Medscape's Antiretroviral Pocket Guide for the Treatment of HIV Infection

Editor's Note:

Medscape's Antiretroviral Pocket Guide for the Treatment of HIV Infection *is largely drawn from the US Department of Health & Human Services (DHHS)* Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. *This invaluable resource from a team of experts is updated regularly as new data become available, and updates to this* Pocket Guide *will reflect that. Another critical piece of information for clinicians is information on antiretroviral drug resistance mutations and their potential impact on virologic efficacy. Dr. Robert Shafer, Associate Professor of Medicine at Stanford University School of Medicine, Stanford, California, is an expert on HIV drug resistance, and he has supplied 4 key tables addressing this topic, which will also be updated as relevant data become available.*

Table 1. Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral-Naive Patients

Regimens should be individualized on the basis of the advantages and disadvantages of each combination, such as pill burden, dosing frequency, toxicities, drug-drug interaction potential, comorbid conditions, and level of plasma HIV RNA. For more thorough information, including other possible options for antiretroviral regimens and those that should not be used, consult the DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents*.

The DHHS Guidelines state that to construct an antiretroviral regimen, select 1 component from Column A + 1 component from Column B. Options below are listed in alphabetical order.

	Column A NNRTI and PI Options			Column B Dual NRTI Options
Preferred components	NNRTI • efavirenz* PI • atazanavir + ritonavir • fosamprenavir + ritonavir (twice daily) • lopinavir / ritonavir† (twice daily; co-formulated)	+	**Preferred components**	• tenofovir / emtricitabine‡ (co-formulated) • zidovudine / lamivudine‡ (co-formulated)
Alternative to preferred components	NNRTI • nevirapine§ PI • atazanavir‖ • fosamprenavir • fosamprenavir + ritonavir (once daily) • lopinavir / ritonavir (once daily; co-formulated)		**Alternative to preferred components**	• abacavir / lamivudine‡ • didanosine + (emtricitabine or lamivudine)

NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

* *Efavirenz is not recommended for use in the first trimester of pregnancy or in sexually active women with childbearing potential who are not using effective contraception.*

† *The pivotal study that led to the recommendation of lopinavir/ritonavir as a preferred PI component was based on twice-daily dosing. A smaller study has shown similar efficacy with once-daily dosing, but also showed a higher incidence of moderate-to-severe diarrhea with the once-daily regimen.*

‡ *Emtricitabine can be used in place of lamivudine and vice versa.*

§ *Nevirapine should not be started in women with CD4+ cell counts >/= 250 cells/mcL or men with CD4+ cell counts >/= 400 cells/mcL because of increased risk for hepatic events in these patients.*

‖ *Atazanavir must be ritonavir-boosted if it is combined with tenofovir.*

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Table 2. Antiretroviral Drugs and Components Not Recommended as Initial Therapy

Antiretroviral Drugs/Components (Alphabetical Order)	Reasons for Not Recommending as Initial Therapy
Darunavir	• Lack of data in treatment-naive patients
Delavirdine	• Inferior virologic efficacy • Inconvenient dosing (3 times daily)
Didanosine + tenofovir	• High rate of early virologic failure • Rapid selection of resistant mutations • Potential for immunologic nonresponse / CD4+ cell count decline
Enfuvirtide	• No clinical trial experience in treatment-naive patients • Requires twice-daily subcutaneous injections
Indinavir (unboosted)	• Inconvenient dosing (3 times daily with meal restrictions)
Indinavir (ritonavir-boosted)	• High incidence of nephrolithiasis
Ritonavir as sole PI	• High pill burden • Gastrointestinal intolerance
Saquinavir soft-gel capsule (unboosted)	• High pill burden • Inferior virologic efficacy
Tipranavir (boosted with ritonavir)	• Lack of data in treatment-naive patients
Zalcitabine + zidovudine	• Inferior virologic efficacy • Higher rate of adverse effects than other 2-NRTI alternatives

PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor

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Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name (Abbreviation) / Trade Name	Formulation	Dosing Recommendations	Adverse Events
Abacavir (ABC) / *Ziagen*	300-mg tablets or 20-mg/mL oral solution	3TC 300mg 300mg twice daily or 600mg once daily	Hypersensitivity reaction that can be fatal; symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (such as sore throat, cough, shortness of breath).
Trizivir — with ZDV + 3TC	*Trizivir*: ABC 300mg + ZDV 300mg + 3TC 150mg	*Trizivir*: 1 tablet twice daily	
Epzicom — with 3TC	*Epzicom*: ABC 600mg +	*Epzicom*: 1 tablet once daily	
Didanosine (ddI) / *Videx*, *Videx EC*, generic didanosine enteric-coated (dose same as *Videx EC*)	*Videx EC*: 125, 200, 250, or 400mg *Videx* buffered tabs: 25, 50, 100, 150, or 200mg *Videx* buffered powders: 100, 167, or 250mg	Body weight > 60 kg: 400mg once daily (buffered tablets or EC capsule) or 200mg twice daily (buffered tablets); with TDF: 250mg/day Body weight < 60 kg: 250mg daily (buffered tablets or EC capsule) or 125mg twice daily (buffered tablets); with TDF: appropriate dose not established, probably < 250mg/day	Pancreatitis, peripheral neuropathy, nausea, diarrhea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Emtricitabine (FTC) / *Emtriva*	*Emtriva*: 200-mg hard gelatin capsule and 10-mg/mL oral solution	*Emtriva*: 200-mg capsule once daily or 240-mg (24-mL) oral solution once daily	Minimal toxicity; lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with use of NRTIs.
Truvada — with TDF	*Truvada*: FTC 200mg + TDF 300mg	*Truvada*: One tablet once daily	
Atripla — with TDF + EFV	*Atripla*: FTC 200mg + TDF 300mg + EFV 600mg	*Atripla*: 1 tablet once daily at bedtime	
Lamivudine (3TC) / *Epivir*	*Epivir*: 150- and 300-mg tablets or 10-mg/mL oral solution	*Epivir*: 150mg twice daily or 300mg daily	Minimal toxicity; lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with use of NRTIs.
Combivir — with ZDV	*Combivir*: 3TC 150mg + ZDV 300mg	*Combivir:* 1 tablet twice daily	

