2x/d	Combination tablet containing ZDV 300 mg and 3TC 150 mg.
ZDV + 3TC + ABC	<i>Trizivir</i>	1 tablet 2x/d	Combination tablet containing ZDV 300 mg, 3TC 150 mg, and ABC 300 mg.
Tenofovir	<i>Viread</i>	300 mg 1x/d with food	Generally well tolerated. Active against HBV. <a href="#">Significant interaction with ddI (see Drug-Drug Combinations below)</a> .

#### Protease Inhibitors (PIs)

Generic	Brand	Dose	Comments and Common Side Effects
Amprenavir	<i>Agenerase</i>	1200 mg (8 cap) 2x/d *	Rash (20%), diarrhea, nausea.
Indinavir	<i>Crixivan</i>	800 mg (2 cap) every 8 hours on empty stomach or with snack containing <2 g of fat *	Kidney stones in 6%-8%: good hydration essential. Occasional nausea and GI upset. Store in original container which contains desiccant; without this, IDV is stable for only about 3 days.
Lopinavir/Ritonavir	<i>Kaletra</i>	Coformulated lopinavir 400 mg + RTV 100 mg (3 cap) 2x/d with food	GI side effects common but mild. Hyperlipidemias.
Nelfinavir	<i>Viracept</i>	1250 mg (5 tab) 2x/d or 750 mg (3 tab) 3x/d with food	Diarrhea common; occasional nausea.
Ritonavir	<i>Norvir</i>	600 mg (6 cap) 2x/d; start with 300 mg 2x/d and increase to full dose over 14 days	Nausea, diarrhea, numb lips; occasional hepatitis. Hyperlipidemias. Store capsules in refrigerator. Stable at room temperature for up to 1 month. Used at lower dosages as pharmacokinetic enhancer of other PIs.
Saquinavir soft gel cap	<i>Fortovase</i>	1600 mg (8 cap) 2x/d or 1200 mg (6 cap) 3x/d with fatty food (>28 g) *	Soft gel formulation with improved absorption. Long-term storage in refrigerator. Stable at room temperature for 3 mo.
<a href="#">Saquinavir hard gel cap</a>	<a href="#">Invirase</a>	<a href="#">Used in combination with ritonavir</a>	<a href="#">Hard gel formulation with poor absorption. Bioequivalent to Fortovase when combined with RTV. Smaller tablet size and easier storage than Fortovase.</a>

\* Frequently dosed with ritonavir to simplify administration and raise drug levels. See Drug-Drug Combinations section for details.

## Guide to Antiretroviral Agents (Cont.)

### Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Generic	Brand	Dose	Comments and Common Side Effects
Delavirdine	<i>Rescriptor</i>	400 mg (2 tab) 3x/d	Transient rash. P450 3A4 inhibitor. 600 mg twice daily dosing being studied. Coadministration with gastric acid lowering agents decreases absorption.
Efavirenz	<i>Sustiva</i>	600 mg (1 tab) 1x/d initially at bedtime	Initial dizziness, insomnia, transient rash, P450 3A4 inducer; avoid clarithromycin coadministration.
Nevirapine	<i>Viramune</i>	200 mg (1 tab) 1x/d for 2 weeks, then 200 mg 2x/d or 400 mg 1x/d	Transient rash, hepatitis → monitor LFTs. P450 3A4 inducer. Once-daily dosing recommendation based on limited clinical data.

### Ribonucleotide Reductase Inhibitors

Generic	Brand	Dose	Comments and Common Side Effects
Hydroxyurea (not FDA-approved for HIV therapy)	<i>Hydrea</i>	500 mg 2x/d	Bone marrow suppression, aphthous ulcers, hair loss, peripheral neuropathy, hepatotoxicity. Augments ddI and d4T and their toxicities. No direct antiviral effect. Used rarely due to reported toxicity.

## Drug-Drug Combinations

This table gives an overview of current knowledge of drug-drug combinations. The NRTIs are not listed since they do not require dose adjustments when combined. In contrast, PIs and NNRTIs tend to have complex metabolism and in combinations affect each other's drug levels and potency. The knowledge on these combinations is still evolving, and few formal dose modification recommendations are available. Caution and close monitoring are advised. Treating physicians should verify all information with an AIDS specialist and check any dose adjustments with a pharmacist.

