Table III. Recommendations for the Use of Drug Resistance Assays

Clinical setting/Recommendation	Rationale
Recommended	
Virologic failure during HAART (see page 15)	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen if indicated.
Suboptimal suppression of viral load after initiation of antiretroviral therapy (see page 15)	Determine the role of resistance and maximize the number of active drugs in the new regimen if indicated.
Consider	
Acute HIV infection	Determine if drug resistant virus was transmitted and change regimen accordingly.
Not generally recommended	
Chronic HIV infection prior to initiation of therapy	Uncertain prevalence of resistant virus. Current assays may not detect minor drug resistant species.
After discontinuation of drugs	Drug resistance mutations may become minor species in the absence of selective drug pressure. Current assays may not detect minor drug resistant species.
Plasma viral load <1000 HIV RNA copies/mL	Resistance assays cannot be reliably performed because of low copy number of HIV RNA.

Table IV. Risks and Benefits of Early Initiation of Antiretroviral Therapy in the Asymptomatic HIV-Infected Patient

Potential Benefits

- Control of viral replication and mutation; reduction of viral burden
- Prevention of progressive immunodeficiency; potential maintenance or reconstruction of a normal immune system
- Delayed progression to AIDS and prolongation of life
- Decreased risk of selection of resistant virus
- Decreased risk of drug toxicity
- Possible decreased risk of viral transmission

Potential Risks

- Reduction in quality of life from adverse drug effects and inconvenience of current maximally suppressive regimens
- Earlier development of drug resistance
- Transmission of drug resistant virus
- Limitation in future choices of antiretroviral agents due to development of resistance
- Unknown long term toxicity of antiretroviral drugs
- Unknown duration of effectiveness of current antiretroviral therapies

Table V. Risk of Progression to AIDS Defining Illness in a Cohort of Homosexual Men Predicted by Baseline $CD4^+$ T Cell Count and Viral Load *

CD4 ≤ 350 Plasma Viral Load (copies/ml) **				% AIDS (AIDS – defining complication) ***			
bDNA		RT-PCR		n	3 years	6 years	9 years
≤ 500		≤ 1,500		– #	–	–	–
501 – 3,000		1,501 – 7,000		30	0	18.8	30.6
3,001 – 10,000		7,001 – 20,000		51	8.0	42.2	65.6
10,001 – 30,000		20,001 – 55,000		73	40.1	72.9	86.2
> 30,000		> 55,000		174	72.9	92.7	95.6
CD4 351 – 500 Plasma Viral Load (copies/ml)				**% AIDS (AIDS – defining complication)**			
bDNA		**RT-PCR**		**n**	**3 years**	**6 years**	**9 years**
≤ 500		≤ 1,500		–	–	–	–
501 – 3,000		1,501 – 7,000		47	4.4	22.1	46.9
3,001 – 10,000		7,001 – 20,000		105	5.9	39.8	60.7
10,001 – 30,000		20,001 – 55,000		121	15.1	57.2	78.6
> 30,000		> 55,000		121	47.9	77.7	94.4
CD4 > 500 Plasma Viral Load (copies/ml)				**% AIDS (AIDS – defining complication)**			
bDNA		**RT-PCR**		**n**	**3 years**	**6 years**	**9 years**
≤ 500		≤ 1,500		110	1.0	5.0	10.7
501 – 3,000		1,501 – 7,000		180	2.3	14.9	33.2
3,001 – 10,000		7,001 – 20,000		237	7.2	25.9	50.3
10,001 – 30,000		20,001 – 55,000		202	14.6	47.7	70.6
> 30,000		> 55,000		141	32.6	66.8	76.3

* Data from the Multi-Center AIDS Cohort Study (MACS), reference **3**.

** MACS numbers reflect plasma HIV RNA values obtained by bDNA testing. RT-PCR values are consistently 2 – 2.5 fold higher than bDNA values, as indicated.

*** In this study AIDS was defined according to the 1987 CDC definition and does not include asymptomatic individuals with CD4+ T cells < 200 mm^3.

Too few subjects were in the category to provide a reliable estimate of AIDS risk.