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Generic Name (Abbreviation) / Trade Name	Formulation	Dosing Recommendations	Adverse Events
Epzicom — with ABC ***Trizivir*** — with ZDV + ABC	*Epzicom*: 3TC 300mg + ABC 600mg *Trizivir*: 3TC 150mg + ZDV 300mg + ABC 300mg	*Epzicom*: 1 tablet once daily *Trizivir*: 1 tablet twice daily	
Stavudine (d4T) / *Zerit*	*Zerit*: 15-, 20-, 30-, 40-mg capsules or 1-mg/mL oral solution	Body weight > 60 kg: 40mg twice daily Body weight < 60 kg: 30mg twice daily	Peripheral neuropathy; lipodystrophy; rapidly progressive ascending neuromuscular weakness (rare); pancreatitis; lactic acidosis with hepatic steatosis (higher incidence with d4T than with NRTIs); hyperlipidemia.
Tenofovir disoproxil fumarate (TDF) / *Viread*	*Viread*: 300-mg tablet	*Viread*: 1 tablet once daily	Asthenia, headache, diarrhea, nausea, vomiting, and flatulence; renal insufficiency; lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with use of NRTIs.
Truvada — with FTC	*Truvada*: TDF 300mg + FTC 200mg	*Truvada*: 1 tablet once daily	
Atripla with FTC + EFV	*Atripla*: TDF 300mg + FTC 200mg + EFV 600mg	*Atripla*: One tablet once daily at bedtime	
Zalcitabine (ddC) / *Hivid*	0.375- or 0.75-mg tablets Anticipated discontinuation of distribution in 2006	0.75mg 3 times daily	Peripheral neuropathy; stomatitis; lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with use of NRTIs; pancreatitis
Zidovudine (AZT, ZDV) / *Retrovir*	*Retrovir*: 100-mg capsules, 300-mg capsules, 10-mg/mL intravenous solution, 10-mg/mL oral solution	*Retrovir*: 300mg twice daily or 200mg 3 times daily	Bone marrow suppression; macrocytic anemia or neutropenia; gastrointestinal intolerance, headache, insomnia, asthenia; lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Combivir	*Combivir*: 3TC 150mg + ZDV 300mg	*Combivir* or *Trizivir*: 1 tablet twice daily	
Trizivir — with 3TC + ABC	*Trizivir*: 3TC 150mg + ZDV 300mg + ABC 300mg		

EFV = efavirenz

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Table 4. Characteristics of Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Generic Name (Abbreviation) / Trade Name	Formulation	Dosing Recommendation	Adverse Events
Delavirdine (DLV) / *Rescriptor*	100-mg or 200-mg tablets	400mg 3 times daily; four 100-mg tablets can be dispersed in >/= 3 oz of water to produce slurry; 200-mg tablets should be taken as intact tablets; separate dosing from buffered didanosine or antacids by 1 hour	Rash*; increased transaminase levels; headaches
Efavirenz (EFV) / *Sustiva*	50-, 100-, 200-mg capsules or 600-mg tablets	600mg daily on an empty stomach, at or before bedtime	Rash*; central nervous system symptoms†; increased transaminase levels; false-positive cannabinoid test; teratogenic in monkeys‡
Atripla w/FTC + TDF	*Atripla*: EFV 600mg + TDF 300mg + FTC 200mg	*Atripla*: One tablet once daily at bedtime	
Nevirapine (NVP) / *Viramune*	200-mg tablets or 50-mg/mL oral suspension	200mg daily for 14 days; thereafter, 200mg by mouth twice daily	Rash, including Stevens-Johnson syndrome*; symptomatic hepatitis, including fatal hepatic necrosis, have been reported‡

* *During clinical trials, NNRTIs were discontinued because of rash among 7% of patients taking nevirapine, 4.3% of patients taking delavirdine, and 1.7% of patients taking efavirenz. Rare cases of Stevens-Johnson syndrome have been reported with the use of all 3 NNRTIs, the highest incidence seen with nevirapine use.*

† *Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of efavirenz was 52%, as compared with 26% among control subjects; 2.6% of those persons on efavirenz discontinued the drug because of these symptoms; symptoms usually subside spontaneously after 2–4 weeks.*

