Pocket Guide

Adult HIV/AIDS Treatment

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Pocket Guide to Adult HIV/AIDS Treatment

2006

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Important Information for the Users of This Pocket Guide

This document is provided as an information resource for physicians and other health care professionals to assist in the appropriate treatment of patients with HIV/AIDS. Recommendations for care and treatment change rapidly, and opinion can be controversial; therefore, physicians and other health care professionals are encouraged to consult other sources, especially manufacturers' package inserts, and confirm the information contained on these tables. The individual physician or other health care professional should use his/her best medical judgment in determining appropriate patient care or treatment because no single reference or service can take the place of medical training, education, and experience. Although these tables have been carefully prepared and reviewed the author makes no warranty as to the reliability, accuracy, timeliness, usefulness or completeness of the information. The data presented herein is for informational purposes only. Determination of appropriate treatment is the responsibility of the treating physician.

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The Pocket Guide has been developed as a resource primarily for the AIDS Education and Training Centers. For US colleagues, requests for individual or small quantities of the Pocket Guide may, therefore, be addressed to your local AETC. The locations of your local AETC may be found at: http://www.aids-ed.org/. Other order information may be addressed to:

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Abbreviations Used in this Pocket Guide to HIV/AIDS Treatment

Drug Abbreviations	
ABC: Abacavir (*Ziagen*)	LPV/r: Lopinavir/Ritonavir (*Kaletra*)
APV: Amprenavir (*Agenerase*)	NAAT: Nucleic Acid Amplification Test
ATV: Atazanavir (*Reyataz*)	NFV: Nelfinavir (*Viracept*)
AZT: Zidovudine (*Retrovir*)	NNRTI: Non-nucleoside Rev Trans. Inhib.
ddI: Didanosine (*Videx*)	NRTI: Nucleoside Rev. Trans. Inhib.
d4T: Stavudine (*Zerit*)	NVP: Nevirapine (*Viramune*)
ddC: Zalcitabine (*Hivid*)	PI: Protease Inhibitor
DLV: Delavirdine (*Rescriptor*)	/r: Ritonavir <400 mg/d.
EFV: Efavirenz (*Sustiva*)	RBT: Rifabutin (*Mycobutin*)
FTC: Emtricitabine (*Emtriva*)	RTV: Ritonavir (*Norvir*)
ENF: Enfuvirtide (*Fuzeon, T-20*)	SQV: Saquinavir (*Invirase*)
FPV: Fosamprenavir (*Lexiva*)	3TC: Lamivudine (*Epivir*)
IDV: Indinavir (*Crixivan*)	TDF: Tenofovir (*Viread*)
INH: Isoniazid	TMP-SMX: Trimethoprim sulfamethoxazole
INV: Invirase (saquinavir, HGC)	TPV: Tipranavir (*Aptivus*)
IVIG: Intravenous immune globulin	VZIG: Varicella zoster immune globulin
Miscellaneous Abbreviations	
ART: Antiretroviral Therapy	q: every
EC: Enteric Coated	qd: daily
HAART: Highly Active Antiretroviral Therapy	qid: four times per day
IV: Intravenous	qm: monthly
IM: Intramuscular	qod: every other day
VL: Viral Load	qw: every week
bid: twice per day	soln: solution
biw: twice per week	tid: three times per day
hs: bedtime (hour of sleep)	tiw: three times per week
mo: month	TAMS: thymidine analogue assoc. mutations
po: by mouth	ULN: upper limit of normal

Baseline Evaluation Table 1. Laboratory Tests

Test	Comment
HIV Serology	• Sensitivity and specificity standard serology is >99% - False positives: Human error - False negatives: Usually "window period" • Acute HIV: HIV RNA level >10,000 c/mL; confirm seroconversion • Rapid tests: Confirm positives
CD4	• Reproducibility: 95% CI = 30% • False high levels – splenectomy (use CD4%) concurrent HTLV-1 • Repeat every 3-6 months • % - CD4 >500 = >29%, 200-500 = 14-28%, <200 = <14%
HIV Viral Load	• Reproducibility: 95% CI = 0.3 $\log_{10}$ c/mL or 50% • Repeat every 3-4 months
CBC	• Repeat every 3-6 months; more frequently as indicated • Macrocytosis with AZT and d4T
Chemical Profile	• Include LFT and renal function • Repeat LFT with all PIs and NNRTIs, ETOH and hepatitis • Repeat renal function with IDV & TDF
Hepatitis Screen	• Anti-HCV, anti-HAV, anti-HbsAg (if prior vaccine) or anti-HBcAg • Abnormal LFT: get anti-HCV & HBsAg • Positive anti-HCV: get quantitative HCV • Neg anti-HBs: Vaccinate for HBV • Pos HBsAg or anti-HCV: get LFTs • Neg anti-HAV: HAV vaccine routine
Fasting Lipid Profile and Glucose	• Patient at risk • Baseline for HAART; repeat at 3-4 mo and then yearly
Toxoplasma IgG	• 10-15% positive in U.S.
PPD	• Indicated if no history of TB or prior pos. PPD • Induration >5 mm is indication for INH x 9 mo
PAP smear	• Baseline, at 6 months and then annual; if "inadequate" – repeat; if atypia – refer to gynecologist
Chest x-ray	• Indicated with pulmonary sx, positive PPD or history of chest disease; some do baseline X-ray routinely.
Urinary NAAT for Gonorrhea & Chlamydia	• "Consider" in sexually active patients (see STD/HIV Table 1) • Repeat at 6-12 month intervals depending on risk
VDRL	• Baseline and repeat annually in sexually active patients • Confirm positives with FTA-ABS
Renal Screen	• Urinalysis and creatinine • If ≥1+ proteinuria or elevated creatinine: quantify urine protein and do renal ultrasound.

Baseline Evaluation Table 2. Prevention of HIV for HIV Providers
(DHHS Prevention Guidelines)

Prevention-Three Steps

Step 1: Screen for risk behaviors
- Behaviors and clinical factors associated with HIV, other STDs, and IV drug use (repeat at every visit)
- STD symptoms: Most are asymptomatic (repeat query at every visit)
- Pregnancy test (if indicated)
- Screening tests

Patients	Test
Routine	
All patients	Syphilis serology - RPR or VDRL*
All women	Trichomonas wet mount or culture
All women ≤25 years and sexually active	Cervical specimen for *C. trachomatis*
Consider	
All men and women, if sexually active	Screening for GC and C. trachomatis by urethral (men) or cervical (women) specimen or first catch urine for NAAT*
Anal receptive sex	Consider anal swab for GC culture and, if available, for *C. trachomatis*
Oral receptive sex	Consider pharyngeal culture for GC
Possible pregnancy	Pregnancy test

* Repeat RPR or VDRL annually. Consider repeating screening tests for *N. gonorrhoeae* and *C. trachomatis* annually or more frequently if sexually active, if previous screening test positive, or other high risk.

Step 2: Behavioral Interventions
- **Prevention messages** should be provided with each visit
- **Communicate factors that influence transmission** and risk reduction; i.e. abstinance, sex with condoms, sex exclusively with HIV-infected person(s) (with precautions to prevent superinfection). Also stress reduced efficacy of oral contraceptives with PIs and NNRTIs. Stress proper condom use.

- **IDU (Risk of needle sharing is 67 transmissions per 10,000 exposures)**
  - **Encourage to stop using drugs ± enter substance abuse treatment**
  - **If patient continues to use drugs:**
    - Never reuse or share needles, water, or drug preparation equipment.
    - Use only syringes from reliable sources (pharmacies).
    - Use new syringe; if not possible-boil or disinfect with bleach (http://www.cdcnpin.org)
    - Use sterile water to prepare drugs; otherwise use tap water.
    - Use new or disinfected cooker and new cotton
    - Clean injection site with new alcohol swab.
    - Safely dispose of needle.

- **Sexual Activity**
  - **Risk of HIV transmission per 10,000 exposures (assumes no condom use) [***MMWR Morb Mortal Wkly Rep* **2005,54(RR-2)]**

insertive fellatio	0.5
receptive fellatio	1
insertive vaginal sex	5
receptive vaginal sex	10
insertive anal sex	6.5
receptive anal sex	50

  - **Condom vs no condom:** Risk is 20X greater without condoms.
  - **Viral load:** Each $\log_{10}$ reduction in viral load reduces probability of transmission 2.5 fold.
  - **Early stage disease:** Risk is increased about 10-fold per coital act during acute HIV infection (prior to seroconversion).
  - **HAART recipients:** Decreases in VL probably reduces risk but transgression in behavior (such as not using condoms) eliminates this benefit. If treatment is discontinued for any reason, warn patient that viral load increases as does risk of transmission.

Step 3: Partner Counseling and Notification

- **Laws:** Follow local and state laws for reporting sex and needlesharing partners.
- **Initial Visit:** Ask if all sex and needle sharing partners have been notified.
- **Follow-ups:** Ask about new sex or needlesharing partners who have not been notified.
- **Referrals:** All contacts should be referred to the health department to arrange for notification and testing without identifying source. Patients who elect not to notify partners should be referred to the health department to conduct these activities.

Drug Information

This section contains information about antiretroviral drug characteristics, interactions with other drugs and adverse effects. Additional detailed information is contained in Bartlett JB and Gallant JG *Medical Management of HIV Infection*, 2005-2006, Johns Hopkins Medicine Health Publishing Business Group. Additional sources of information are the National Institute of Health's AIDSInfo web site: http://www.aidsinfo.nih.gov/ as well as the drug "package inserts" which are usually available on the manufacturers' web sites as "full prescribing information."

Drug Table 1. Antiretroviral Agent Characteristics
(Most common and/or important toxicities are in *italics*.)