TABLE VII – Advantages and Disadvantages of Class-sparing regimens

Regimen	Possible Advantages	Possible Disadvantages	Drug Interaction Complications	Impact on Future Options
PI-based HAART Regimen	• Clinical, virologic, and immunologic efficacy well-documented • Continued benefits sometimes seen despite viral breakthrough • Resistance requires multiple mutations • Targets HIV at two steps of viral replication (RT and PI)	• May be difficult to use and adhere to • Long-term side effects may include lipodystrophy*, hyperlipidemia, and insulin resistance	• Mild to severe inhibition of cytochrome P450 pathway; ritonavir is most potent inhibitor, but this effect can be exploited to boost levels of other PIs	• Preserves NNRTIs for use in treatment failure • Resistance primes for cross-resistance with other PIs
NNRTI-based HAART regimen (protease-sparing)	• Sparing of PI-related side effects • Generally easier to use and adhere to compared with PIs	• Comparability to PI-containing regimens with regard to clinical endpoints unknown • Resistance conferred by a single, or few mutations	• Fewer drug-drug interactions compared with PIs	• Preserves PIs for later use • Resistance usually leads to cross-resistance across entire NNRTI class
Triple NRTI regimen (NNRTI- and PI-sparing)	• Generally easier to use and adhere to compared with PIs • Sparing of PI and NNRTI side effects • Resistance to 1 NRTI does not confer cross-resistance to entire class	• Comparability to PI-containing regimens with regard to clinical endpoints unknown • Long-term virologic efficacy with high baseline viral load may be suboptimal	• Generally manageable drug interaction problems	• Preserves both PI and NNRTI classes for later use • Limited cross-resistance within the NRTI class

* Some side effects being attributed to protease inhibitor therapy, such as lipodystrophy, have not been proven to be strictly associated with the use of protease inhibitor-containing regimens. Lipodystrophy has also been described uncommonly in patients on NRTIs alone and in patients on no antiretroviral therapy.

Table VIII. Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV-Infected Patient

Clinical Category	$CD4^+$ T Cell Count and HIV RNA	Recommendation
Symptomatic (AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	$CD4^+$ T Cells < 500/mm^3 **or** HIV RNA > 10,000 (bDNA) or > 20,000 (RT-PCR)	Treatment should be offered. Strength or recommendation is based on prognosis for disease-free survival as shown in Table V and willingness of the patient to accept therapy. *
Asymptomatic	$CD4^+$ T Cells > 500/mm^3 **and** HIV RNA < 10,000 (bDNA) or < 20,000 (RT-PCR)	Many experts would delay therapy and observe; however, some experts would treat.

* Some experts would observe patients with $CD4^+$ T cell counts between 350 – 500/mm^3 and HIV RNA levels < 10,000 (bDNA) or < 20,000 (RT-PCR)

Table IX. Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection

This table provides a guide to the use of available treatment regimens for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens in which clinical trials data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load) and sustained increase in CD4+ T cell count (in most cases over 48 weeks), and favorable clinical outcome (i.e. delayed progression to AIDS and death). Particular emphasis is given to regimens that have been compared directly with other regimens that perform sufficiently well with regard to these parameters to be included in the "strongly recommended" category. Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

It is important to note that all antiretroviral agents, including those in the 'Strongly Recommended' category, have potentially serious toxic and adverse events associated with their use. The reader is strongly encouraged to consult tables X-XVI while formulating an antiretroviral regimen.

Antiretroviral drug regimens are comprised of one choice each from columns A and B. Drugs are listed in alphabetical, not priority order.

	Column A	**Column B**
Strongly Recommended	Efavirenz Indinavir Nelfinavir Ritonavir + Saquinavir (SGC* or HGC*)	Stavudine + Lamivudine Stavudine + Didanosine Zidovudine + Lamivudine Zidovudine + Didanosine
	Column A	**Column B**
Recommended as an Alternative	Abacavir Amprenavir Delavirdine Nelfinavir + Saquinavir-SGC Nevirapine Ritonavir Saquinavir-SGC	Didanosine + Lamivudine Zidovudine + Zalcitabine
No Recommendation; Insufficient Data**	Hydroxyurea in combination with other antiretroviral drugs Ritonavir + Indinavir Ritonavir + Nelfinavir	
	Column A	**Column B**
Not Recommended; Should Not Be Offered (All monotherapies, whether from column A or B***)	Saquinavir-HGC****	Stavudine + Zidovudine Zalcitabine + Lamivudine Zalcitabine + Stavudine Zalcitabine + Didanosine

* Saquinavir-SGC, soft-gel capsule (Fortovase): Saquinavir-HGC, hard-gel capsule (Invirase).

** This category includes drugs or combinations for which information is too limited to allow a recommendation for or against use.

*** Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high CD4+ T cell counts to prevent perinatal transmission, as discussed under "Considerations in the Pregnant Woman".