‡ *Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur with significantly higher frequency in female patients with pre-nevirapine CD4+ T-cell counts > 250 cells/mm³ or in male patients with pre-nevirapine CD4+ T-cell counts > 400 cells/mm³. Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when nevirapine is given as single doses to mothers or infants for prevention of mother-to-child HIV transmission.*

Table 5. Characteristics of Protease Inhibitors (PIs)

Generic Name / Trade Name	Formulation	Dosing Recommendations	Adverse Effects
Amprenavir (APV) / *Agenerase*	50-mg capsules, 15-mg/mL oral solution (capsules and solution *not* interchangeable on mg-per-mg basis) **Note:** APV 150-mg capsule is no longer available; consider using fosamprenavir in these patients	1400mg twice daily (oral solution) **Note:** APV and RTV oral solution should not be co-administered because of competition of the metabolic pathway of the 2 vehicles	GI intolerance, nausea, vomiting, diarrhea; rash; oral paresthesias; hyperlipidemia; transaminase elevation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia. **Note:** Oral solution contains propylene glycol; contraindicated in pregnant women, children < 4 years old, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole.
Atazanavir (ATV) / *Reyataz*	100-, 150-, 200-mg capsules	400mg once daily If taken with efavirenz or tenofovir: RTV 100mg + ATV 300mg once daily	Indirect hyperbilirubinemia; prolonged PR interval — some patients experienced asymptomatic first-degree AV block; use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.
Darunavir (DRV) / *Prezista*	300-mg tablet	600mg twice daily + RTV 100mg twice daily, with food	Hyperlipidemia; hyperamylasemia transaminase elevation; headache; GI symptoms
Fosamprenavir (f-APV) / *Lexiva*	700-mg tablet	ARV-naive patients: • f-APV 1400mg twice daily; or • (f-APV 1400mg + RTV 200mg) once daily; or • (f-APV 700mg + RTV 100mg) twice daily PI-experienced pts (once-daily regimen not recommended): • (f-APV 700mg + RTV 100mg) twice daily Co-administration w/EFV (unboosted f-APV not recommended): • (f-APV 700mg + RTV 100mg) twice daily; or • (f-APV 1400mg + RTV 300mg) once daily	Skin rash (19%); diarrhea, nausea, vomiting; headache; hyperlipidemia; transaminase elevation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.

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Generic Name / Trade Name	Formulation	Dosing Recommendations	Adverse Effects
Indinavir (IDV) / *Crixivan*	200-, 333-, 400-mg capsules	800mg every 8 hours With RTV: (IDV 800mg + RTV 100 or 200mg) every 12 hours	Nephrolithiasis; GI intolerance, nausea; indirect hyperbilirubinemia; headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.
Lopinavir + Ritonavir (LPV/r) / *Kaletra*	Each tablet contains LPV 200mg + RTV 50mg Oral solution: Each 5mL contains LPV 400mg + RTV 100mg **Note:** Oral solution contains 42% alcohol	LPV 400mg + RTV 100mg (2 tablets or 5mL) twice daily, or LPV 800mg + RTV 200mg (4 tablets or 10mL); **Note:** once-daily dosing only recommended for treatment-naive patients not for patients receiving EFV, NVP, f-APV, or NFV With EFV or NVP: For treatment-experienced pts: LPV 600mg + RTV 150mg (3 oral tablets) twice daily, or LPV 533mg + RTV 133mg (6.7-mL oral solution) twice daily with food	GI intolerance, nausea, vomiting, diarrhea (higher incidence with once-daily than twice-daily dosing); asthenia; hyperlipidemia (especially hypertriglyceridemia); elevated scrum transaminases; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.
Nelfinavir (NFV) / *Viracept*	250-mg tablets or 625-mg tablets 50-mg/g oral powder	1250mg twice daily, or 750mg 3 times daily	Diarrhea; hyperlipidemia; hyperglycemia; fat maldistribution; possible increased bleeding episodes among patients with hemophilia; serum transaminase elevation.
Ritonavir* (RTV) / *Norvir*	100-mg capsules, or 600-mg/7.5-mL solution	600mg every 12 hours (when ritonavir is used as sole PI) As pharmacokinetic booster for other PIs — 100mg to 400mg/day — in 1–2 divided doses	GI intolerance, nausea, vomiting, diarrhea; paresthesias — circumoral and extremities; hyperlipidemia, especially hypertriglyceridemia; hepatitis; asthenia; taste perversion; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.
Saquinavir tablets and hard-gel capsules (SQV-hgc) / *Invirase*	200-mg capsules 500-mg tablets	Unboosted SQV not recommended With RTV: (RTV 100mg + SQV 1000mg) twice daily	GI intolerance, nausea and diarrhea; headache; elevated transaminase enzymes; hyperlipidemia; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.