\* Comments on each combination are given below.

#### Abbreviations

APV	Amprenavir	DLV	Delavirdine
IDV	Indinavir	EFV	Efavirenz
LPV	Lopinavir	NVP	Nevirapine
NFV	Nelfinavir	ADV	Adefovir
RTV	Ritonavir	TNV	Tenofovir
SQV[-S]	Saquinavir [soft gel formulation]		

	Amprenavir	Indinavir	Lopinavir/ Ritonavir	Nelfinavir	Ritonavir	Saquinavir	Delavirdine	Efavirenz
<b>Nevirapine</b>	No data	↓ IDV [1]	↓ LPV [2]	No significant interaction [3]	No significant interaction [4]	↓ SQV [5]	No data	↓ EFV [6]
<b>Efavirenz</b>	↓ APV [7]	↓ IDV [8]	↓ LPV [9]	No significant interaction [10]	Modest ↑ in both [11]	↓ SQV level; do not combine [12]	No data	
<b>Delavirdine</b>	APV [13]	↑ IDV [14]	No data	↑ NFV [15]	↑ RTV [16]	↑ SQV [17]		
<b>Saquinavir</b>	↓ APV; ↓ SQV [18]	Antagonistic in vitro (in one lab)	↑ SQV-S [19]	↑ SQV-S [12]	↑ SQV [21]			
<b>Ritonavir</b>	↑ APV ↓ RTV [22]	↑ IDV [23]	↓ RTV [24]	↑ NFV [25]				
<b>Nelfinavir</b>	↑ APV [26]	↑ IDV [27]	↑ NFV [28]					
<b>Lopinavir/Ritonavir</b>	↓ APV ↓ LPV [29]	↑ IDV [30]						
<b>Indinavir</b>	↑ APV; ↓ IDV [31]							

#### Tenofovir/didanosine interaction

Tenofovir increases ddI (EC) C<sub>max</sub> by +49% and AUC by +46% when doses separated by 2 hours. When coadministered with food the effect is enhanced (C<sub>max</sub> +64%; AUC +60%). Studies evaluating dose reduction of ddI are in progress.

#### Contraindicated Combinations

- ZDV + d4T combination is antagonistic in vivo
- ddI and ddC should not be combined due to increased risk of peripheral neuropathy
- IDV + SQV combination is antagonistic in vitro and in practice extremely difficult to dose