Drug Name	Form	Usual Adult Dose		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Abacavir (ABC, *Ziagen*)	300 mg tab; (see also: *Trizivir* and *Epzicom*) 20 mg/mL po soln.	300 mg bid or 600 mg qd		
***Combivir* (CBV)**	AZT 300 mg + 3TC 150 mg (tab)	1 bid		
Didanosine (*Videx*; *Videx EC*; ddI)*	Buffered tabs: 25, 50, 100, 150, 200 mg Buffered powder: 100, 167, 250 mg EC caps: 125, 200, 250, and 400 mg		>60 kg	<60 kg
		Tabs	400 mg qd or 200 mg bid	250 mg qd or 125 mg bid
		Powder	250 mg bid	167 mg bid
		EC Caps	400 mg qd	250 mg qd (pref.)
		With TDF	250 mg qd	200 mg qd
Emtricitabine (*Emtriva*, FTC)	200 mg cap 10 mg/mL po soln	200 mg qd (cap) 24 mL (240 mg) qd (liquid)		
Epzicom	ABC 600 mg + 3TC 300 mg	1 tablet qd		
Lamivudine (*Epivir*; 3TC)	150, 300 mg tab (see also: *Combivir*, *Trizivir* & *Epzicom*) 10 mg/mL po soln.	150 mg bid or 300 mg qd		
Stavudine (*Zerit*; d4T)*	15, 20, 30, 40 mg cap; 1 mg/mL po soln.	Wt >60 kg: 40 mg bid Wt <60 kg: 30 mg bid		
Tenofovir (*Viread*, TDF)	300 mg tab (see also: *Truvada*)	300 mg qd		
Trizivir	AZT 300 mg + 3TC 150 mg + ABC 300 mg (tab)	1 bid		
Truvada	TDF 300 mg + FTC 200 mg	1 tablet qd		

* The comb. of ddI & d4T should be avoided, especially in pregnant women.
‡ Drug change or dose change could be considered on a case-by-case basis noting the risk of resistance with underdosing.
§ Class adverse reaction – lactic acidosis with steatosis. (see pg 19).

	Food Effects	Renal Failure Dosing			Liver Failure Dosing	Toxicity (main toxicity – *italics*)
		CrCl 30-59 mL/min	CrCl 10-29 mL/min	CrCl <10 or dialysis		
	No effect	Standard			Usual	*Hypersensitivity*- fever, rash, GI sx, dyspnea§ ¶¶ Do not rechallenge.
	No effect	Fixed Formulation not recommended			Usual	AZT side effects§ HBV flare##
	Take 1/2 hr before or 2 hr after meal Separate dosing of IDV, RTV, DLV, ATV	>60 kg 200 mg/d <60 kg 125 mg/d	>60 kg 125 mg/d <60 kg 100 mg/d	>60 kg 125 mg/d <60 kg 75 mg/d¶	Usual	*Pancreatitis, peripheral neuropathy*, GI intolerance§
	No effect	200 mg q 48h 120 mg qd (liquid)	200 mg q 72h 80 mg qd (liquid)	200 mg q 96 h¶ 60 mg qd (liquid)	Usual	Minimal. Skin hyperpigmentation§ HBV flare##
	No effect	Not recommended in renal failure			Usual	ABC hypersensitivity¶¶ Do not rechallenge. HBV flare##
	No effect	150 mg qd	150 mg x 1 then 100 mg/d	150 mg x 1 then 25-50 mg/d¶	Usual	Minimal. HBV flare##
	No effect	>60 kg-20 mg q 12 h <60 kg-15 mg q 12 h	>60 kg-20 mg q 24 h <60 kg-15 mg q 24 h	>60 kg-20 mg q 24 h <60 kg-15 mg q 24 h¶	Usual	*Peripheral neuropathy, Pancreatitis, hyperlipidemia, lipoatrophy,* ascending paresis (rare)§
	No effect	300 mg q 48 hr	300 mg 2 days/wk	300 mg q 7 days¶	Usual	Fanconi syndrome +/- renal failure (rare)§, HBV flare##
	No effect	Fixed formulation not recommended in renal or hepatic failure				*Hypersensitivity reaction (ABC), bone marrow suppression (AZT),* GI Intolerance (AZT)§
	No effect	1 tab q 48h	Not recommended		Usual	TDF renal toxicity (rare) HBV flare##

¶ Give post dialysis
¶¶ Registry for hypersensitivity reactions 800-270-0425
Patients with chronic HBV (HbsAg) may have flare if TDF, 3TC, or FTC are discontinued or if HBV becomes resistant.

Drug Table 1. Antiretroviral Agent Characteristics (Cont'd.)
(Most common and/or important toxicities are in *italics*.)

Drug Name	Form	Usual Adult Dose
Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Cont'd.)		
Zalcitabine (*Hivid*; ddC)	0.375, 0.75 mg tab	0.75 mg tid
Zidovudine (*Retrovir*, AZT)	100 cap, 300 mg tab; (see also: *Combivir* & *Trizivir*) 10 mg/ mL IV soln. 10 mg/ mL po soln.	300 mg bid 200 mg tid
Protease Inhibitors (PIs) Doses with/without RTV Boosting (see Drug Table 13)		
Atazanavir (*Reyataz*, ATV)	100, 150, and 200 mg capsules	400 mg qd; ATV 300 mg/RTV 100 mg qd. RTV boosting is required if ATV is combined with TDF or EFV and often preferred.
Fosamprenavir (FPV, Lexiva)	700 mg tabs	1400 mg bid or 700 mg/RTV 100 mg bid or 1400 mg/RTV 200 mg qd (treatment naïve only)
Indinavir (IDV, *Crixivan*)	100, 200, 333, 400 mg caps	800 mg q 8 h; separate buffered ddI ≥1 hr; IDV 400 mg/RTV 400 mg bid or IDV 800 mg/RTV 100-200 mg bid
Lopinavir/ Ritonavir (LPV/r, *Kaletra*)	LPV 200 mg + RTV 50 mg (tab); LPV 80 mg + RTV 20 mg/ mL po soln (42% alcohol)	400 mg LPV + 100 mg RTV (2 tabs) bid or 800 mg LPV + 200 mg RTV (4 tabs) qd§ Soln: 5 mL bid or 10 mL qd$ With EFV or NVP: LPV/r 600/150 (3 tabs) bid

** Childs-Pugh score
$ QD regimen only for treatment naïve patients not taking EFV or NVP.
# See Drug Tables 11 & 12 for dosing recommendations when using dual PI or PI plus NNRTI.

	Food Effects	Renal Failure Dosing			Liver Failure Dosing	Toxicity (main toxicity – *italics*)
		CrCl 30-59 mL/min	CrCl 10-29 mL/min	CrCl <10 or dialysis		
	No effect	Standard	0.75 mg bid	0.75 mg qd	Usual	*Peripheral neuropathy,* Stomatitis§
	No effect	300 mg bid	300 mg qd or 300 mg bid	300 mg qd	200 mg bid	*Anemia, neutropenia,* headache, asthenia, GI intolerance§
	Take with food. Avoid concurrent buffered ddI, antacids.	Standard			CPS** 7-9: 300 mg qd CPS** >9**: Avoid	Benign increase in indirect bilirubin, increase in ALT/AST, GI intolerance, prolongation of QTc; caution with conduction defects or drugs that do this (e.g. clarithromycin)‡‡
	No effect	Standard			CPS** 5-8: 700 mg bid CPS** >9: Avoid	*Rash* (caution with severe sulfa allergy), increase in ALT/AST, GI intolerance, headache, hepatitis‡‡
	1 hr before or 2 hr after meal unless with RTV	Standard			600 mg q 8 h	GI intolerance Nephrolithiasis, increase in ALT/AST, benign increase in indirect bilirubin, paronychia‡‡
	Take with food	Standard			§§	GI Intolerance (esp. diarrhea), increase in ALT/AST, asthenia‡‡

§§ More frequent monitoring required. Drug change or dose change could be considered on a case-by-case basis noting the risk of resistance with underdosing

‡‡ Class adverse effects include lipodystrophy with hyperglycemia, fat redistribution, hyperlipidemia, and possible increased bleeding with hemophilia. ATV does not cause Hyperlipidemia. All PIs may cause hepatitis (see Drug Table 3).

Drug Table 1. Antiretroviral Agent Characteristics (Cont'd.)
(Most common and/or important toxicities are in *italics*.)

Drug Name	Form	Usual Adult Dose
Protease Inhibitors (PIs) (Cont'd) Doses with/without RTV Boosting (see Drug Table 13)		
Nelfinavir (NFV, *Viracept*)	250, 625 mg tabs 50 mg/g powder	1250 mg bid or 750 mg tid
Ritonavir (RTV, *Norvir*)	100 mg caps 600 mg/ 7.5 mL po soln	600 mg q12h #; separate ddI ≥2 h
Saquinavir (SQV, *Invirase*)††	200, 500 mg caps	SQV 400 mg + RTV 400 mg bid or SQV 1000 mg + RTV 100 mg bid or SQV 2000 mg + RTV 100 mg qd
Tipranavir (TPV, *Aptivus*)	250 mg caps	500 mg bid + RTV 200 mg bid
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Delavirdine (DLV, Rescriptor)	100, 200 mg tabs	400 mg tid Separate buffered ddI or antacid ≥1 h
Efavirenz † (EFV, Sustiva)	50, 100, 200 mg caps, 600 mg tabs	600 mg hs
Nevirapine$$ (NVP,Viramune)	200 mg tabs 50 mg/5 mL po susp.	200 mg qd x14 days, then 200 mg bid
Fusion Inhibitors		
Enfuvirtide (ENF, Fuzeon, T-20)	90 mg single-use vials to be reconstituted with 1.1 mL H_20	108 mg (1 mL) SQ q12h into upper arm, anterior thigh or abdomen (Rotate sites).

† Efavirenz should be avoided in first trimester of pregnancy and used with caution in women with reproductive potential.

†† *Invirase* taken with ritonavir. Invirase not recommended as sole PI.

$$ Nevirapine should be avoided in women with a baseline CD4 count >250 cells/mm^3 due to high rate of symptomatic hepatitis (11%).