Generic Name / Trade Name	Formulation	Dosing Recommendations	Adverse Effects
Saquinavir soft-gel capsule (SQV-sgc) / *Fortovase*	200-mg capsules Anticipated discontinuation of distribution in 2006	Unboosted SQV-sgc: 1,200mg 3 times daily With RTV: (RTV 100mg + SQV-sgc 1000mg) twice daily	GI intolerance, nausea, diarrhea, abdominal pain and dyspepsia; headache; hyperlipidemia; elevated transaminase enzymes; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.
Tipranavir (TPV) / *Aptivus*	250-mg capsules	500mg twice daily with ritonavir 200mg twice daily Unboosted tipranavir is *not* recommended	Hepatotoxicity — clinical hepatitis, including hepatic, decompensation has been reported, monitor closely, especially in patients with underlying liver diseases; skin rash — TPV has a sulfonamide moiety, use with caution in patients with known sulfonamide allergy; rare cases of fatal and nonfatal intracranial hemorrhage have been reported; hyperlipidemia (especially hypertriglyceridemia); hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia.

ARV = antiretroviral; pts = patients; GI = gastrointestinal; AV = atrioventricular

* *Dose escalation for ritonavir when used as sole PI: days 1 and 2, 300mg twice daily; days 3–5, 400mg twice daily; days 6–13, 500mg twice daily; day 14, 600mg twice daily.*

Table 6. Characteristics of Fusion Inhibitors

Generic Name / Trade Name	Formulation	Dosing Recommendations	Adverse Effects
Enfuvirtide (T20) / *Fuzeon*	Injectable — in lyophilized powder Each single-use vial contains 108mg of enfuvirtide to be reconstituted with 1.1mL of sterile water for delivery of approximately 90mg/1mL	90mg (1mL) subcutaneous twice daily	Local injection site reactions — almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis); increased rate of bacterial pneumonia; hypersensitivity reaction (< 1%). Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; rechallenge is not recommended.

Table 7. Drug Interactions Among NRTIs, Other Antiretrovirals, and Selected Other Drugs

Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Didanosine (ddI)**	**Stavudine (d4T)**	**Tenofovir (TDF)**	**Zidovudine (ZDV)**
Atazanavir (ATV)	Buffered ddI + ATV simultaneously — levels: ↓ AUC of ATV 87%; take ATV with food 2 hours before or 1 hour after buffered ddI Simultaneous ddI-EC + ATV (with food): ↓ AUC of ddI 34%, ATV no change; administer separately; ATV should be taken with food and ddI-EC on an empty stomach	No data	ATV 400mg + TDF 300mg — levels: ATV AUC ↓ 25% and Cmin ↓ 40%; TDF AUC ↑ 24%; avoid concomitant use without RTV ATV + RTV 300/100mg once daily + TDF 300mg once daily — levels: ATV AUC ↓ 25% and Cmin ↓ 23%; ATV Cmin higher with RTV than without; TDF AUC ↑ 30%; monitor for toxicities Dose: ATV + RTV 300/100mg once-daily co-administered with TDF 300mg once daily	ZDV: no change in AUC but 30% change in Cmin Significance unknown
Darunavir (DRV)	No data	No data	Levels: TDF AUC ↑ 22%, Cmax ↑ 24% and Cmin ↑ 37%; clinical significance unknown; monitor for TDF toxicity	No data
Didanosine (ddI)		Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; should be avoided unless potential benefit far outweighs potential risks.	Levels: ddI-EC AUC ↑ by 48% to 60%, Cmax ↑ by 48% to 64% For patients > 60kg, 250mg/day of ddI-EC is recommended; for patients < 60kg, 200mg ddI-EC is recommended; the ddI doses apply to patients with creatinine clearance > 60mL/min. Monitor for ddI-associated toxicities.	No significant interactions
Indinavir (IDV)	Buffered ddI and IDV simultaneously: levels, ↓ AUC of IDV; take IDV 1 hour before or after buffered ddI ddI-EC can be taken together with IDV	No significant PK interaction	Levels: IDV Cmax ↑ 14% Dose: standard	No significant PK interaction

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Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Didanosine (ddI)**	**Stavudine (d4T)**	**Tenofovir (TDF)**	**Zidovudine (ZDV)**
Lopinavir / ritonavir (LPV/r)	No data	No data	LPV/r 400/100mg AUC ↓ 15%; TDF AUC ↑ 34%; clinical significance of interaction is unknown; monitor for tenofovir toxicities.	No data
Methadone	Levels: ddI-EC unchanged. Buffered ddI AUC ↓ 63%; methadone unchanged. Dose: no change ddI-EC; may consider buffered ddI dose increase or maintain standard.	Levels: d4T ↓ 27% methadone unchanged Dose: no dose adjustment	No change in methadone or TDF levels	ZDV AUC ↑ 43%; monitor for ZDV-related adverse effects
Ribavirin	Co-administration not recommended; ribavirin increases the intracellular levels of the active metabolite of ddI and may cause serious toxicities	No data	Level: ribavirin unchanged; no data on TDF level	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible, or closely monitor virologic response
Tipranavir/ ritonavir (TPV/r)	Levels: ddI-EC ↓ 10%* TPV Cmin ↓ 34% with EC ddI-EC* Buffered ddI ↓ 3% to 33%* Dose: ddI-EC and TPV/r should be separated by at least 2 hours	No significant PK interaction	TPV AUC and Cmin ↓ 9% to 18% and 12% to 21%, respectively*; clinical significance is unknown	Levels: ZDV AUC and Cmax ↓ 31% to 42% and 46% to 51%, respectively*; appropriate doses for the combination of ZDV and TPV/r have not been established

NRTIs = nucleoside reverse transcriptase inhibitors; AUC = area under the curve; PK = pharmacokinetic.