**** Use of Saquinavir-HGC (Invirase) is not recommended, except in combination with ritonavir.

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

Generic Name Trade Name	**Zidovudine (AZT, ZDV)** Retrovir	**Didanosine (ddI)** Videx	**Zalcitabine (ddC)** HIVID	**Stavudine (d4T)** Zerit	**Lamivudine (3TC)** Epivir	**Abacavir (ABC)** Ziagen
Form	100 mg capsules 300 mg tablets 10 mg/mL IV solution 10 mg/mL oral solution	25, 50, 100, 150, 200 mg tablets 167, 250 mg sachets	0.375, 0.75 mg tablets	15, 20, 30, 40 mg capsules 1mg/mL for oral solution	150 mg tablets 10 mg/mL oral solution	300 mg tablets 20 mg/mL oral solution
Dosing Recommendations	200 mg tid or 300 mg bid or with 3TC as Combivir, 1 bid	Tablets >60kg: 200 mg bid or 400 mg qd <60kg: 125 mg bid or 250 mg qd	0.75 mg tid	>60kg: 40 mg bid <60kg: 30 mg bid	150 mg bid <50kg: 2 mg/kg bid or with ZDV as Combivir 1 bid	300 mg bid
Food Effect	Take without regard to meals	Levels ↓ 55% Take ½ hour before or 1 hour after meal	Take without regard to meals	Take without regard to meals	Take without regard to meals	Take without regard to meals Alcohol ↑ ABC levels 41%; no effect on alcohol
Oral bioavailability	60%	30 - 40%	85%	86%	86%	83%
Serum half-life	1.1 hour	1.6 hour	1.2 hour	1.0 hour	3-6 hours	1.5 hours
Intracellular half-life	3 hours	25 – 40 hours	3 hours	3.5 hours	12 hours	3.3 hours
Elimination	Metabolized to AZT glucuronide (GAZT) Renal excretion of GAZT	Renal excretion 50%	Renal excretion 70%	Renal excretion 50%	Renal excretion unchanged	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82%
Adverse Events	Bone marrow suppression: Anemia and/or neutropenia Subjective complaints: GI intolerance, headache, insomnia, asthenia Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.	Pancreatitis * Peripheral neuropathy Nausea Diarrhea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.	Peripheral neuropathy Stomatitis Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.	Peripheral neuropathy Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.	(Minimal toxicity) Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.	Hypersensitivity reaction (can be fatal); fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite** Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.

* Cases of fatal and nonfatal pancreatitis have occurred in treatment-naive and treatment-experienced patients during therapy with ddI or in combination with other drugs, particularly d4T or d4T + hydroxyurea.

* * Patients who develop signs or symptoms of hypersensitivity (which may include fever, rash, fatigue, nausea, vomiting, diarrhea, and abdominal pain) should discontinue abacavir as soon as a hypersensitivity reaction is suspected. Abacavir should not be re-started, because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Cases of abacavir hypersensitivity syndrome should be reported to the Abacavir Hypersensitivity Registry at 1-800-270-0425.

Table XI. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Generic Name Trade Name	**Nevirapine** Viramune	**Delavirdine** Rescriptor	**Efavirenz** Sustiva
Form	200 mg tablets 50 mg/5 mL oral suspension	100 mg tablets	50, 100, 200 mg capsules
Dosing Recommendation	200 mg po qd x 14 days, then 200 mg po bid	400 mg po tid, or four 100 mg tablets in $\geq$ 3 oz water to produce slurry Separate dosing with ddI or antacids by 1 hour	600 mg po qHS
Food Effect	Take without regard to meals	Take without regard to meals	Avoid taking after high fat meals, Levels ↑ 50%
Oral bioavailability	> 90%	85%	Data not available
Serum half-life	25 – 30 hours	5.8 hours	40 – 55 hours
Elimination	Metabolized by cytochrome P450 (3A inducer); 80 % excreted in urine (Glucuronidated metabolites, < 5% unchanged), 10% in feces	Metabolized by cytochrome P450 (3A inhibitor) 51% excreted in urine (<5% unchanged), 44% in feces	Metabolized by cytochrome P450 (3A mixed inducer/inhibitor); 14 – 34 % excreted in urine (glucuronidated metabolites, < 1% unchanged), 16 – 61 % in feces.
Adverse Events	Rash * Increased transaminase levels Hepatitis	Rash * Increased transaminase levels Headaches	Rash * Central nervous systems symptoms ** Increase transaminase levels False positive cannabinoid test Teratogenic in monkeys ***
Drug Interactions	**For more information on Drug Interactions please see Table XIV.**		

* In clinical trials, the NNRTI was discontinued because of rash in 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 three NNRTIs.

** May include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. The overall frequency of any of these symptoms associated with use of efavirenz was 52% compared with 26% in controls; 2.6% of those on efavirenz discontinued the drug due to these symptoms.