	Food Effects	Renal Failure Dosing			Liver Failure Dosing	Toxicity (main toxicity – *italics*)
		CrCl 30-59 mL/min	CrCl 10-29 mL/min	CrCl <10 or dialysis		
	Take with meal.	Standard			§§	Diarrhea, increased ALT/AST‡‡
	Food improves GI tolerance	Standard				GI intolerance, paresthesia, increased ALT/AST, taste perversion‡‡
	Take within 2 hrs of meal	Standard			§§	GI intolerance, increased ALT/AST‡‡
	Take TPV/r with meal	Standard			Avoid with mod-severe liver disease	Hepatitis, increased ALT/AST, rash (caution with severe sulfa allergy), GI intolerance‡‡
	No effect	Standard			§§	Rash, increased ALT/AST
	Take on an empty stomach	Standard			§§	CNS x 2-3 wk, Rash, increased ALT/AST, false + cannibinoid test
	No effect	Standard		Standard; give post dialysis	Avoid with moderate to severe hepatic disease	Rash, increased ALT/AST, hepatic necrosis, esp. in females with a baseline CD4 >250 cells/mm^3 $
	N/A	Standard			Usual dose	Site reactions, bacterial pneumonia

§§ More frequent monitoring required. Drug change or dose change could be considered on a case-by-case basis noting the risk of resistance with underdosing

‡‡ Class adverse effects include lipodystrophy with hyperglycemia, fat redistribution, hyperlipidemia, and possible increased bleeding with hemophilia. ATV does no cause Hyperlipidemia.

Drug Table 2. Adverse Reactions to Antiretroviral Agents

LIFE THREATENING REACTIONS	
Hepatic necrosis	
Agent	NVP
ADR Features	Abrupt onset flu-like illness with GI symptoms, fever, rash (50%), eosinophilia and hepatic necrosis usually in first 6-18 weeks of NVP; may be drug rash, eosinophilia, and systemic symptoms.
Frequency	1-2% of all NVP recipients. Rate of symptomatic hepatitis is 11% in treatment-naïve women with baseline CD4 count >250 cells/mm^3 and 6% in men with baseline CD4 count > 400 cells/mm^3.
Monitor	Patient warning. ALT: Baseline and at 2, 4, 8, 12, 16 weeks then q 3 months.
Intervention	Promptly d/c ART, but may progress despite this. Supportive care (steroids, antihistamines appear useless).
Cutaneous: Steven-Johnson Syndrome and Toxic Epidermal Necrolysis	
Agent	NVP, less common is EFV (reported with FPV, ABC, ddI, LPV, AZT, ATV and IDV).
ADR Features	Usually first few weeks with fever, myalgia, skin rash with blistering ± mucous membrane involvement.
Frequency	NVP 0.5-1%, EFV 0.1%.
Monitor	Patient warning.
Intervention	Promptly discontinue ART if mucous membrane involved, conjunctivitis, blisters, bullae, and/or system symptoms. Intensive care of wounds including pain meds and antibiotics and IVs; may require treatment in a burn center. Use of steroids is controversial.
Lactic acidosis	
Agent	d4T + ddI > ddI > d4T > AZT (Rare or never with ABC, TDF, 3TC, and FTC); long duration use.
ADR Features	GI symptoms, wasting, fatigue, ± multiorgan failure, pancreatitis, respiratory failure.
Frequency	1-10 per 1,000 patient-years for d4T, ddI or AZT.
Monitor	Clinical symptoms. No routine lactate levels, but obtain if clinically indicated; normal level is <2.0 mMol/L. Surrogate for lactic acid levels: High CPK and ALT; low HCO3; anion gap
Intervention	Promptly discontinue ART; supportive care with mech. Ventilation, dialysis, etc. Recovery may take months. Long-term residual effects are common. For ART avoid NRTI or use ABC, 3TC, FTC, and/or TDF.

LIFE THREATENING REACTIONS (CONT'D.)	
Hypersensitivity	
Agent	ABC.
ADR Features	Symptoms (in rank order): high fever, diffuse skin rash, nausea, headache, add. Pain, diarrhea, arthralgias, pharyngitis, and dyspnea. Virtually all have ≥ systems involved (may help distinguish common intercurrent illnesses). Median onset: day 9 of ABC; 90% in first 6 weeks.
Frequency	4-9% of ABC recipients. Genetic predisposition defined for some and possibly most patients.
Monitor	Patient warning (in questionable cases may want to administer next dose under observation – this reaction always progresses with next dose).
Intervention	D/C ABC. Never re-challenge (if dx is probable). Supportive care (steroids and antihistamines are not useful). Symptoms usually resolve in 48 hrs after d/c ABC.
SERIOUS REACTIONS	
Pancreatitis	
Agent	ddI + d4T > ddI > d4T, ddC (3TC in children).
ADR Features	Abdominal pain with elevated amylase and/or lipase.
Frequency	ddI 1-7%. Appears to be less frequent in HAART era. More frequent with other risks–especially alcoholism, hx pancreatitis, concurrent d4T, ddI and TDF without ddI dose adjustment.
Monitor	Patient warning. Amylase with clinical symptoms.
Intervention	Supportive care, pain meds and bowel rest (NPO).
Nephrotoxicity – Fanconi syndrome	
Agent	TDF.
ADR Features	Renal failure ± Fanconi syndrome. Note: increased creatinine, hypophosphopatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis.
Frequency	Occurs primarily in patients who have inadequate dose adjustment of TDF with baseline renal dysfunction.
Monitor	Urinalysis and creatinine or BUN at 3-6 month intervals (?) Also of interest are serum K and PO_4. (Note: This reaction may be more common in African-American males).
Intervention	Supportive care. D/C TDF.

Drug Table 2. Adverse Reactions to Antiretroviral Agents (Cont'd.)

SERIOUS REACTIONS (CONT'D.)	
Renal calculi	
Agent	IDV.
ADR Features	Renal colic, abdominal pain, hematuria. UA shows RBC, pyuria,and crystals.
Frequency	5-35%; correlates with high peak IDV blood level.
Monitor	Urinanalysis ± creatinine or BUN q 3-6 month with IDV. Clinical warning. (Note-this may be more common in Africa due to dehydration).
Intervention	Prevention is hydration with ≥1.5 L/d. Manage as nephrolithiasis. IDV should be stopped or given with better hydration (Most use alternative PI or NNRTI).
Marrow suppression	
Agent	ZDV.
ADR Features	Neutropenia and/or anemia usually after weeks-months.
Frequency	Anemia 1-4%, neutropenia 2-8%. Risk increased with advanced HIV.
Monitor	CBC at baseline and q 3 months for ZDV recipients.
Intervention	Transfusion or EPO for serious anemia or GCSF for neutropenia. D/C ZDV.
Transaminasemia	
Agent	All PIs and NNRTIs.
ADR Features	Elevated ALT that is otherwise not explained (ETOH, hepatitis B, hepatitis C etc.). PI/NNRTI: mechanism is unknown. Liver biopsy usually does not show hepatic injury. Most are asymptomatic– exceptions are NVP-associated hepatic necrosis and NNRTI-associated lactic acidosis with steatosis.
Frequency	8-15% for most PIs and NNRTIs.
Monitor	ALT q 3-6 months.
Intervention	Must distinguish ALT elevations due to other drugs (lactic acidosis with steatosis due to d4T, ddI or ZDV, hypersensitivity due to ABC, or NVP hepatic necrosis) and due to other causes (hepatitis viruses, ETOH, etc.). Many D/C the PI or NNRTI if the ALT is >5x ULN (Grade 3 toxicity) or 10x ULN (Grade 4).

MISCELLANEOUS REACTIONS	
GI intolerance	
Agent	All PIs, ZDV, and ddI.
ADR Features	Nausea, vomiting, diarrhea, anorexia. Begins with first dose. Diarrhea: LPV/r, NFV, buffered ddI.
Frequency	Common.
Monitor	Patient warning.
Intervention	Symptomatic– may improve with food (except ddI and IDV without RTV); NFV and LPV/r-associated diarrhea is usually managed with Imodium calcium; many improve with continuation of treatment.
Peripheral neuropathy	
Agent	ddI, d4T, and ddC.
ADR Features	Paresthesias and pain of lower extremities at weeks to months.
Frequency	10-30% (or more) based on duration.
Monitor	Patient warning; symptoms and ankle jerk reflexes.
Intervention	D/C implicated agent. Symptomatic treatment– pain meds, foot bridge, etc. Reversible if drug stopped early. Rx pain with gabapentin, tricyclics, lamotrigine, and/or narcotics, topical lidocaine.
Rash	
Agent	NNRTIs (NVP & EFV), APV, FPV, TPV/r, and ABC.
ADR Features	Maculopapular ± pruritus.
Frequency	NVP & EFV–15%, FPV–20%, APV–20%, ABC–5%, and TPV/r–10-14%.
Monitor	Patient warning.
Intervention	R/O NNRTI associated Stevens-Johnson syndrome or TEN and ABC hypersensitivity. Also R/O rash due to HIV-associated dermatologic complications and drug rashes due to other meds especially TMP-SMX, dapsone etc. Most “treat through” maculopapular rashes.

Drug Table 2. Adverse Reactions to Antiretroviral Agents (Cont'd.)

MISCELLANEOUS REACTIONS (CONT'D.)	
CNS Toxicity	
Agent	EFV.
ADR Features	"Disconnected syndrome" with bad dreams, somnolence, impaired concentration reduced attention etc. Begins with first dose. May predispose to depression with long-term treatment.
Frequency	>50% with EFV.
Monitor	Patient warning. May wish to avoid heavy machinery operation or similar type jobs for 1st 1-2 weeks.
Intervention	Usually resolves in 2-3 weeks.
Insulin resistance	
Agent	PIs especially IDV.
ADR Features	FBS >126 mg/dL ± symptoms of diabetes.
Frequency	3-5%; higher frequency with family history of diabetes.
Monitor	FBS at baseline, 3 months, and then q 3-6 months.
Intervention	Diet and exercise, metformin or rosiglitazone (no drug interactions with PIs) if indicated; may need insulin. May switch to NNRTI regimen.
Hyperlipidemia	
Agent	PIs (except ATV) and d4T. Rank order for PIs: TPV/r>LPV/r>NFV>FPV>IDV>SQV.
ADR Features	Increase total and LDL cholesterol and triglycerides; triglycerides esp high with RTV, LPV/r and TPV/r. Begins within weeks.
Frequency	Variable.
Monitor	Fasting lipid profile at baseline, 3-6 months and then annually.
Intervention	Based on National Cholesterol Education Program (*JAMA* 2001;285:2486) See Drug Tables 6 & 7. Preferred statins: pravastatin or atorvastatin (with dose adjustment for coadministration with ARV if necessary.) Consider ART regimen change to avoid d4T and PIs other than ATV.