* *Study conducted with TPV/r dose(s) other than US Food and Drug Administration (FDA)-approved dose of 500/200mg twice daily.*

Table 8. Drug Effects on Concentration of Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drug Affected	Delavirdine (DLV)	Efavirenz (EFV)	Nevirapine (NVP)
Atazanavir (ATV)	No data	Levels: with unboosted ATV, ATV AUC ↓ 74%; EFV no change Dose: ATV 300 + RTV 100 mg once daily with food — ATV concentrations similar to unboosted ATV; if desired ATV concentrations not achieved with ATV/r 300/100 mg, may need to increase the dose of ATV/r; insufficient information for specific recommendation. EFV dose — standard.	No data A decrease in ATV levels is expected. Co-administration is not recommended Effect of NVP on ritonavir-boosted ATV combination unknown; if used, consider monitoring ATV level
Darunavir (DRV)	No data	Levels: DRV AUC and Cmin ↓ 13% and 31%, respectively; EFV AUC and Cmin ↑ 21% and 17%, respectively. Dose: clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Levels: NVP AUC and Cmin ↑ 27% and 47%, respectively; DRV unchanged Dose: standard
Fosamprenavir-(f-APV)	Levels: presumably, similar PK effects as APV: AUC ↑ 130%, and DLV AUC ↓ 61% Dose: co-administration not recommended	Levels: f-APV Cmin ↓ 36% (when dosed at 1400mg once daily with 200mg RTV) Dose: f-APV 1400 mg + RTV 300mg once daily; or f-APV 700mg + RTV 100mg twice daily	No data
Indinavir (IDV)	Levels: IDV ↑ > 40%; DLV — No effect Dose: IDV 600mg every 8 hours; DLV standard	Levels: IDV ↓ 31% Dose: IDV 1000mg every 8 hours, or consider IDV/RTV. EFV standard	Levels: IDV ↓ 28%; NVP no effect Dose: IDV 1000 mg every 8 hours, or consider IDV/RTV; NVP standard
Lopinavir/ ritonavir (LPV/r)	Levels: LPV levels expected to increase Dose: insufficient data	Levels: with LPV/r tablets 600/150mg twice daily + EFV 600mg once daily, LPV Cmin and AUC ↑ 35% *and* 36%, respectively. No formal study of LPV/r tablets 400/100mg twice daily + EFV. EFV no change. Dose: LPV/r tablets 600/150mg twice daily, when used in with EFV in treatment-experienced patients. EFV dose — standard.	Levels: with LPV/r capsules, LPV Cmin ↓ 55% Dose: LPV/r tablets 600/150mg twice daily, when used in combination with NVP in treatment-experienced patients; NVP standard
Nelfinavir (NFV)	Levels: NFV ↑ 2 times; DLV ↓ 50% Dose: no data	Levels: NFV ↑ 20% Dose: standard	NFV ↑ 10%; NVP no effect Dose: standard

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Drug Affected	Delavirdine (DLV)	Efavirenz (EFV)	Nevirapine (NVP)
Nevirapine (NVP)	No data	Levels: NVP no effect EFV: AUC ↓ 22%	
Ritonavir (RTV)	Levels: RTV ↑ 70%; DLV no effect Dose: appropriate doses not established	Levels: RTV ↑ 18%; EFV ↑ 21% Dose: standard	Levels: RTV ↓ 11%; NVP no effect Dose: standard
Saquinavir (SQV)	Levels: SQV* ↑ 5 times; DLV no effect Dose: *Fortovase* 800mg 3 times daily; DLV standard; monitor transaminase levels	Levels: SQV* ↓ 62%, EFV ↓ 12%. SQV is not recommended as sole PI when EFV is used Dose: Consider SQV/RTV 400/400mg twice daily	Levels: SQV ↓ 25%, NVP no effect Dose: Consider SQV-sgc/RTV 400/400mg or 1000/100mg twice daily or SQV-hgc/RTV 1000/100mg twice daily
Tipranavir (TPV)	No data	Levels: with TPV/r 500/100mg twice daily; TPV AUC and Cmin ↓ 31% and 42%, respectively. EFV unchanged. With TPV/r 750/200mg twice daily, TPV PK unchanged. Dose: no dose adjustments necessary	Levels: No data on the effect of NVP on TPV/r PK. NVP PK unchanged.†

PK = pharmacokinetic; AUC = area under the curve; PI = protease inhibitor

* *Study conducted with* Invirase

† *Study conducted with TPV/r dose(s) other than US Food and Drug Administration (FDA)-approved dose 500/200mg twice daily*

Table 9. Drug Effects on Concentration of Protease Inhibitors (PIs) When Co-administered