*** No data are available regarding teratogenicity of other NNRTIs in non-human primates.

Table XII. Characteristics of Protease Inhibitors (PIs)

Generic Name Trade Name	**Indinavir** Crixivan	**Ritonavir** Norvir	**Nelfinavir** Viracept
Form	200, 333, 400 mg caps	100 mg caps. 600 mg/7.5 mL po solution	250 mg tablets 50 mg/g oral powder
Dosing Recommendations	800 mg q8h Separate dosing with ddI by 1 hour	600 mg q12 * Separate dosing with ddI by 2 hours	750 mg tid or 1250 bid
Food Effect	Levels decrease 77% Take 1 hour before or 2 hours after meals; may take with skim milk or low fat meal	Levels increase 15% Take with food if possible, this may improve tolerability	Levels increase 2-3 fold Take with meal or snack
Oral bioavailability	65%	(not determined)	20 – 80%
Serum half-life	1.5 – 2 hours	3 – 5 hours	3.5 – 5 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor (less than ritonavir)	P450 cytochrome 3A4 > 2D6 Potent 3A4 inhibitor	P450 cytochrome 3A4 inhibitor (less than ritonavir)
Storage	Room temperature	Refrigerate capsules Oral solution should NOT be refrigerated	Room temperature
Adverse Effects	• Nephrolithiasis • GI intolerance, nausea • Lab: Increased indirect bilirubinemia (inconsequential) • Misc.: Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia • Hyperglycemia + • Fat redistribution and lipid abnormalities ++ • Possible increased bleeding episodes in patients with hemophilia	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias – circumoral and extremities • Hepatitis • Asthenia • Taste perversion • Lab.: Tryglycerides increase > 200%, transaminase elevation, elevated CPK and uric acid • Hyperglycemia + • Fat redistribution and lipid abnormalities ++ • Possible increased bleeding episodes in patients with hemophilia	• Diarrhea • Hyperglycemia + • Fat redistribution and lipid abnormalities ++ • Possible increased bleeding episodes in patients with hemophilia
Drug Interactions	**For more information on Drug Interactions please see Table XIV.**		

* Dose escalation for Ritonavir: Day 1 – 2: 300 mg bid; day 3 – 5: 400 mg bid; day 6 – 13: 500 mg bid; day 14: 600 mg bid
Combination treatment regimen with Saquinavir (400 mg po bid) plus Ritonavir (400 mg po bid)

\+ Cases of worsening glycemic control in patients with pre-existing diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.

++ Fat redistribution and lipid abnormalities have been increasingly recognized with the use of protease inhibitors. Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluates for risks for cardiovascular events and pancreatitis. Possible interventions include dietary modification, lipid lowering agents, or discontinuation of PIs.

Table XII. Characteristics of Protease Inhibitors (PIs) - Cont.

Generic Name Trade Name	**Saquinavir** Invirase	 Fortovase	**Amprenavir** Agenerase
Form	200 mg caps	200 mg caps	50 mg, 150 mg tablets 15 mg/mL oral solution (tabs and solution NOT interchangeable on mg per mg basis)
Dosing Recommendations	400 mg bid with ritonavir; Invirase not recommended otherwise	1,200 mg tid **	1200 mg bid
Food Effect	No food effect when taken with ritonavir	Levels increase 6-fold Take with large meal	High fat meal decreases AUC 21%; can be taken with or without food, but high fat meal should be avoided.
Oral bioavailability	Hard gel capsule: 4% erratic	Soft gel capsule (not determined)	Not determined in humans
Serum half-life	1 – 2 hours	1 – 2 hours	7.1 – 10.6 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor (less than ritonavir)	P450 cytochrome 3A4 inhibitor (less than ritonavir)	P450 cytochrome 3A4 inhibitor (less than ritonavir; similar to indinavir, nelfinavir)
Storage	Room temperature	Refrigerate or store at room temperature (up to 3 months)	Room temperature
Adverse Effects	• GI intolerance, nausea and diarrhea • Headache • Elevated transaminase enzymes • Hyperglycemia + • Fat redistribution and lipid abnormalities ++ • Possible increased bleeding episodes in patients with hemophilia	• GI intolerance, nausea, diarrhea, abdominal pain and dyspepsia • Headache • Elevated transaminase enzymes • Hyperglycemia + • Fat redistribution and lipid abnormalities ++ • Possible increased bleeding episodes in patients with hemophilia	• GI intolerance; nausea, vomiting, diarrhea • Rash • Oral paresthesias • Lab: Increase in liver function tests • Hyperglycemia + • Fat redistribution and lipid abnormalities ++ • Possible increased bleeding episodes in patients with hemophilia
Drug Interactions	**For more information on Drug Interactions please see Table XIV.**		

** Saquinavir soft gel capsule given as 1600 bid produced lower daily exposure and trough serum concentrations compared with the standard 1200 mg tid regimen. Trends in immunologic and virologic responses favored the standard tid regimen. The clinical significance of the inferior trends observed in the bid dosing group are not known; however, until the availability of the results from longer follow-up studies, bid dosing of saquinavir soft gel capsules is not recommended.