MISCELLANEOUS REACTIONS (CONT'D.)	
Fat atrophy	
Agent	d4T (primarily).
ADR Features	Thinning of buccal fat in face; extremities and buttocks.
Frequency	Common with long term use.
Monitor	Self image is most important.
Intervention	Discontinue d4T early if possible – changes are either slow to reverse or are irreversible. Injectable agents: poly-L-lactic acid (*Sculptra*).
Fat accumulation	
Agent	PIs.
ADR Features	Increase abdominal girth, breast size, buffalo hump.
Frequency	20-80% of those receiving HAART.
Monitor	Self image is most important.
Intervention	May change to NNRTI based regimen for cosmetic reasons; restorative surgery.

Drug Table 3. Antiretroviral Agents, "Black Box" Warnings

Agent	Reaction
Abacavir	• Fatal hypersensitivity reactions: Do not restart if hypersensitivity reaction cannot be ruled out. • Lactic acidosis and steatosis*
Amprenavir	• Oral soln. contains large amounts of propylene glycol– avoid with renal failure, hepatic failure, pregnancy, & with metronidazole
Atazanavir	None
Delavirdine	None
Didanosine	• Fatal and nonfatal pancreatitis: Do not restart • Lactic acidosis with steatosis • Fatal lactic acidosis when combined with stavudine in pregnancy
Efavirenz	None
Emtricitabine	• Lactic acidosis with steatosis* • Flare of hepatitis B (HbsAg) when antiretroviral is stopped. May need to treat HBV. • Safety and efficacy for HBV treatment is not established.
Enfuvirtide	None
Indinavir	None
Lamivudine	• Lactic acidosis with steatosis.* • Patients with HIV infection should receive only dosage and formulations appropriate for treatment of HIV. • Flare of hepatitis B (HbsAg) when antiretroviral is stopped. May need to treat HBV.
Lopinavir	None
Nelfinavir	None
Nevirapine	• Hepatotoxicity including fulminant and cholestatic hepatitis & hepatic necrosis, especially in females with baseline CD4 count >250 cells/mm^3; monitor intensively in first 18 wks of therapy. • Severe, life-threatening skin reaction including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, etc. • Do not restart if there is serious liver injury or serious drug reaction.
Ritonavir	• Potentially serious drug interactions with nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids.
Saquinavir	• Invirase can be used only with ritonavir.
Stavudine	• Lactic acidosis with steatosis • Fatal and non-fatal pancreatitis when used with ddI. • Fatal lactic acidosis when combined with Didanosine in pregnancy

* Described with NRTI class, however unlikely to occur with ABC, FTC, 3TC, and TDF.

Drug Table 3. Antiretroviral Agents, "Black Box" Warnings (Cont'd.)

Agent	Reaction
Tenofovir	• Lactic acidosis and steatosis* • Flare of hepatitis B (HbsAg) when antiretroviral is stopped. May need to treat HBV.
Tipranavir	• Clinical reports of hepatitis and hepatic decompensation with death. Increased risk of hepatitis in patients with chronic hepatitis due to HBV or HCV.
Zalcitabine	• Severe peripheral neuropathy • Pancreatitis (rare) • Hepatic failure in patients with HBV infection (rare) • Lactic acidosis and steatosis*
Zidovudine	• Hematologic toxicity– anemia & leukopenia • Prolonged use may cause myopathy. • Lactic acidosis and steatosis*

* Described with NRTI class, however unlikely to occur with ABC, FTC, 3TC, and TDF since they are least likely to cause mitochondrial toxicity *in vitro*.

Drug Table 4. National Cholesterol Education Program: Indications for Dietary or Drug Therapy for Hyperlipidemia

Coronary Heart Disease Risk Status	Goal	Threshold for diet Rx	Threshold for drug Rx
No CHD & 0-1 Risks*	LDL <160 mg/dL	LDL ≥130 mg/dL	LDL >190 mg/dL (LDL 160-190 Drug therapy optional)
No CHD & ≥2 Risks*	LDL <130 mg/dL	LDL ≥100 mg/dL	10 Yr CHD Risk <10%‡ LDL >160 mg/dL
			10 yr CHD Risk 10-20%‡ LDL >130 mg/dL

Adapted from: *JAMA* 2001; 285:2486-2497. Updated - *Circulation* 2004;110:207.

Editors Note: This table is a basic condensation of complex guidelines. Readers should consult the National Heart, Lung, and Blood Institute's web site: http://www.nhlbi.nih.gov/guidelines/cholesterol/

* CHD Risk Factors: Age (men >45 yrs; women >55 yrs or premature menopause without estrogen replacement); hypertension, current smoking, hx of cardiovascular disease in first degree relative (<55 yrs for male relative and <65 yrs for female relative), or serum HDL cholesterol <40 mg/dL. If high HDL (>60 mg/dL) subtract one risk factor.

† Atherosclerotic Cardio Vascular Disease (ASCVD) includes peripheral artery disease, symptomatic carotid artery disease, and abdominal aortic aneurysm.

‡ Calculation of 10 year risk of CHD requires tables which may be found in the *JAMA* 2001;285:2486 or the National Heart, Lung, and Blood Institute's website: http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

Drug Table 4. National Cholesterol Education Program: Indications for Dietary or Drug Therapy for Hyperlipidemia (Cont'd.)

Coronary Heart Disease Risk Status	Goal	Threshold for diet Rx	Threshold for drug Rx
CHD or CHD equivalent: • **Clinical ASCVD†** • **Diabetes mellitus** • **Multiple Risk Factors conferring 10 yr risk of CHD of >20%‡**	LDL <100 mg/dL	LDL ≥70 mg/dL	LDL >130 mg/dL (100-129 mg/dL: drug optional)
Triglycerides are an independent consideration • For patients with serum triglycerides >500 mg/dL the primary goal is reduction of triglycerides to prevent Pancreatitis and reduce risk of CHD • For patients with serum triglycerides 200-499 mg/dL reduction of non-HDL cholesterol becomes a secondary goal after reaching LDL goal.			

Adapted from: *JAMA* 2001; 285:2486-2497. Updated - *Circulation* 2004;110:207.

Editors Note: This table is a basic condensation of complex guidelines. Readers should consult the National Heart, Lung, and Blood Institute's web site: http://www.nhlbi.nih.gov/guidelines/cholesterol/

† Atherosclerotic Cardio Vascular Disease (ASCVD) includes peripheral artery disease, symptomatic carotid artery disease, and abdominal aortic aneurysm.

‡ Calculation of 10 year risk of CHD requires tables which may be found in the *JAMA* 2001;285:2486 or the National Heart, Lung, and Blood Institute's website: http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

Drug Table 5. Drug Therapy for Hyperlipidemia: Recommendations of the ACTG [Dube MP et al, *CID* 2000;31:1216]

Lipid Problem	Preferred	Alternative	Comment
Isolated high LDL	Statin*	Fibrate†	Start low doses and titrate up. With PIs watch for myopathy
High cholesterol and triglycerides	Statin* or fibrate†	Start one and add other	Combination may increase risk of myopathy
Isolated high triglycerides	Fibrate†	Statin*	Combination may increase risk of myopathy

NOTE: Optimal management of hyperlipidemia should begin with specific risk factor reduction interventions such as: low fat diet; regular exercise; moderation of alcohol intake; smoking cessation, blood pressure control, and diabetes control (where applicable). The likelihood of success with drug therapy for hyperlipidemia is substantially reduced in the absence of such interventions.

* **Statin:** Pravastatin 20 mg/day (max. 40 mg/day), fluvastatin 20-40 mg/day, or atorvastatin 10 mg/day. Use particular caution when giving LPV/r, TPV/r, or NFV with Atorvastatin; also see **Drug Table 6. Drug Interactions: Combinations That Should Not Be Used**.

† **Fibrate:** Gemfibrozil 600 mg bid ≥30 minutes before meal or
Fenofibrate tablets (e.g. *Tricor*) 160 mg qd
Micronized fenofibrate (capsules) 67 mg qd to start, max. dose 201 mg qd.

Drug Table 6. Drug Interactions: Combinations That Should Not Be Used

Class	Contraindicated Agent	ART Agents	Alternatives
Ca++ channel blocker	Bepridil	ATV, FPV, RTV, TPV	---------
Antiarrythmics	Flecainide, Propafenone	LPV/r, RTV, TPV	---------
	Amiodarone, quinidine	IDV, RTV, TPV	
Lipid lowering	Simvastatin, Lovastatin	All PIs, DLV	Pravastatin or Fluvastatin, possibly Atorvastatin Rosuvastatin
Antimyco-bacterials	Rifampin	APV, ATV, DLV, FPV, IDV, LPV/r, NFV, NVP, SQV, TPV	Use Rifabutin*
	Rifabutin	DLV, SQV (unless used with RTV)	Clarithromycin, azithromycin
	Rifapentine	All PIs, NVP, DLV, EFV	Rifampin or rifabutin
Antihistamine	Astemizole, Terfenadine	All PIs, DLV, EFV	Loratadine, Fexofenadine, Cetirizine, or Desloratadine
Antineoplastics	Irinotecan	ATV; caution with other PIs	---------
GI	Cisapride	All PIs, DLV, EFV	Reglan
	H2 blockers, proton pump Inhibitors	DLV, ATV	
Neuroleptic	Pimozide	All PIs and DLV	---------
Psychotropic	Midazolam†, Triazolam	All PIs, DLV, EFV	Temazepam or Lorazepam
	Alprazolam	DLV	
Ergot alkaloids	Ergotamine	All PIs, DLV, EFV	Consider sumatriptan
Herbs	St. John's wort	All PIs & EFV, DLV, NVP	Alternative antidepressants
Intranasal steroid	Fluticasone	RTV, LPV/r, TPV/r	Beclomethasone
Alpha adrenergic blockers	alfuzosin	RTV	Consider tamsulosin or doxazosin

* See Table 7 for Rifabutin and antiretroviral dose adjustments

† Midazolam may be used with caution as a single dose given for a procedure.