## Comments on Drug-Drug Combinations

1	<b>IDV &amp; NVP</b>	NVP decreases IDV levels by 30%. (IDV decrease is most pronounced in patients with a high IDV level within the interpatient variability of IDV levels). Consider IDV dosage increase, eg, 1000 mg every 8 hours (5 <sup>th</sup> CROI, 1998). The addition of RTV can prevent this interaction (see #23).
2	<b>LPV/RTV &amp; NVP</b>	Decrease in LPV Cmin by 35% -40% and AUC by 20%-25%; considered not significant in patients naive to PIs. If PI resistance suspected, consider LPV dose increase to 533/133 mg (4 cap) 2x/d (Abbott data, 2000).
3	<b>NFV &amp; NVP</b>	Steady-state studies indicate no significant changes in NVP or NVP levels, suggesting standard doses of each (5 <sup>th</sup> CROI, 1998).
4	<b>RTV &amp; NVP</b>	NVP decreases RTV levels by 11%, not requiring dose adjustment.
5	<b>SQV &amp; NVP</b>	SQV-hard gel AUC decreased by 27%, which is of concern as SQV-hard gel by itself reaches marginal levels only. No effect on NVP level. No data on nevirapine and SQV-soft gel formulation.
6	<b>NVP &amp; EFV</b>	Decrease in EFV AUC by 22% and EFV Cmin by 36%; NVP levels unchanged; dose increase of EFV to 800 mg 1x/d being discussed, but no safety data are available for this dose (7 <sup>th</sup> CROI, 2000).
7	<b>APV &amp; EFV</b>	Decrease in APV Cmax by 36%, AUC by 39%, and Cmin by 43% (5 <sup>th</sup> CROI, 1998). See comments 22 and 25 below for dosing options.
8	<b>IDV &amp; EFV</b>	EFV decreases IDV AUC by 31% and Cmax by 16%; consider dose increase to IDV 1000 mg every 8 hours (ICAAC, 1998). The addition of RTV can prevent this interaction (see #23)
9	<b>LPV/RTV &amp; EFV</b>	Decrease in LPV Cmin by 35%-40% and AUC by 20%-25%; considered not significant in patients naive to PIs. If PI resistance suspected, consider LPV dose increase to 533/133 mg (4 cap) 2x/d (Abbott data, 2000).
10	<b>NFV &amp; EFV</b>	EFV increases NFV level by 20%. No change in EFV level. Clinical efficacy documented in several studies with standard dose of both drugs (6 <sup>th</sup> CROI, 1999).
11	<b>RTV &amp; EFV</b>	EFV increases RTV AUC by 18% and Cmax by 24%. No dose adjustment for EFV necessary. Consider dose reduction of RTV. Monitor LFTs (ICAAC, 1998). See comment 21 for further dosing options.
12	<b>SQV &amp; EFV</b>	EFV decreases SQV-S AUC by 62% and Cmax by 50%. Avoid combination with SQV as sole PI (ICAAC, 1998). See comment 21 for further dosing options.
13	<b>APV &amp; DLV</b>	DLV increases APV Cmax/AUC/Cmin by 1.3-fold/4-fold/6-fold, respectively (Glasgow, 2000). <a href="#">APV decreases DLV levels.</a>
14	<b>IDV &amp; DLV</b>	Compared with IDV 800 mg 3x/d alone, IDV 400 or 600 mg with DLV 400 mg 3x/d leads to increase in IDV Cmin of 140% and 400% respectively. IDV 1200 mg with DLV 600 mg 2x/d with food increases IDV Cmin/AUC/Cmax by 0%/+40%/+70%. Consider dosing IDV 600 mg with DLV 400 mg 3x/d, or IDV 1200 mg with DLV 600 mg 2x/d with or without food (ICAAC, 1999, Glasgow, 2000).
15	<b>NFV &amp; DLV</b>	Increase in NFV levels by 113%. 40% decrease in DLV AUC (Pharmacia & Upjohn data 8/98).
16	<b>RTV &amp; DLV</b>	DLV increases RTV levels by 70%. May merit RTV dose reduction, eg, 400 mg 2x/d. Limited data (5 <sup>th</sup> CROI, 1998, P&U data 8/98).
17	<b>SQV &amp; DLV</b>	DLV dosed 400 mg 3x/d or 600 mg 2x/d decreases SQV clearance by 63%, resulting in increase in SQV AUC/Cmin/Cmax. Dose of SQV 1400 mg 2x/d or 1000 mg 3x/d with DLV 600 mg 2x/d or 400 mg 3x/d being evaluated (7 <sup>th</sup> CROI, 2000).
18	<b>APV &amp; SQV</b>	Decrease in APV Cmax/AUC/Cmin by 37%/32%/14%, respectively, and increase in SQV Cmax by +21%, but decrease of SQV AUC by 19% and Cmin by 48% (Geneva, 1998). <a href="#">Triple interaction SQV/RTV/APV currently being studied.</a>
19	<b>LPV/RTV &amp; SQV</b>	<a href="#">SQV 1000 mg 2x/d with standard-dose LPV showed sustained SQV levels equivalent to dosing of SQV/RTV 1000/100 mg 2x/d and unchanged LPV levels with good viral efficacy (Pharmacology Workshop, 2002).</a>
20	<b>NFV &amp; SQV</b>	NFV increases SQV-S levels 3-fold or higher. Consider dosage of NFV 750 mg + SQV-S 800 mg 3x/d, or NFV 1250 mg + SQV-S 1200 mg 2x/d (under study) (6 <sup>th</sup> CROI, 1999).
21	<b>RTV, SQV &amp; EFV</b>	RTV increases SQV levels 3-fold or higher. Good results from studies of 400 mg 2x/d for each drug. <a href="#">No food effect of this combination. Addition of EFV to RTV/SQV 400 mg 2x/d does not significantly change levels (7th CROI, 2000; ICAAC, 2001).</a> SQV 1000 mg/RTV 100 mg 2x/d results in similar SQV levels. <a href="#">Once-daily SQV/RTV (1600/100 mg) with food showed good clinical efficacy (ICAAC, 2001).</a> <a href="#">Soft-gel or hard-gel caps appear bioequivalent in all dosage combinations with RTV (9th CROI, 2002; Pharmacology Workshop, 2002).</a>
22	<b>APV, RTV &amp; EFV</b>	RTV increases APV levels significantly, ie, APV 1200 mg with RTV 200 mg 2x/d increases APV Cmax/AUC/Cmin by +33%/+131%/+680%. The addition of EFV 600 mg 1x/d to this combination results in Cmax -9%, AUC +8% and Cmin +27% (Falloon, 1999; Lamotte, 2000). APV decreases RTV Cmin 3-fold compared with RTV Cmin in RTV/IDV or RTV/SQV combinations, which may affect the levels of other PIs added to APV/RTV combination (Pharmacology Workshop, 2001). <a href="#">FDA-approved dose: APV/RTV 600/100 mg 2x/d or 1200/200 mg 1x/d.</a>