Drug Affected	Fosampre-navir (f-APV)	Atazanavir (ATV)	Lopinavir / Ritonavir (LPV/r)	Nelfinavir (NFV)	Ritonavir (RTV)	Saquinavir (SQV)*	Tipranavir (TPV)
Darunavir (DRV)	No data	**Levels:** ATV concentrations from ATV 300mg once daily when administered with DRV/r were similar to ATV/r 300/100mg once daily. DRV was unchanged **Dose:** Administer ATV 300mg once daily with DRV/r for exposure similar to ATV/r 300/100mg once daily	**Levels:** DRV AUC and Cmin ↓ 53% and 65%, respectively. LPV AUC and Cmin ↑ 37% and 72%, respectively **Dose:** should not be co-administered, as doses are not established	No data	**Levels:** 14-fold ↑ in DRV exposure in combination with RTV 100mg twice daily. **Dose:** DRV should only be used in combination with RTV 100mg twice daily to achieve sufficient DRV exposure	**Levels:** DRV AUC and Cmin ↓ 26% and 42%, respectively. SQV exposure similar to when administered with RTV 1000/100mg twice daily. **Dose:** should not be co-administered, as doses are not established	No data
Fosamprenavir (f-APV)	—	**Levels:** with f-APV/ATV 1400/400mg once daily, ATV AUC and Cmin ↓ 33% and 57%, respectively With f-APV/r 700/100mg twice daily + ATV 300mg once daily, ATV AUC and Cmax ↓ 22% and 24%, respectively; f-APV was unchanged **Dose:** insufficient data for dose recommendation	**Levels:** with co-administration of f-APV 700mg twice daily and LPV/r capsules 400/100mg twice daily, f-APV Cmin ↓ 64% and LPV Cmin ↓ 53%. An increased rate of adverse events was seen with co-administration. **Dose:** should not be co-administered, as doses are not established	—	**Levels:** f-APV AUC and Cmin ↑ 100% and 400%, respectively, with 200mg RTV **Dose:** f-APR 1400mg + RTV 200mg once daily; or f-APV 700mg + RTV 100mg twice daily	**Levels:** APV AUC ↓ 32% Dose: insufficient data for dose recommendation	**Levels:** APV AUC and Cmin ↓ 44% and 55%, respectively, when given as APV/r 600/100mg twice daily with TPV/r. No data with f-APV, but a ↓ in AUC is expected **Dose:** Should not be co-administered, as doses are not established
Indinavir (IDV)	**Levels:** APV AUC ↑ 33% **Dose:** not established	Co-administration of these agents is not recommended because of potential for additive hyper-bilirubinema	**Levels:** IDV AUC and Cmin ↑ **Dose:** IDV 600mg twice daily	**Levels:** IDV ↑ 50%; NFV ↑ 80% **Dose:** limited data for IDV 1200mg twice daily + NFV 1250mg twice daily	**Levels:** IDV ↑ 2–5 times **Dose:** IDV/RTV 400/400mg, 800/100mg, or 800/200mg twice daily. Caution: Renal events may ↑ with ↑ IDV concentrations	**Levels:** IDV — no effect, SQV ↑ 4-7 times Dose: insufficient data	No data Should not be co-administered, as doses are not established

Drug Affected	Fosampre-navir (f-APV)	Atazanavir (ATV)	Lopinavir / Ritonavir (LPV/r)	Nelfinavir (NFV)	Ritonavir (RTV)	Saquinavir (SQV)*	Tipranavir (TPV)
Lopinavir / ritonavir (LPV/r)	—	**Levels:** with ATV 300mg once daily + LPV/r 400/100mg twice daily, ATV Cmin ↑ 45%; ATV AUC and Cmax were unchanged. LPV PK similar to historical data.	—	—	Additional ritonavir is generally not recommended	—	**Levels:** LPV AUC and Cmin ↓ 55% and 70%, respectively **Dose:** Should not be co-administered, as doses are not established
Nelfinavir (NFV)	**Levels:** APV AUC ↑ 1.5-fold **Dose:** insufficient data	—	**Levels:** with LPV capsules, LPV ↓ 27%; NFV ↑ 25% **Dose:** no data with LPV/r tablets; no dosing recommendation	—	—	—	No data Should not be co-administered, as doses are not established
Ritonavir (RTV)	—	**Levels:** ATV AUC ↑ 238% **Dose:** ATV 300mg once daily + RTV 100mg once daily	Lopinavir is co-formulated with ritonavir as *Kaletra* Additional ritonavir is generally not recommended	**Levels:** RTV — no effect; NFV ↑ 1.5 times **Dose:** not established	—	**Levels:** RTV no effect. SQV ↑ 20 times.[†‡] **Dose:** 1000/100mg SQV sgc or hgc/RTV twice daily or 400/400mg twice daily	**Levels:** TPV AUC ↑ 11-fold

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Drug Affected	Fosampre-navir (f-APV)	Atazanavir (ATV)	Lopinavir / Ritonavir (LPV/r)	Nelfinavir (NFV)	Ritonavir (RTV)	Saquinavir (SQV)*	Tipranavir (TPV)
Saquinavir (SQV)	Levels: APV AUC ↓ 32% Dose: insufficient data	Levels: SQV AUC ↑ 60% with SQV/ATV/RTV 1600/300/100mg once daily; compared with SQV/RTV 1600/100mg once daily Dose: No dose re-commendations can be made	Levels: SQV† AUC and Cmin ↑ Doses: SQV 1000mg twice daily; LPV/r standard	Levels: SQV ↑ 3–5 times; NFV ↑ 20%† Dose: NFV standard; *Fortovase* 800mg 3 times daily or 1200mg twice daily	—	—	Levels: SQV AUC and Cmin ↓ 76% and 82%, respectively, when given as SQV/r 600/100mg twice daily with TPV/r. Dose: Should not be co-administered, as doses are not established