Drug Table 7. Drug Interactions: Combinations with PIs or NNRTIs Requiring Dose Modifications

Class	Agent	ART
Antifungal	Itraconazole	All PIs: monitor for toxicities LPV/r & LPV: max. Itraconasole doe ≤200 mg bid IDV– Use IDV dose of 600 mg tid (unless boosted) + max. Itraconazole dose ≤200 mg bid
	Ketoconazole	IDV– IDV 600 mg tid
		LPV/r, RTV, TPV/r, FPV/r– Ketoconazole ≤200 mg/d, FPV ≤400 mg/d
		NVP– Not recommended
	Voriconazole	IDV is OK. EFV and RTV 400 mg bid are contraindicated. No data for other PIs or NVP but potential for bidirectional inhibition. Monitor for toxicities.
Oral contraceptives	-------	Additional method of contraception recommended with: EFV, FPV, LPV/r, NFV, NVP, RTV, and TPV. (IDV & ATV are OK but no data with boosted IDV and boosted ATV. However, manufacturer still recommends alternate contraception)
		No data– SQV
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine	Avoid carbamazepine + IDV and phenytoin + LPV; all other combinations of NNRTIs or PIs & designated anticonvulsants should be given with caution and monitoring of anticonvulsant and PI levels or consider valproic acid or levetiracetam (*Keppra*)
Methadone	-------	NVP and EFV may decrease methadone substantially; monitor for withdrawal. IDV has no interaction; other PIs may decrease methadone levels and require monitoring for withdrawal but clinical significance is unclear. Methadone decreases buffered ddI levels - consider ddI EC (no interaction).
Antibiotics	Clarithromycin	RTV, LPV/r, DLV, and TPV/r– Decrease clarithromycin dose in renal failure.
		EFV, ATV – Consider azithromycin as an alternative.
Erectile Dysfunction Agents	Sildenafil	PIs & DLV: ≤25 mg q 48 hr and monitor
	Vardenafil	PIs & DLV: ≤2.5 mg q 72 hr
	Tadalafil	PIs & DLV: start with 5 mg and do not exceed 10 mg/72 hr.

Drug Table 7. Drug Interactions: Combinations with PIs or NNRTIs Requiring Dose Modifications (Cont'd.)

Class	Agent	ART
Anti-Mycobacterials	Rifabutin	All PIs with RTV boosting: standard dose PI/r + RBT 150 mg qod or 150 mg 3x/wk
		FPV 1400 mg bid + RBT 150 mg/d or 300 mg 3x/wk
		ATV 400 mg/d + RBT 150 mg qod or 150 mg 3x/wk
		EFV 600 mg/d + RBT 450-600 mg/d or 600 mg 3x/wk
		IDV 1000 mg q 8h + RBT 150 mg/d or 300 mg 3x/wk
		LPV/r 400/100 mg bid + RBT 150 mg qod or 150 mg 3x/wk
		NFV 1000 mg tid + RBT 150 mg/d or 300 mg 3x/wk
		NVP standard + RBT standard (no adjustment)
		RTV 600 mg bid + RBT 150 mg qod or 150 mg 3x/wk
		TPV/r 500/200 mg + RBT 150 mg qod or 150 mg 3x/wk
	Rifampin	All PIs & NNRTIs contraindicated except EFV (600 or 800 mg/day) using standard doses of rifampin. NVP - if necessary, use with caution and monitor LFTs
Lipid Lowering	Simvastatin	EFV: may require simvastatin dose increase.
	Atorvastatin	All PIs may substantially increase atorvastatin levels. Consider pravastatin or rosuvastatin as an alternative. With coadministration use lowest possible dose of atrovastatin (10 mg). EFV may reduce atorvastatin levels. Coadministration of EFV may require atorvastatin dose increase with close monitoring of LFTs and CPK.
	Pravastatin	No dose change for most agents. EFV, NFV, & SQV/r 400/400 mg bid: pravastatin decreased; clinical significance unknown, may need to increase pravastatin dose.

Drug Table 7. Drug Interactions: Combinations with PIs or NNRTIs Requiring Dose Modifications (Cont'd.)

Class	Agent	ART
Miscellaneous	Antacids	APV, ATV, ddC, DLV, TPV/r-separate dosing by 1 hr to avoid reduced ARV bioavailability.
	Ca++ channel blockers Bepridil	ATV, FPV, RTV, TPV– contraindicated. All PIs and DLV require dose titration and close monitoring
	All Others	All PIs and DLV require dose titration and close monitoring
	Desipramine and other TCAs	RTV– Consider desipramine dose reduction
	Diltiazem	All PIs– start diltiazem with 50% dose & monitor EKG.
	Grapefruit juice	IDV ↓, SQV ↑ Not likely to be significant with boosted PIs.
	H2 Blockers	Administered ATV 2 hrs before or 1 hr after H2 blocker.
	Ribavirin	ddI toxicity potentiated by ribavirin-avoid use
	Theophylline	RTV– Monitor theophylline levels
	Trazodone	RTV– Lowest trazodone dose & monitor CNS
	Warfarin	RTV, DLV, EFV– Monitor INR closely if given with any PI or NNRTI

Drug Table 8. Drug Interactions: Nucleosides

Drug	AZT	d4T	ddI	TDF
Methadone	AZT AUC ↑ 40%; no dose change. Monitor CBC.	d4T ↓ 27%; no dose change	Buffered ddI ↓ 61% consider ↑ ddI dose or use ddI EC	No change in methadone or TDF levels
ddI	–	Increased toxicity: pancreatitis, peripheral neuropathy and lactic acidosis. Avoid if possible.	–	ddI ↑ 44% >60 kg: 250 mg/d ddI EC <60 Kg: 200 mg/d ddI EC
Ribavirin	Monitor for severe anemia. I*n vitro* inhibition of AZT activation not shown *in vivo*.	No data	Magnifies ddI toxicity; contraindicated.	No effect on TDF levels.
ATV	AZT AUC unchanged but C_{min} ↓ 30%; significance unknown.	–	Buffered ddI– take ATV 2 hr before or 1 hr after ddI or use ddI EC– separate dosing due to food restrictions.	ATV AUC ↓ 25%; TDF AUC ↑ 24%; Avoid concomitant use unless ATV combined with RTV (ATV/r).
IDV	–	–	Buffered ddI - take 1 hr apart	–
Cidofovir, Gancyclovir, Valgancyclovir	Gancyclovir + AZT increases marrow toxicity. Monitor CBC.	–	Avoid ddI and oral gancyclovir ddI AUC ↑ 111% (po) and 50-70% (IV).	Combination may increase levels of both drugs - monitor for toxicity
LPV/r	–	–	–	TDF AUC ↑ 34%. Use standard doses and monitor for TDF toxicity.
TPV	AZT ↓ 33-43%; Clinical significance unknown.	–	Separate dose of ddI EC by ≥2 hr.	–

Drug Table 9. Co-administration of PIs and NNRTIs- Dose Adjustments

	DLV	EFV	NVP
ATV	ID	ATV 300 mg + RTV 100 mg + EFV SD	ATV 300 mg + RTV 100 mg qd + NVP SD
FPV	ID	• FPV 1400 mg qd + RTV 300 mg qd + EFV SD • FPV 700 mg bid + RTV 100 mg bid + EFV SD	FPV 700 mg + RTV 100 mg bid + NVP SD
IDV	DLV SD + IDV 600 mg q8h	• IDV 1000 mg q8h + EFV SD or • IDV 800 mg q12h + RTV 200 mg bid + EFV SD	IDV 1000 mg q8h + NVP SD
LPV/r	ID	LPV/r 600/150 mg bid + EFV SD	LPV/r 600/150 mg bid + NVP SD
NFV	ID	NFV SD + EFV SD	NVP SD + NFV SD
RTV	ID	RTV SD + EFV SD	RTV SD + NVP SD
SQV	FTV 800 mg tid + DLV SD	SQV 400 mg bid + RTV 400 mg bid + EFV SD	• SQV 400 mg bid + RTV 400 mg bid + NVP SD • SQV 1000 mg bid + RTV 100 mg bid + NVP SD
TPV	ID	TPV 500 mg bid* + RTV 200 mg bid + EFV SD	ID

All Doses in mg

Abbreviations: ID= Inadequate Data, SD= Standard Dose

* The recommendation is for TPV 500 although the study was conducted with TPV 750.

Drug Table 10. Co-administration of PIs: Dose Adjustments

Drug	FPV	IDV	LPV/r	NFV	RTV	SQV
ATV	ID	Avoid	ATV 300 mg qd + LPV/r 400/100 mg bid	ID	ATV 300 mg qd + RTV 100 mg qd	Consider ATV 300 mg + RTV 100 mg + SQV 1500 mg qd
FPV		ID	No conclusive data. Consider FPV 1400 mg bid + LPV/r 600/150 mg bid	ID	• FPV 700 mg bid + RTV 100 mg bid ***or*** • FPV 1400 mg qd + RTV 200 mg qd	ID
IDV			IDV 600 mg bid + LPV/r SD	IDV 1200 mg bid + NFV 1250 mg bid Limited clinical data.	• IDV 400 mg bid + RTV 400 mg bid ***or*** • IDV 800 mg bid + RTV 100 mg bid	ID
LPV/r				LPV/r SD + NFV 1000 mg bid		LPV/r SD + SQV 1000 mg bid
NFV					NFV 500-750 mg bid + RTV 400 mg bid	NFV SD + SQV 1200 mg bid NFV SD + SQV 800 mg tid Limited clinical data.
RTV						• RTV 400 mg bid + SQV 400 mg bid ***or*** • RTV 100 mg bid + SQV 1000 mg bid

All Doses in mg

Abbreviations: ID= Inadequate Data, SD= Standard Dose

Adult ART Table 1A. Indications for ART: DHHS Guidelines– 2004*

Clinical Category	CD4+ Count	Viral Load	Recommendation
Symptomatic (AIDS or severe symptoms)	Any Value	Any Value	Treat
Asymptomatic, AIDS	CD4+ <200 cells/mm^3	Any Value	Treat
Asymptomatic	CD4+ >200 cells/mm^3 but <350 cells/mm^3	Any Value	Offer treatment especially if VL is >20,000 c/mL, but controversial†
Asymptomatic	CD4+ >350 cells/mm^3	>100,000 c/mL	Consider Therapy or Observe† Data inconclusive for either alternative
Asymptomatic	CD4+ >350 cells/mm^3	<100,000 c/mL	Defer therapy and observe

* There are special considerations for pregnant women; consult **Pregnancy Tables 1-3**
† Patient readiness, probability of adherence, and prognosis based on CD4 count and HIV load need to be considered