## Comments on Drug-Drug Combinations (Cont.)

23	<b>IDV &amp; RTV</b>	RTV increases IDV AUC up to +480%. Compared with IDV alone, 400 mg of both drugs 2x/d leads to same IDV peak and higher trough levels and acts as true dual-PI combo. No reports of nephrolithiasis in this combination. IDV/RTV 800/100 mg or 800/200 mg 2x/d augments IDV to higher peak and trough levels without antiviral activity of RTV. No significant food effect on IDV absorption with either dose combination. Other dose combinations under study (6 <sup>th</sup> CROI, 1999). The addition of NVP or EFV to IDV/RTV does not significantly lower IDV levels (ICAAC, 2001).
24	<b>LPV/RTV &amp; RTV</b>	Addition of RTV to LPV/r increases LPV concentration. Studies in progress. RTV Cmin is 3-fold lower in LPV/RTV combination compared with 100 mg RTV 2x/d in IDV/RTV or SQV/RTV combination (Pharmacology Workshop, 2001).
25	<b>NFV &amp; RTV</b>	RTV increases level of NFV and NFV M8 metabolite. NFV/RTV 2000/200 mg 1x/d increases combined NFV + M8 Cmin/AUC/Cmax by 50% compared with NFV 1250 mg 2x/d in HIV neg. volunteers. Rashes noted (Pharmacology Workshop, 2001). RTV 400 mg with NFV 500 mg or 750 mg 2x/d results in NFV AUC equivalent to standard dose. Higher dose results in higher AUC of M8, but also lower RTV level. Limited clinical data (6 <sup>th</sup> CROI, 1999).
26	<b>APV, NFV &amp; EFV</b>	Full dose of APV+NFV results in decrease in APV Cmax by -14%, but increase in AUC by +46% and Cmin by +235%. No significant effect on NFV levels. The addition of EFV 600 mg 1x/d resulted in same APV Cmax and AUC and mild reduction of Cmin by -14%. Consider dosing APV/NFV or APV/NFV/EFV at full dose of each drug (7 <sup>th</sup> CROI, 2000).
27	<b>IDV &amp; NFV</b>	NFV increases IDV level by 51%; IDV does not affect NFV level. NFV/IDV 1250/1200 mg 2x/d with a low-fat snack on empty stomach shows good drug levels and clinical efficacy (6 <sup>th</sup> CROI, 1999).
28	<b>LPV/RTV &amp; NFV</b>	Limited data from single-dose PK suggests unchanged NFV AUC, but increase in NFV Cmin and M8 metabolite.
29	<b>LPV/RTV &amp; APV</b>	Coadministration of APV 450-750 mg with standard dose LPV/RTV 2x/d results in significant decrease of APV Cmin by 220-420% and trend to lower LPV Cmin, compared with APV/RTV 100 mg or LPV/RTV alone from historical controls. Additional RTV 100 mg 2x/d did not compensate for this interaction (Pharmacology Workshop, 2001). Interaction confirmed by additional studies (ICAAC, 2001; 9 <sup>th</sup> CROI, 2002).
30	<b>LPV/RTV &amp; IDV</b>	Single-dose PK show increase in IDV level; IDV dose reduction suggested (Abbott data, 2000). <a href="#">Small case series reported IDV 800 mg or 600 mg 2x/d with standard-dose LPV/RTV (Pharmacology Workshop, 2002).</a>
31	<b>APV &amp; IDV</b>	Increase in APV Cmax/AUC/Cmin by +18%/+32%/+25%, respectively, and decrease in IDV Cmax by -22%, AUC by -38% and Cmin by -27% (GlaxoWellcome data, 1999).