AUC = area under the curve; PK = pharmacokinetic; sgc = soft-gel capsule; hgc = hard-gel capsule

* *Several drug interaction studies have been completed with saquinavir given as* Invirase *or* Fortovase*. Results from studies conducted with* Invirase *may not be applicable to* Fortovase*.*

† *Study conducted with* Fortovase

‡ *Study conducted with* Invirase

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Table 10. Protease Inhibitors (PIs) — Resistance Mutations

	L23	L24	D30	V32	L33	M46	I47	G48	I50	F53	I54	Q58	G73	z	V82	I84	N88	L90
Atazanavir / ritonavir (ATV/r)					F	IL	V	V	***L***		VTALM		ST			**V**	***S***	M
Darunavir / ritonavir (DRV/r)				I	F		V		**V**		**LM**		ST	**V**		**V**		M
Fosampre-navir / ritonavir (FPV/r)				**I**	F	IL	**V**		***V***		**LM**		ST	V		**V**		M
Indinavir / ritonavir (IDV/r)		I		I		IL	V			L	**V**TALM		ST	V	**AFTS**	**V**	S	M
Lopinavir / ritonavir (LPV/r)		I		I	F	IL	V***A***		**V**	L	**V**TALM		ST	V	**AFTS**	**V**		M
Nelfinavir (NFV)	**I**		***N***		F	IL	V	**V**		L	**VTALM**		ST		**AFTS**	**V**	***DS***	***M***
Saquinavir / ritonavir (SQV/r)		I						***V***		L	VTALM		ST			**V**	S	**M**
Tipranavir / ritonavir (TPV/r)					**F**	IL	V				VTA	E	ST		AFT***L***	**V**		M

Data and commentary courtesy of Robert Shafer, MD, Associate Professor of Medicine, Stanford University School of Medicine, Stanford, California.

Legend: *Bold red indicates phenotypic evidence for reduced susceptibility in vitro and clinical evidence for reduced virologic response. Italicized bold red indicates drugs that are usually contraindicated when the mutation is present.*

Notes:

1. *The 18 positions in the above table were selected because, with 2 exceptions (L33V and V82I), they are invariant in the absence of therapy.*
2. *All PIs except NFV have optimal activity when co-administered with RTV. Because NFV levels are not predictably increased by RTV, it is rarely a good choice for salvage therapy. RTV is not listed because it is used almost entirely as a pharmacologic booster. Therefore, few data are available on the effect of PI-resistance mutations on RTV clinical activity.*
3. *Amino acid substitutions at several polymorphic positions, such as L10IVFR, K20RMTI, M36IV, L63P, and A71VTI decrease PI susceptibility or increase virus fitness, but only when present with one of the above mutations.*
4. *For the most recently approved PIs, TPV/r and DRV/r, most available data are based on the virologic results from 2 registration trials — RESIST for TPV/r and POWER for DRV. In RESIST, 21 mutations at 16 positions were associated with decreased virologic response, including 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54AMV, 58E, 69K, 74P, 82LT, 83D, and 84V. In POWER, 11 mutations at 10 positions were associated with decreased virologic response to DRV/r including V11I, V32I, L33F, I47V, I50V, I54LM, G73S, L76V, I84V, and L89V. Underlined mutations in both lists appear in the chart.*
5. *I50L increases susceptibility to all PIs except ATV; N88S increases FPV susceptibility; L76V increases ATV and SQV susceptibility.*
6. *Several additional mutations at the 17 positions in the above chart also appear to be strongly selected by therapy, including M46V, G48M, I54S, G73CA, V82M, I84AC, and N88TG.*
7. *Although protease cleavage site mutations influence susceptibility and virus fitness, there are no data suggesting a role for sequencing protease cleavage sites in clinical settings.*

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Table 11. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) — Resistance Mutations

	184	Type I TAMs	Type II TAMs	K65	L74	T69	Q151	Misc.
Lamivudine (3TC)	**VI**			**R**		Insertion	M	
Emtricitabine (FTC)	**VI**			**R**		Insertion	M	
Tenofovir disoproxil fumarate (TDF)		41L, 210W, 215Y		**R**		**Insertion**	M	K70E
Abacavir (ABC)		41L, 210W, 215Y		**R**	VI	**Insertion**	**M**	**F115Y**
Didanosine (ddI)		41L, 210W, 215Y		**R**	**VI**	**Insertion**	**M**	T69D
Stavudine (d4T)		**41L, 210W, 215Y**	**67N, 70R, 215F, 219QE**	R		**Insertion**	**M**	**V75TMA**
Zidovudine (ZDV)		**41L, 210W, 215Y**	**67N, 70R, 215F, 219QE**			**Insertion**	**M**	

Data and commentary courtesy of Robert Shafer, MD, Associate Professor of Medicine, Stanford University School of Medicine, Stanford, California.

TAMs = thymidine analog mutations.