Adult ART Table 1B. Indications for ART: IAS-USA Guidelines– 2004

Clinical Category	CD4+ Count	Viral Load
Symptomatic (AIDS or severe symptoms)	Treat*	––
CD4+ <200 cells/mm^3	Treat†	––
CD4+ 200-350 cells/mm^3	Consider†	Especially if CD4 count is closer to 200, VL is >50,000-100,000 c/mL, or CD4 decline is >100 cells/mm^3/yr
CD4+ 350-500 cells/mm^3	Monitor†	Consider if VL is >100,000 c/mL or CD4 decline is >100 cells/mm^3/yr
CD4+ >500 cells/mm^3	Monitor†	–

* Evidence from published prospective clinical trials
† Evidence from cohort studies

Adult ART Table 2A. Starting Regimens for Antiretroviral Naïve Patients: DHHS Guidelines– 2004

Regimens	# of pills per day
Preferred Regimens NNRTI-Based	
efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir DF)– except for pregnant women or women with pregnancy potential	2-3
Preferred Regimens PI-Based	
lopinavir/ritonavir + (lamivudine or emtricitabine) + zidovudine	6-7
Alternative Regimens NNRTI-Based	
• efavirenz + (lamivudine or emtricitabine) + (didanosine, stavudine, or abacavir)– except for pregnant women or women with pregnancy potential • nevirapine + (lamivudine or emtracitabine) + (zidovudine, stavudine*, abacavir, tenofovir or didanosine)– except with baseline CD4 count >250 cells/mm^3 in women or >400 cells/mm^3 in men	2-4 3-6
Alternative Regimens PI-Based	
• atazanavir + (lamivudine or emtricitabine) + (zidovudine, didanosine, abacavir, or stavudine*) or (tenofovir + ritonavir 100 mg) • fosamprenavir+ (lamivudine or emtricitabine) + (zidovudine, stavudine*, tenofovir, didanosine, or abacavir) • fosamprenavir/ritonavir† + (lamivudine or emtricitabine) + (zidovudine, stavudine*, tenofovir, didanosine, or abacavir) • indinavir + ritonavir† + (lamivudine or emtricitabine) + (zidovudine, stavudine*, tenofovir, didanosine, or abacavir) • nelfinavir + (lamivudine or emtricitabine) + (zidovudine, stavudine*, tenofovir, didanosine, or abacavir) • saquinavir (*Invirase*)† + ritonavir† + (lamivudine or emtricitabine) + (zidovudine, stavudine*, tenofovir, didanosine, or abacavir) • lopinavir/ritonavir + (lamivudine or emtricitabine) + (stavudine*, tenofovir, didanosine, or abacavir)	3-6 5-8 5-8 7-12 5-8 7-15 5-8
Triple NRTI Regimen – As Alternative to PI- or NNRTI-based regimens	
• abacavir + lamivudine + (zidovudine or stavudine*)	2-4

* Stavudine is associated with higher rates of lipoatrophy and mitochondrial toxicity than other NRTIs.
† Low-dose (100-400 mg) ritonavir

Adult ART Table 2B. Starting Regimens for Antiretroviral Naïve Patients: IAS-USA Guidelines– 2004

Preferred	
NNRTI Component	• Efavirenz • Nevirapine for selected patients
PI Component	• Atazanavir/ritonavir • Saquinavir/ritonavir • Lopinavir/ritonavir • Indinavir/ritonavir
NRTI Component	• (Zidovudine or tenofovir) plus (lamivudine or emtricitabine) • Didianosine plus emtricitabine
Alternatives	
PI Component	• Fosamprenavir/ritonavir • Atazanavir • Nelfinavir
NRTI Component	• Abacavir + lamivudine • Didanosine + lamivudine • Zidovudine + abacavir • Stavudine + lamivudine
Special Circumstances Only	Zidovudine, lamivudine and abacavir

Adult ART Table 2C. Starting Regimens for Resource Limited Countries: W.H.O. Guidelines– 2004

	Regimen			
Criteria	**NVP/d4T/3TC**	**NVP/AZT/3TC**	**EFV/3TC/d4T**	**EFV/AZT/3TC**
Use in pregnancy or pregnancy potential	Yes	Yes	No	No
Use in TB coinfection	Alternative regimen	Alternative regimen	Yes	Yes
Availability in fixed combination	Yes	Yes	No	No
Lab monitoring requirements	None	Hct	None	Hct

Adult ART Table 3. Advantages and Disadvantages of Initial Antiretroviral Regimens

Drugs	Advantages	Disadvantages
Non-Nucleoside Reverse Transcriptase Inhibitors		
Class	Extensive experience Less lipodystrophy Saves PI option	Low genetic barrier to resistance Class resistance Drug interactions ADR– skin rash
EFV	Potent Low pill burden, once daily dosing	CNS toxicity Teratogenic
NVP	Extensive experience with single dose in pregnancy No food effect	ADR– rash and hepatotoxicity including hepatic necrosis Contraindicated in women with baseline CD4 >250 cells/mm^3
Protease Inhibitors		
Class	Class-extensive experience Saves NNRTI option	ADR– metabolic complications Multiple drug interactions GI intolerance
ATV	Once daily dosing Low pill burden No hyperlipidemia	ADR– Jaundice & PR interval prolongation Drug interaction with TDF and EFV (can be overcome by ATV/RTV)
LPV/r	Potency Coformulated with RTV	ADR– GI intolerance Food requirement Minimal experience with and reduced levels in pregnancy
FPV/r	Low pill burden No food effect Once daily dosing	ADR– skin rash
IDV/r	No food requirement BID dosing with boosting	ADR– Nephrolithiasis Requirement for po fluid
NFV	Substantial and favorable experience in pregnancy	ADR– diarrhea High rate virologic failure Food requirement
SQV/r	Reduced pill burden with Invirase 500 mg tab. Once daily option.	ADR– GI intolerance

Adult ART Table 3. Advantages and Disadvantages of Initial Antiretroviral Regimens (Cont'd.)

Drugs	Advantages	Disadvantages
Nucleoside Reverse Transcriptase Inhibitors		
AZT/3TC/ABC	Co-formulated Minimal drug interactions No food effect Preserves PI and NNRTI options	Higher rate of virologic failure ADR-ABC hypersensitivity and AZT marrow suppression HBV flare when 3TC stopped
Nucleoside Reverse Transcriptase Inhibitor Pairs		
AZT/3TC	Extensive experience Co-formulated No food effect	ADR-GI intolerance and marrow suppression (AZT) HBV flare when 3TC stopped
d4T/3TC or FTC	No food effect Once daily	ADR of d4T† HBV flare when 3TC or FTC stopped
TDF/FTC*	Well tolerated Co-formulated Once daily	HBV flare when TDF or FTC stopped
ddI/3TC or FTC	Once daily	ADR-ddI† HBV flare when 3TC or FTC stopped Food effect
ABC/3TC*	Co-formulated Once daily No food effect	ADR-ABC hypersensitivity HBV flare when 3TC stopped

* FTC and 3TC are similar except for convenience of co-formulations; FTC has longer intracellular half life and has less extensive experience.

† ADRs– d4T lipoatrophy, hyperlipidemia, lactic acidosis, peripheral neuropathy; ddI-peripheral neuropathy, pancreatitis and lactic acidosis

Adult ART Table 4. Antiretroviral Regimens or Components That Are Not Generally Recommended

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy	• Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals	Pregnant women with HIV-RNA <1,000 c/mL using zidovudine monotherapy for prevention of perinatal HIV transmission
Two-agent drug combinations	• Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals	For patients currently on this treatment, it is reasonable to continue if virologic goals are achieved
ABC + TDF + 3TC, TDF + ddI + 3TC, NNRTI + ddI + TDF	High rate of virologic failure and resistance	No exception
Antiretroviral Components Not Recommended As Part of Antiretroviral Regimen		
Amprenavir oral solution in: • Pregnant women; • Children <4 yr old; • Patients with renal or hepatic failure; and • Patients treated with metronidazole or disulfiram	Oral liquid contains large amount of the excipient propylene glycol, which may be toxic in the patients at risk	No exception
ATV + IDV	Potential for additive hyperbilirubinemia	No exception
d4T + ddI in pregnancy	Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	When no other antiretroviral options are available and potential benefits outweigh the risks*
d4T + ZDV	Antagonistic	No exception
ddC + d4T or ddC + ddI	Additive peripheral neuropathy	No exception
Efavirenz in pregnancy	Teratogenic in nonhuman primate and humans.	When no other antiretroviral options are available and potential benefits outweigh the risks*

Adult ART Table 4. Antiretroviral Regimens or Components That Are Not Generally Recommended (Cont'd.)

	Rationale	Exception
Hydroxyurea	• Decreases CD4 count • Augments d4T- and ddI-associated side effects, such as pancreatitis & peripheral neuropathy • Inconsistent evidence of improved viral suppression • Contraindicated in pregnancy (Pregnancy Category D)	No exception
Saquinavir hard gel capsule (*Invirase*) as single PI	• Poor oral bioavailability (4%) • Inferior antiretroviral activity when compared to other protease inhibitors	No exception. SQV should only be used with RTV boosting.
FTC + 3TC	No potential benefit	No exception
Not Recommended As Part of Initial Antiretroviral Regimen		
TPV	Lack of clinical trial data when used in initial regimen	No exception
DLV	Modest antiretroviral effect.	*
RTV as single PI	GI intolerance.	*
d4T + ddI	Increased peripheral neuropathy, lactic acidosis, and pancreatitis.	*
NFV + SQV	High pill burden of 16-22 caps/day.	*
AZT + ddC	Modest antiretroviral effect.	*

* Reasonable to use only in unusual circumstances that cannot be defined.

Adult ART Table 5. Methods to Achieve Readiness to Start HAART & Maintain Adherence

Patient-related:
- Negotiate a plan or regimen that the patient understands and to which s/he commits
- Take time needed, >2 visits, to ensure readiness before 1st prescription
- Recruit family, friends, peer and community support
- Use memory aids– timers, pagers, written schedule, pill boxes/medication organizers
- Plan ahead– keep extra meds in key locations, obtain refills
- Use missed doses as opportunities to prevent future misses
- Active drug and alcohol use and mental illness predict poor adherence; race, sex, age, educational level, income, and past drug use do not.