+ Cases of worsening glysemic control in patients with pre-existing diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.

++ Fat redistribution and lipid abnormalities have been increasingly recognized with the use of protease inhibitors. Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluates for risks for cardiovascular events and pancreatitis. Possible interventions include dietary modification, lipid lowering agents, or discontinuation of PIs.

Table XIII. Drugs That Should Not Be Used With Antiretrovirals

Drug Category	Indinavir	Ritonavir *	Saquinavir	Nelfinavir	Amprenavir
Ca++ channel blocker	(none)	bepridil	(none)	(none)	bepridil
Cardiac	(none)	amiodarone flecainide propafenone quinidine	(none)	(none)	(none)
Lipid Lowering Agents	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin
Anti-Mycobacterial	rifampin	(none)	rifampin rifabutin	rifampin	rifampin
Antihistamine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine
Gastrointestinal Drugs	cisapride	cisapride	cisapride	cisapride	cisapride
Neuroleptic	(none)	clozapine pimozide	(none)	(none)	(none)
Psychotropic	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam
Ergot Alkaloids (vasoconstrictor)	dihydroergotamine (D.H.E. 45) ergotamine ** (various forms)	dihydroergotamine (D.H.E. 45) ergotamine ** (various forms)	dihydroergotamine (D.H.E. 45) ergotamine ** (various forms)	dihydroergotamine (D.H.E. 45) ergotamine ** (various forms)	dihydroergotamine (D.H.E. 45) ergotamine ** (various forms)

* Some of the contraindicated drugs listed are based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

** This is likely a class effect.

Suggested Alternatives

Simvastatin, lovastatin: atorvastatin, pravastatin, fluvastatin, cerivastatin (alternatives should be used with caution)
Rifabutin: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin, ethambutol (MAI treatment)
Astemizole, terfenadine: loratidine, fexofenadine, cetirizine
Midazolam,triazolam: temazepam, lorazepam

Table XIII. Drugs That Should Not Be Used With Antiretrovirals - Cont.

Drug Category	Nevirapine	Delavirdine	Efavirenz
Ca++ channel blocker	(none)	(none)	(none)
Cardiac	(none)	(none)	(none)
Lipid Lowering Agents	(none)	simvastatin lovastatin	(none)
Anti-Mycobacterial	(none)	rifampin rifabutin	(none)
Antihistamine	(none)	astemizole terfenadine	astemizole terfenadine
Gastrointestinal Drugs	(none)	cisapride H-2 blockers Proton pump inhibitors	cisapride
Neuroleptic	(none)	(none)	(none)
Psychotropic	(none)	midazolam triazolam	midazolam triazolam
Ergot Alkaloids (vasoconstrictor)	(none)	dihydroergotamine (D.H.E. 45) ergotamine ** (various forms)	dihydroergotamine (D.H.E. 45) ergotamine ** (various forms)

** This is likely a class effect.

Suggested Alternatives

Simvastatin, lovastatin: atorvastatin, pravastatin, fluvastatin, cerivastatin (alternatives should be used with caution)
Rifabutin: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin ethambutol (MAI treatment)
Astemizole, terfenadine: loratidine, fexofenadine, cetirizine
Midazolam,triazolam: temazepam, lorazepam

Table XIV. Drug Interactions Between Antiretrovirals and Other Drugs
Protease Inhibitors (PIs)