# Guide to Antiretroviral Resistance Mutations

These tables give an overview of mutations associated with resistance to antiretrovirals. Interaction between mutations is complex and cannot be fully represented in a concise table format; thus, use of interpretation software is strongly recommended (eg, the Stanford algorithm available at <http://hivdb.stanford.edu/hiv/> -- click "Mutation list analysis"). The table below reflects data published by the International AIDS Society--USA on November 24, 2001, available at [http://www.iasusa.org/resistance\\_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html) and may aid in the interpretation of genotypic analysis results. Results of genotypic testing always indicate mutations in the majority virus population only (>20%). Mutations caused by previous antiretrovirals may only be present in minority virus populations and may thus not be detected, but may re-emerge if the drug(s) in question is resumed. Thus, any mutations reported by previous genotypic testing of a given patient should be taken into account when deciding on future treatment.

## Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

<b>ZDV</b>	41				67		70								210	215	219	
<b>ddl</b>	(41)			65	(67)		(70)	74							184	(210)	(215)	(219)
<b>ddC</b>	(41)			65	(67)	69	(70)	74							184	(210)	(215)	(219)
<b>d4T<sup>†</sup></b>	41				67		70									210	215	219
<b>3TC</b>		44											118		184			
<b>ABC</b>	41			65	67		70	74				115			184	210	215	219
<b>TN<sup>v</sup></b>	(41)			65	(67)	69	(70)									(210)	(215)	(219)
<b>MDR*</b>			62						75	77			116		151			
<b>MDR**</b>	41		62		67	SS	70									210	215	219
<b>MDR***</b>	41				67		70									210	215	219

<sup>†</sup> A mutation at codon 75 has been associated with d4T resistance in vitro

\* Multi-NRTI resistance: the 151 complex

\*\* Multi-NRTI resistance: the 69 insertion complex

\*\*\* Nucleoside-associated mutations (NAMs) associated with cross-resistance among NRTIs except 3TC, and cross-resistance with tenofovir (if 4 or more are present). These are also indicated in parentheses in the rows for specific NRTIs affected

## Nonnucleoside Reverse Transcriptase Inhibitors

<b>DLV</b>		103			181						236
<b>EFV</b>	100	103		108	181	188	190	225			
<b>NVP</b>	100	103	106	108	181	188	190				
<b>MDR*</b>		103				188					
<b>MDR**</b>	100		106		181		190			230	

\* Either of these mutations is associated with substantially reduced efficacy of all currently available NNRTIs

\*\* Accumulation of 2 or more of these mutations can be associated with cross-resistance to all currently available NNRTIs

## Protease Inhibitors

<b>APV</b>	10				32			46	47		<u>50</u>		54			73		<u>84</u>		90	
<b>IDV</b>	10	20	24		32		36	<u>46</u>					54		71	73	77	<u>82</u>	<u>84</u>		90
<b>LPV/RTV*</b>	10	20	24		32	33		46	47		50	53	54	63	71	73		82	84		90
<b>NFV</b>	10			<u>30</u>			36	46							71		77	82	84	88	<u>90</u>
<b>RTV</b>	10	20			32	33	36	46					54		71		77	<u>82</u>	<u>84</u>		90
<b>SQV</b>	10										<u>48</u>		54		71	73	77	82	84		<u>90</u>
<b>MDR**</b>	10							<u>46</u>					54					<u>82</u>	<u>84</u>		<u>90</u>

Note: Underlined mutations are primary resistance mutations for that agent; other mutations are secondary resistance mutations. Mutations have not yet been categorized as primary or secondary for lopinavir/ritonavir

\* Only the presence of multiple mutations is associated with diminished response to lopinavir/ritonavir

\*\* Accumulation of 4-5 or more of these mutations will probably cause multi-PI resistance

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