Provider/ Health team-related:
- Educate patient re: goals of therapy, pills, food effects, and side effects
- Assess adherence potential before HAART; monitor at each visit
- Ensure access at off-hours and weekends for questions or addressing problems
- Utilize full health care team; ensure med refills at pharmacy
- Consider impact of new diagnoses and events on adherence
- Provide training updates on adherence for all team members and utilize team to reinforce adherence
- Monitor adherence and intensify management in periods of low adherence
- Educate volunteers, patient community representatives

Regimen-related:
- Avoid adverse drug interactions
- Simplify regimen re: dose frequency, pill burden, and food requirements
- Inform patient about side effects
- Anticipate and treat side effects

Adult ART Table 6. Therapeutic Failure– Definitions

Virologic Failure	• Failure to achieve VL <400 c/mL by 24 wks or <50 c/mL by 48 wks. Note: Most patients will have a decrease in VL of ≥1 $\log_{10}$ c/mL at 1-4 weeks. • Viral suppression followed by repeated positive viral load
Immunologic Failure	Failure to increase CD4 count 25-50 cells/mm^3 during first year. Note: Mean increase is about 150 cells/mm^3 in first year with HAART in treatment naïve patients.
Clinical Failure	Occurrence or recurrence of HIV-related event ≥3 months after start of HAART. Note: Must excude immune reconstitution syndromes.

Adult ART Table 7. Management of Virologic Failure

Resistance Tests (see Table 8. Indications for Resistance Testing)

- Usually genotypic test, especially with early sequence failure (phenotype often complements genotypic tests in late stage disease.
- Testing should be done during therapy or within 4 weeks of cessation of the failed regimen.
- A viral load of >1,000 c/mL is usually required for the currently available resistance tests.

Using Resistance Rest Results

- Interpretation of resistance tests results is complex and is best done by an expert.
- Interpretation should include the history of prior antiretroviral treatments and resistance test results which may involve strains which are now minority species and not tested.
- Failure to define resistance mutations in the presence of failed treatment usually indicates non-adherence or a pharmacologic reason (e.g. malabsorbtion, drug interaction, food effect, etc.). These issues should drive the evaluation.
- For no mutation when off drugs for >4 weeks, an option is re-administration of the prior regimen with a repeat resistance test at 2-4 weeks.
- Resistance tests are best at indicating drugs that will not work rather than those that do.

Blips

Blips are defined as single VL measurements of 50-200 c/mL. Tests should be repeated but interpreted as a laboratory error and therapeutically inconsequential. Sustained elevated results should be considered virologic failure.

Viral Load Thresholds to Change Therapy

The threshold to change therapy and to define virologic failure may be different. Some thresholds used are: VL >200-400 c/mL, 500-1000 c/mL, and >5000 c/mL. There is no correct answer except that the extremes have consequences– too low may eliminate drug options, too early and too high risks evolution of multiple resistance mutations (especially NNRTIs and PIs) that also limit options. In general, the tendency is to be more aggressive with failure after limited new regimens and loss aggressive with multiple failures.

Adult ART Table 7. Management of Virologic Failure (Cont'd.)

Sequences
Expectations vary with the number of treatment regimens given for virologic failure. Best results are with the first and second regimens; subsequent regimens are less efficacious. Thus, expectations are largely dictated by the history of the magnitude and frequency of failures.
Options for Late-Stage Disease
• Therapeutic drug monitoring (merit not clearly established). • Retreating (recycling) prior regimens (not generally recommeded). • MegaHAART (regimens with up to 3 PIs and 2 NNRTIs; not generally recommeded). • New drugs: Use of enfuvirtide, tipranavir, or TMC114 (all have established merit for "salvage;" both tipranavir and TMC114 show better outcomes when combined with enfuviride). • Structured treatment interruption: there is strong evidence against this strategy • Continuation of a failed regimen. In the absence of new options, it is best to continue the failed regimen because discontinuation usually leads to rapid decrease in CD4 cell count and increase in VL. The explanation of this paradoxical response is unclear but is usually attributed to partial activity of the antiviral agents or reduced replication capacity of the virus due to resistance mutations (e.g. 184V) that are maintained by treatment.

Adult ART Table 8. Indications for Resistance Testing

Indicated	Virologic failure with VL >1,000 c/mL Suboptimal viral suppression with VL >1,000 c/mL Acute HIV infection
Consider Testing	Chronic HIV infection before initiating therapy
Not Indicated	After discontinuation of antiretroviral therapy >1 month duration Viral load <1,000 c/mL

Adult ART Table 9. Resistance Mutations: *Topics HIV Med* 2005;13:124

Drug	Codon Mutations
Nucleosides and Nucleotides	
3TC	65R, 184VI
ABC	65R, 74V, 115F, 184V
AZT	41L, 44D, 67N, 70R, 118I, 210W, 215YF, 219Q
d4T	41L, 44D, 65R, 67N, 70R, 118I, 210W, 215YF, 219QE
ddI	65R, 74V
FTC	65R, 184VI
TDF	65R
Multinucleoside Q151M	62V, 75I, 77L, 116Y, 151M
Multinucleoside 69 insertion	41L, 62V, 69 insert, 70R, 210W, 215YF, 219QE
Multinucleoside TAMS	41L, 67N, 70R, 210W, 215YF, 219QE
Non-Nucleoside Reverse Transcriptase Inhibitors	
DLV	103N, 106M, 181C, 188L, 236L
EFV	100I, 103N, 106M, 108I, 181CI, 188L, 190SA, 225H
NVP	100I, 103N, 106AM, 108I, 181CI, 188 CLH, 190A
Multi-NNRTI resistance	103N, 106M, 188L
Multi-NNRTI resistance-accumulation	100I, 106A, 181CI, 190SA, 230L

Adult ART Table 9. Resistance Mutations (Cont'd.)

Drug	Major*	Minor
Protease inhibitors		
APV, FPV	50V, 84V	10 FIRV, 32I, 46I, 47V, 54LVM, 73S, 82AFST, 90M
ATV	50L, 84V, 88S	10IFV, 16E, 20RMI, 24I, 32I, 33IFV, 36ILV, 46I, 48V, 54LVMT, 60E, 62V, 71VITL, 73CSTA, 82A, 85V, 90M, 93L
IDV	46IL, 82AFT, 84V	10IRV, 20MR, 24I, 32I, 36I, 54V, 71VT, 73SA, 77I, 90M
LPV/r	31I, 32I, 47VA, 82AFTS	10 FIRV, 20MR, 24I, 33F, 46IL, 50V, 53L, 54VL AMTS, 63P, 71VT, 73S, 84V, 90M
NFV	30N, 90M	10FI, 36I, 46IL, 71V, 77I, 82AFTS, 84V, 88I
RTV	82AFTS, 84V	10FIRV, 20MR, 32I, 33F, 36I, 46IL, 50V, 54VL, 54VI, 71VT, 77I, 90M
SQV	48V, 90M	10IRV, 54VL, 71VT, 73S, 77I, 82A, 84V
TPV	33F, 82LF, 84V	10V, 13V, 20MRV, 35G, 36I, 43T, 46L, 47V, 54AMV, 58E, 69K, 74P, 83D, 90M
Entry Inhibitors		
T-20	Gp41 envelope– 36DS, 37V, 38AM, 39R, 42T, 43D	

* Major - usually develop first; associated with decreased drug binding; Minor - also contributes to drug resistance; may affect drug binding *in vitro* less than primary mutations. Use of Major and Minor designations for NRTIs and NNRTIs has been suspended.

Pregnancy Table 1. Antiretroviral Drugs in Pregnancy– DHHS Guidelines*

Advisory	Drugs
Nucleosides and Nucleotides	
Recommended	AZT and 3TC (standard doses)
Alternatives	ddI, FTC, d4T and ABC (standard doses)
Not recommended	ddC and ddI/d4T combination
Insufficient Data to Recommend Use	TDF (concern for potential fetal bone effects)
Non-nucleoside RT Inhibitors	
Recommended	NVP (Use with caution or avoid in women with CD4 >250 cells/mm^3 who are starting ART)
Not recommended	EFV (use in second trimester can be considered); DLV
Insufficient Data to Recommend Use	DLV
Protease Inhibitors	
Recommended	NFV 1250 mg bid and SQV/r 800/100 mg bid
Alternatives	IDV/r (800/100 mg bid), LPV/r (standard dose)
Insufficient Data to Recommend Use	APV, FPV, ATV, TPV
Fusion Inhibitors	
Insufficient data to recommend use	All

* Based on Table 3 in "Recommendations for Use of Antiviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States" US Public Health Services, November 17, 2005.

Pregnancy Table 2: Antiretroviral Drugs and Specific Concerns for Pregnancy

Agent	Human Studies in Pregnancy	Concerns
Nucleosides and nucleotides		
ABC	No studies	Hypersensitivity reaction
ddI	PACTG 249-well tolerated and good pharmacokinetics	Lactic acidosis rates increased, esp. when combined with d4T
3TC	Well tolerated, good pharmacokinetics	AZT + 3TC-preferred
TDF	No studies	Primate study shows neonatal bone toxicity in 25%
ddC	No studies	Rarely used and toxic
AZT	Extensive studies showing efficacy in reducing MTCT	Possible motochondriod toxicity reported from France; not supported in US studies
Non-nucleosides		
DLV	No studies; anecdotal cases: 3/7 ectopic pregnancies	Concerns for potency and tid regimen
EFV	Teratogenic in humans and primates-FDA warning to avoid in 1st trimester	Teratogenecity
NVP	Good pharmacokinetics shown in PACTG 250 safety and efficacy of single perinatal dose to prevent transmission shown in many trials	Chronic Rx: High rate of serious adverse reactions-hepatic necrosis with baseline CD4 >250 cells/mm^3 and severe rash reactions
Protease inhibitors		
APV	No studies	Avoid oral solution (propylene glycol) Concern for pharmacokinetics
ATV	No studies	Hyperbilirubinemia Concern for pharmacokinetics
FPV	No studies	Concern for pharmacokinetics
IDV	AUC decreased 60-80% in pregnancy	Decreased AUC in pregnancy Concern for hyperbilirubinemia
LPV/r	No studies– PACTG 354 pending	Concern for pharmacokinetics
NFV	PACTG 353 showed doses of 1250 mg bid achieved therapeutic levels (but not 750 mg tid)	Concerns for potency of NFV
SQV	PACTG 386 showed SQV/r 800/100 mg bid produced adequate levels (but not SQV 1200 mg tid)	A preferred PI-based regimen. Consider SQV 1000 mg + RTV 100 mg bid (lower pill burden with 500 mg tab).
TPV	No data	

Pregnancy Table 3. Antiretroviral Regimens in Pregnant Women

A. ACTG 076 Protocol (Should be used as part of ART regimen in all pregnant women, if possible)
Antepartum: AZT 300 bid or 200 tid po, Wk 14 until delivery
Intrapartum: AZT IV 2 mg/kg over first hr. then 1 mg/kg/hr until delivery
Postpartum: (Infant): AZT syrup 2 mg/kg po q 6h (or 1.5 mg/kg q 6h IV) x 6 wks

B. Regimen for 2nd & 3rd Trimesters
Standard ART, but:
- Include AZT* according to ACTG 076 Protocol;
- Treat based upon maternal clinical/immunologic status but avoid: EFV, hydroxyurea, AZT with d4T, d4T with ddI, APV solution†
- Previously untreated pregnant women with VL <1000 c/mL and CD4 >350 cells/mm^3 may be treated with AZT monotherapy, AZT + 3TC, or HAART.