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Indinavir (IDV)**	**Ritonavir (RTV)**	**Saquinavir* (SQV)**
ANTIFUNGALS			
Ketoconazole	Levels: IDV ↑ 68% Dose:IDV 600 mg tid	Levels: keto. ↑ 3X Dose:Use with caution; do not exceed 200 mg ketoconazole daily	Levels: SQV ↑ 3X Dose: Standard
ANTI-MYCOBACTERIALS			
Rifampin	Levels: IDV ↓ 89% Contraindicated	Levels: RTV ↓ 35% Dose: No Data Increased liver toxicity possible	Levels: SQV ↓ 84% Contraindicated
Rifabutin	Levels: IDV ↓32% Rifabutin ↑2X Dose: ↓rifabutin to 150 mg qd, IDV 1000 mg tid	Levels: Rifabutin ↑4X Dose: ↓rifabutin to 150 mg qod Or dose 3x per week	Levels: SQV ↓40% Not recommended
Clarithromycin	Levels: Clari. ↑ 53% No dose adjustment	Levels: Clari. ↑ 77% Dose adjust for renal insufficiency	Levels: Clari. ↑ 45% SQV ↑ 177% No dose adjustment
ORAL CONTRACEPTIVES	Levels: Norethindrone↑26% ethinylestradiol↑24% No dose adjustment	Levels: ethinylestradiol ↓ 40% Use alternative or additional method	No data
LIPID LOWERING AGENTS			
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS			
Phenobarbitol **Phenytoin** **Carbamazepine**	Unknown but may decrease IDV levels substantially Monitor anticonvulsant levels.	Unknown Use with caution Monitor anticonvulsant levels.	Unknown but may decrease SQV levels substantially Monitor anticonvulsant levels.
Methadone	No data	Methadone ↓ 37%, May require dose increase	No data
Miscellaneous	Grapefruit juice ↓ IDV levels by 26% Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr. period	Desipramine ↑ 145%, Reduce dose Theophylline ↓47%, monitor theo. levels. Many possible interactions Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr. period	Grapefruit juice increases SQV levels Dexamethasone decreases SQV levels Sildenafil AUC ↑ 2-11 fold. Use a 25 mg starting dose of sildenafil.

* Some drug interaction studies were conducted with INVIRASE. May not necessarily apply to use with FORTOVASE.

Drugs in which plasma concentrations may be decreased by coadministration with Norvir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

Table XIV. Drug Interactions Between Antiretrovirals and Other Drugs - Cont.
Protease Inhibitors (PIs)

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Nelfinavir (NFV)**	**Amprenavir (APV)**
ANTIFUNGALS		
Ketoconazole	No dose adjustment necessary	Levels: APV ↑ 31% Keto ↑ 44%. Combination under investigation
ANTI-MYCOBACTERIALS		
Rifampin	Levels ↓ 82% Contraindicated	Levels: APV AUC ↓ 82% No change in rifampin AUC. Avoid concomitant use.
Rifabutin	Levels: NFV ↓32% Rifabutin ↑2X Dose: ↓rifabutin to 150 mg qd. ↑NFV dose to 1000 mg tid.	Levels: APV AUC ↓15% Rifabutin ↑193% Dose: No change in APV dose; Decrease rifabutin to 150 mg qd.
Clarithromycin	No data	Levels: APV AUC ↑ 18%. No change in Clari. AUC. No dose adjustment
ORAL CONTRACEPTIVES	Levels: Norethindrone ↓ 18% ethinylestradiol ↓47% Use alternative or additional method	Levels: Potential for metabolic interactions; use alternative or additional method.
LIPID LOWERING AGENTS		
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS		
Phenobarbitol **Phenytoin** **Carbamazepine**	Unknown but may decrease NFV levels substantially Monitor anticonvulsant levels.	Unknown but may decrease APV levels substantially Monitor anticonvulsant levels.
Methadone	No data	No data
Miscellaneous	Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr. period	Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr. period.

Table XIV. Drug Interactions Between Antiretrovirals and Other Drugs - Cont.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Nevirapine (NVP)**	**Delavirdine (DLV)**	**Efavirenz (EFV)**
ANTIFUNGALS			
Ketoconazole	Levels: Keto. ↓ 63% NVP ↑ 15-30% Dose: Not recommended	No data	No data
ANTI-MYCOBACTERIALS			
Rifampin	Levels: NVP ↓ 37% Not recommended	Levels: DLV ↓ 96% Contraindicated	Levels: EFV ↓ 25% No dose adjustment
Rifabutin	Levels: NVP ↓ 16% No data for rifabutin dose	Levels: DLV ↓80% Rifabutin ↑ 100% Not Recommended	Levels: EFV unchanged; Rifabutin ↓ 35% Dose: ↑ rifabutin dose to 450 mg qd.
Clarithromycin	Levels: NVP ↑26%, clari. ↓ 30%. No dose adjustment.	Levels: clari. ↑100%, DLV ↑ 44% Dose adjust for renal failure	Levels: clari. ↓39% Alternative recommended
ORAL CONTRACEPTIVES	No data	No data	Levels: Ethinylestradiol ↑ 37% No data on other component. Use alternative or additional methods
LIPID LOWERING AGENTS			
Simvastatin **Lovastatin**	No data	Levels: Potential for large increase in statin levels. Avoid concomitant use.	No data
ANTICONVULSANTS			
Phenobarbitol **Phenytoin** **Carbamazepine**	Unknown Use with caution Monitor anticonvulsant levels.	Unknown but may decrease DLV levels substantially Monitor anticonvulsant levels.	Unknown Use with caution Monitor anticonvulsant levels.
METHADONE	Levels: NVP unchanged, methadone ↓ significantly. Titrate methadone dose to effect.	No data	No data
MISCELLANEOUS	No data	May increase levels of Dapsone, Warfarin and Quinidine Sildenafil: potential for increased concentrations and adverse effects. Do not exceed 25 mg in a 48 hr. period	Monitor Warfarin when used concomitantly