Legend: *Bold red indicates phenotypic evidence for reduced susceptibility in vitro and clinical evidence for reduced virologic response.*

Notes:

1. *Because NRTIs are usually used in combination and because they retain activity even in the presence of drug resistance, there are no strict contraindications for using specific NRTIs in treating viruses with specific mutations.*
2. *M184V is the most common NRTI-resistance mutation. Although it causes high-level in vitro resistance to 3TC and FTC, these drugs are often still used because M184V reduces viral replication and increases susceptibility to ZDV, TDF, and d4T.*
3. *Two other mutations can increase NRTI susceptibility. L74V increases viral susceptibility in vitro to ZDV and TDF. However, the clinical significance of this interaction is not known. K65R increases viral susceptibility to ZDV; this appears to be clinically significant.*
4. *T69 insertions usually occur with type I TAMs. Q151M generally occurs with 2 or more of the following mutations: A62V, V75I, F77L, and F116Y. Although 3TC/FTC retain some activity against viruses with T69 insertions and Q151M, NRTI combinations are not highly active against these multidrug-resistant variants.*
5. *Patients primarily infected with virus strains containing T215FY often develop viruses with "revertants" at this position, such as T215CDEISV. Although these mutations do not reduce susceptibility, they suggest that infection occurred with a virus that may have had T215Y or T215F.*
6. *The presence of multiple TAMs can lead to several-fold decreased 3TC/FTC susceptibility, but this change in susceptibility is much less than that observed with M184VI, K65R, or the multidrug-resistant viruses that have T69 insertions or Q151M.*
7. *E44DA and V118I are accessory NRTI-resistance mutations that usually occur with type I TAMs. V118I occurs in about 1% to 2% of treated persons and therefore does not necessarily indicate drug-selective pressure.*
8. *Additional mutations at the above drug-resistance positions, such as D67GE, T69NSI, K70G, L74I, Q151L, K219NR, are often observed in heavily treated persons.*
9. *Mutations beyond position 238 of RT may have subtle effects on NRTI and NNRTI susceptibility but are generally not considered useful for clinical purposes.*

Table 12. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs) — Resistance Mutations

	98	100	101	103	106	108	179	181	188	190	225	227	230	236	238
Efavirenz (EFV)	G	**I**	E**P**	**NST**	A**M**	I	DE	CIV	**L**HC	A**SE**	H		**L**		NT
Nevirapine (NVP)	G	**I**	**EP**	**NST**	**AM**	I	DE	**CIV**	**LHC**	**ASE**	H	L	**L**		NT
Delavirdine (DLV)	G	**I**	**EP**	**NST**	**AM**	I	DE	**CIV**	**LHC**				**L**	**L**	NT

Data and commentary courtesy of Robert Shafer, MD, Associate Professor of Medicine, Stanford University School of Medicine, Stanford, California.

Legend: *Bold red indicates phenotypic evidence for reduced susceptibility in vitro and clinical evidence for reduced virologic response.*

Notes:

- *Cross-resistance among the NNRTIs is high because many of the mutations reduce the susceptibility to multiple drugs and because the presence of one NNRTI-resistance mutation often suggests that others are also present as minor variants.*
- *A98S, K101RQ, K103R, V106I, V179I, and K238R are polymorphic substitutions that have little if any effect on drug resistance with 1 exception: K103R slightly increases the level of resistance to each of the NNRTIs when present in combination with V179D.*
- *Mutations beyond position 238 of RT may have subtle effects on nucleoside reverse transcriptase inhibitor (NRTI) and NNRTI susceptibility but are generally not considered useful for clinical purposes.*

Table 13. Fusion Inhibitor (Enfuvirtide [ENF]) — Resistance Mutations

G36	I37	V38	Q39	Q40	Q41	N42	N43	L44	L45
DEVS	V	**EA**MG		**H**		T	**D**KS	M	M

Data and commentary courtesy of Robert Shafer, MD, Associate Professor of Medicine, Stanford University School of Medicine, Stanford, California.

Legend: *Bold red mutations reduce enfuvirtide susceptibility > 10-fold in site-directed mutants and most clinical isolates.*

Notes:

- *Positions 36 to 45 in the first heptad repeat (HR1) region of the gp41 transmembrane glycoprotein, the ENF-binding site.*
- *N42S is the only common naturally occurring polymorphism between codons 36–45. It occurs in about 15% of untreated isolates. Most other mutations at these positions are likely to have been selected by ENF therapy, although their effect on ENF susceptibility has not been studied.*
- *Several additional mutations appear to reduce susceptibility usually in combination with position 3–45 mutations, including L33T, N126K, and S138A. ENF targets gp41 during a kinetic window opened by CD4 binding and closed by coreceptor engagement; therefore, genetic changes that accelerate this process may also reduce ENF susceptibility. Nonetheless, HR1 36–45 mutations explain most of the decrease in ENF susceptibility in viruses from persons with virologic failure.*
- *There is a low genetic barrier to ENF resistance, and failure with the emergence of genotypic and phenotypic resistance due to just 1 or 2 mutations may occur within weeks if ENF is not used with a sufficiently potent background regimen. Continued therapy in the face of resistance appears to show little virologic benefit. There are some data, however, suggesting that certain ENF-resistance mutations, particularly those at position 38, may be associated with CD4+ cell count increases.*