Table XIV. Drug Interactions Between Antiretrovirals and Other Drugs- Cont.
Nucleoside Reverse Transcriptase Inhibitors (NRTIs).

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Zidovudine (ZDV)**	**Stavudine (d4T)**	**Didanosine (ddI)**
METHADONE	No data	Levels: d4T ↓27%, methadone unchanged. No dose adjustment.	Levels: ddI ↓41%, methadone unchanged. Consider ddI dose increase.
MISCELLANEOUS	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible.	No data	No data

Table XV. Drug Interactions: Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors

Effect of Drug on Levels (AUCs)/Dose

Drug Affected	Ritonavir	Saquinavir *	Nelfinavir	Amprenavir
Indinavir (IDV)	Levels: IDV ↑ 2-5X Dose: Limited data for IDV 400 mg bid + RTV 400 mg bid, or IDV 600 mg bid + RTV 200 mg bid, or IDV 800 mg bid + RTV 100 or 200 mg bid	Levels: IDV no effect SQV ↑ 4-7x # Dose: Insufficient data	Levels: IDV ↑ 50% NFV ↑ 80% Dose: Limited data for IDV 1200 mg bid + NFV 1250 mg bid	Levels: APV AUC ↑ 33%. Dose: no change
Ritonavir (RTV)	•	Levels: RTV no effect SQV ↑ 20x + # Dose: Invirase or Fortovase 400 mg bid + RTV 400 mg bid	Levels: RTV no effect NFV ↑ 1.5x Dose: Limited data for RTV 400 mg bid + NFV 500-750 mg bid	Levels: APV AUC ↑ 2.5-fold. Dose: insufficient data
Saquinavir (SQV)	•	•	Levels: SQV ↑ 3-5x NFV ↑ 20% # Dose: Standard NFV Fortovase 800 mg tid	Levels: APV AUC↓32% Dose: insufficient data
Nelfinavir (NFV)	•	•	•	Levels: APV AUC ↑ 1.5-fold. Dose: insufficient data

* 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

\+ Conducted with Invirase

\# Conducted with Fortovase

Table XV. Drug Interactions: Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors - Cont.

Effect of Drug on Levels (AUCs)/Dose

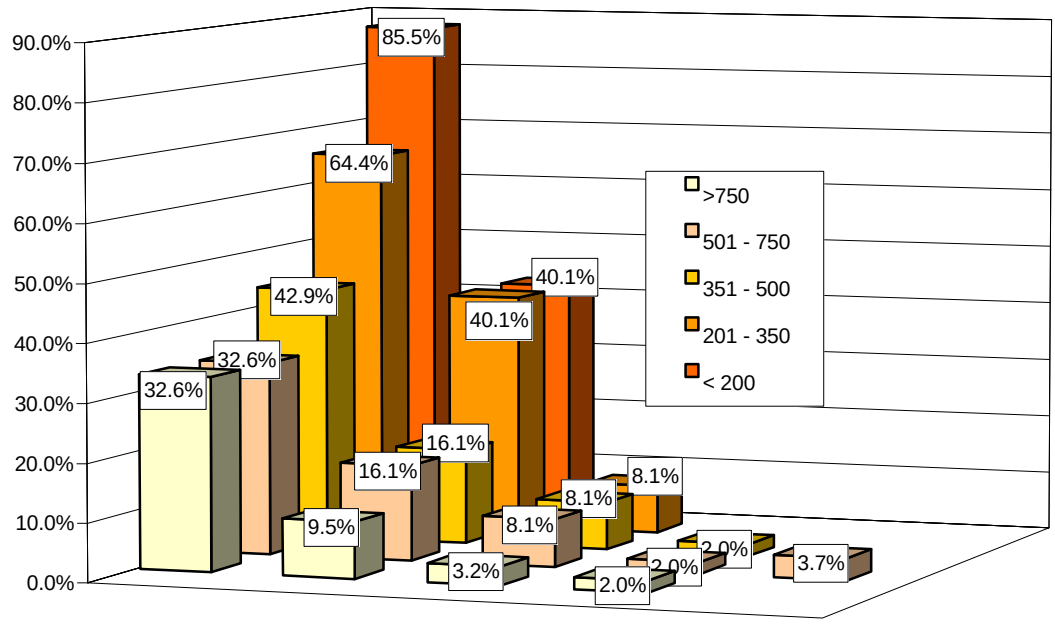
Drug Affected	Nevirapine	Delavirdine	Efavirenz
Indinavir (IDV)	Levels: IDV ↓ 28% NVP no effect Dose: IDV 1000 mg q8h	Levels: IDV ↑ >40% DLV no effect Dose: IDV 600 mg q 8h DLV: standard	Levels: IDV ↓ 31% Dose: IDV 1000mg q 8h
Ritonavir (RTV)	Levels: RTV ↓ 11% NVP no effect Dose: Standard	Levels: RTV ↑70% DLV: no effect Dose: DLV: standard RTV: no data	Levels: RTV ↑ 18% EFV ↑ 21% Dose: RTV 600 mg bid (500 mg bid for intolerance)
Saquinavir (SQV)	Levels: SQV ↓ 25% NVP no effect Dose: No data	Levels: SQV ↑ 5X+ DLV no effect Dose: Fortovase 800 mg tid, DLV standard (monitor transaminase levels)	Levels: SQV ↓ 62% + EFV ↓ 12% Co-administration not recommended
Nelfinavir (NFV)	Levels: NFV ↑ 10% NVP no effect Dose: Standard	Levels: NFV ↑ 2x DLV↓ 50% Dose: No data (monitor for neutropenic complications)	Levels: NFV ↑ 20% Dose: Standard
Amprenavir (APV)	No data	No data	Levels:APV AUC ↓ 36% Dose: APV 1200 mg tid as single PI, or 1200 mg bid + RTV 200 mg bid
Nevirapine (NVP)	•	No data	No data
Delavirdine (DLV)	No data	•	No data

+ Conducted with Invirase

Table XVII. Drugs Available Through Treatment Investigational New Drug Protocols

Drug	Adefovir (Preveon) *	Tenofovir Disoproxil Fumarate (Tenofovir DF)	ABT-378/ritonavir (ABT-378/r)
Source	Gilead 800-GILEAD-5	Gilead Compassionate Access Study 1-800-GILEAD-5 or 1-800-276-0231	Abbott Early Access Program 1-888-711-7193
Class	Nucleotide RT Inhibitor	Nucleotide Reverse Transcriptase Inhibitor	Protease Inhibitor
Usual Dose	60 mg po qd or 120 mg po qd + L-carnitine 500 mg po qd	300 mg po qd	(ABT-378 400mg + ritonavir 100mg) po bid
Side Effects (major)	Proximal renal tubular dysfunction, nausea, elevated LFTs	elevation of creatine phosphokinase, elevation of transaminases	nausea, diarrhea, skin rash, hyperlipidemia, elevation of transaminases
Comments	Activity vs. HBV, CMV, HSV	▪ Eligibility of patients with prior history of adefovir-induced nephrotoxicity will be determined on a case by case basis ▪ Also active against Hepatitis B	▪ Concomitant use with amprenavir, indinavir, nelfinavir, or saquinavir allowed ▪ Concomitant use with ritonavir and delavirdine prohibited
Enrollment Criteria	Failure or intolerance with current therapy; absence of clinically significant renal dysfunction and no concurrent use of nephrotoxic drugs	▪ HIV-RNA $\geq$ 10,000 copies/mL ▪ CD4 $\leq$ 50 cells/μL or, ▪ CD4 > 50 and $\leq$ 200 cells/μL with documented AIDS-defining OI within 90 days ▪ Serum creatinine < 1.5 mg/dL ▪ No concomitant nephrotoxic drugs	▪ Documented failure and/or intolerance to $\geq$ 2 PI ▪ HIV-RNA $\geq$ 10,000 copies/mL within 3 months ▪ CD4 $\leq$ 200 cells/μL within 3 months

* No longer in development



MACS bDNA:	>30K	10K-30K	3K-10K	501-3K	<500
RT -PCR:	>55K	20K-55K	7K-20K	1.5K-7K	<1500

Plasma Viral Load (copies/ml)

Figure 1. Likelihood of developing an AIDS-related illness in three years. Viral load represents the actual data obtained on the specimens from the MACS cohort as well as the values showing the equivalent expected RT-PCR values. Values shown in this figure differ slightly from those in Table V because better discrimination of outcome was achieved by re-analysis of the data using viral load as the initial parameter for categorization followed by CD4+T lymphocyte stratification of the patients. (Adapted from reference 4.)