C. Choices for Untreated Women Presenting In Labor and Their Infants
NVP: 200 mg po onset labor; **Infant:** single 2 mg/kg po at 48-72 hrs;$
AZT +3TC: 600 mg po onset labor and 300 mg po q3h until delivery PLUS 3TC 150 mg po onset labor and 150 mg po q12h until delivery; **Infant:** AZT 4mg/kg po q12h PLUS 3TC 2mg/kg po q12h for 7 days
AZT: 2 mg/kg IV bolus then 1 mg/kg/hr IV infusion until delivery; **Infant:** AZT 2 mg/kg po q6h for 6 wk (ACTG 076 Protocol)
NVP + AZT: NVP:200 mg po onset labor PLUS AZT 2 mg/kg IV bolus *then* 1 mg/kg/hr IV infusion until delivery; **Infant:** NVP single 2 mg/kg po at 48-72 hrs PLUS AZT 2 mg/kg po q6h for 6 wk$

* Unless unacceptable side effects or toxicity or requires d4T-containg regimen

† **AZT & d4T:** Pharm. antagonism; do not use together. **APV** oral solution (only) is contraindicated in pregnancy because it contains large quantities of propylene glycol which cannot be metabolized in pregnancy. **D4T & ddI:** concerns about lactic acidosis; use only when other NRTIs have failed or caused unacceptable side effects/toxicity (*New Engl J Med* 1999; 340:1723). **EFV and hydroxyurea are** teratogenic.

$ If single dose NVP is given to the mother, alone or in combination with ZDV, consideration should be given to adding maternal ZDV/3TC starting as soon as possible (intrapartum or immediately postpardum) and continuing for 3 to 7 days, which may reduce development of nevirapine resistance.

Pregnancy Table 4. Management of Pregnant Patients Including C-Section

Scenario: No prior ART

- Standard clinical, immunologic and virologic evaluation and resist-ance testing (same as other pts).
- AZT (ACTG 076 Protocol), initiated after the 1st trimester, is recommended for all patients.
- If VL >1,000 c/mL or CD4 <350 cells/mm^3, HAART with AZT (ACTG 076 Protocol). If in 1st trimester consider delaying ART until after 10-12 wks gestation due to concerns for antiretroviral agents at the time of organogenesis. This risk is not established with the possible exception of EFV. See also, Pregnancy Tables 1 & 2.
- VL <1,000 c/mL and CD4 >350 cells/mm^3, consider HAART with AZT (ACTG 076 Protocol). If in 1st trimester consider delaying ART until after 10-12 wks gestation.
- If presentation is late (≥36 weeks) recommend C-section as a way to reduce transmission but counsel on risks as well.

Scenario: Currently receiving ART

- Continue therapy without interruption through labor and delivery.
- Include AZT in the regimen whenever possible.
- If in 1st trimester counsel the patient about the benefits/risks of ART; consider discontinuation until after 10-12 wks gestation
- If late in pregnancy and VL is substantially >1,000 c/mL, counsel that it is unlikely that VL will reach <1,000 c/mL before delivery and, therefore, scheduled C-section may provide additional benefit in preventing transmission of HIV.
- At delivery the infant should be started on AZT therapy (see Table 3A).

Scenario: Woman in labor, no prior treatment

Options (see Table 3C):

- Itrapartum IV AZT for mother followed by six weeks of AZT for the newborn.
- Oral AZT and 3TC during labor, followed by one week of oral AZT-3TC for the newborn;
- A single dose of nevirapine at the onset of labor, followed by a single dose of nevirapine for the newborn at age 48 hours.
- The two-dose nevirapine regimen combined with intrapartum IV AZT and six weeks of ZDV for the newborn.

Scenario: Infants Born to Mothers Who Have Received No Antiretroviral Therapy During Pregnancy or Intrapartum

- Offer the 6 wk neonatal AZT protocol and be initiated preferably within 6-12 hours of delivery.
- Infant should undergo diagnostic testing to determine need for ART.
- The mother should undergo evaluation to determine indications for ongoing ART.

C-Section Planned But Presents in Labor or With Ruptured membranes

- Initiate ACTG 076 Protocol, Intrapartum in Table 3A;
- Rapid progression of labor: vaginal delivery
- If long labor anticipated: consider C-section after loading dose of AZT OR give pitocin to expedite delivery

Pregnancy Table 5. Delivery Procedures

Procedure	Therapy
Cesarean Section	• Schedule for 38 wk. • If on ARV, IV AZT starting 3 hrs before C-section and continue all other antiretroviral drugs
Vaginal Delivery	• If on ARV give IV AZT with initiation of labor and continue all other antiretroviral drugs. • Avoid rupture of membranes, fetal scalp electrodes, forceps delivery, and vacuum extractor.

Antiretroviral Pregnancy Registry (www.APRegistry.com): This is an observational database on women who have exposure to antiretroviral drugs during pregnancy. The main goal is to determine teratogenicity. No names or other identifiers are collected.

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Pregnancy Table 6: Drugs for Opportunistic Infections in Pregnancy

Agent	Class*	Recommendation
Acyclovir	B	Treatment reserved for severe herpes or varicella; well tolerated and no consequences with >700 exposures
Albendazole	C	Teratogenic in rodents; reserve for severe microsporiodosis in 2nd and 3rd trimester
Amphotericin	B	Standard indications
Atovaquone	C	Standard indications; limited experience
Azithromycin	B	Standard indications
Cidofovir	C	Teratogenic in animals; risk in women unknown
Ciprofloxacin	C	Arthropathy in beagle dogs; not recommended in pregnancy
Clarithromycin	C	Teratogenic in animals and increased rate of abortions in women– azithromycin preferred for MAC
Clindamycin	B	Standard indications
Dapsone	C	Limited experience; may increase risk of kernicterus
Doxycycline	D	Risk to infant teeth; avoid
Erythromycin	B	Standard indications
Ethambutol	B	Appears safe in humans
Famciclovir	B	Limited data in humans; reserve for severe herpes
Fluconazole	C	Bone defects in animals; reserve for severe & established fungal infections. Ampho B often preferred
Flucytosine	C	Bone defects in animals; use only after first trimester
Foscarnet	C	Teratogenic in animals and no data in humans; use for disseminated CMV
Ganciclovir	C	Teratogenic in animals; limited but favorable experience in humans
Interferon	C	Delay treatment until after pregnancy
INH	C	Standard indications + pyridoxine
Itraconazole	C	Teratogenic in animals and concern for azoles in pregnancy; use for systemic mycosis– ampho B often preferred
Metronidazole	B	Extensive favorable experience in pregnant women standard indications
Paromomycin	C	Not absorbed; fetal toxicity unlikely
Pentamidine	C	Embryocidal in animals; limited experience in women

Pregnancy Table 6: Drugs for Opportunistic Infections in Pregnancy (Cont'd.)

Agent	Class*	Recommendation
Primaquine	C	Limited experience; theoretical risk of hemolytic anemia with G6PD deficiency
Ribavirin	X	Teratogenic in animals; not indicated in pregnancy
Rifabutin	B	Not teratogenic in animals
Rifampin	C	Teratogenic in animals; indicated for TB; vitamin K at birth
Sulfadiazine	B	Possible kernicterus if used near delivery
TMP-SMX	C	Teratogenic in rodents; avoid use in first trimester if possible
Valacyclovir	B	Prodrug of acyclovir
Voriconazole	D	Teratogenic in rodents; ampho B preferred

Pregnancy Table 7: Drugs to Avoid During Pregnancy

Agent	Class*	Recommendation
ACE Inhibitors and AR blockers	D	Consider labetalol for hypertension
Warfarin	X	Consider LMWH or heparin.
Anticonvulsants-carbamazapine, valproic acid, phenytoin, and phenobarbital	D	Can be continued if indicated. Consider alternate anticonvulsants.
HMG-CoA reductase inhibitor	D	Consider alternative (e.g. fibrinic acid, niacin)
Paroxetine	D	Consider alternative antidepressant
Miscellaneous: ergotamine, thalidomide, retinoids, Raloxifene, benzodiazepines, and misoprostol	X	Contraindicated

* Classes:
A - controlled studies show no risk
B - no evidence of risk in humans
C - risk not ruled out
D - positive evidence of risk
X - contraindicated in pregnancy

Opportunistic Infections

This section presents information about the prevention and treatment of opportunistic infections with special emphasis on tuberculosis. Additional information may be obtained from current guidelines (see References on page 3).

Adult OI Table 1. 2001 USPHS/IDSA Guidelines for Prevention of Opportunistic Infections

Pathogen	Indication	First Choice
Strongly Recommended		
P. jiroveci **(formerly** ***P. carinii*****)**	CD4 <200 cells/mm^3 ***or*** CD4 % <14, thrush, hx AIDS defining illness or FUO	TMP-SMX 1 DS/d* ***or*** TMP-SMX 1 SS/d*
Tuberculosis	See Adult OI Table 4. Latent TB	
Toxoplasmosis	+ anti-Toxoplasma IgG and CD4 <100 cells/mm^3	TMP-SMX 1 DS* qd
Mycobacterium avium **complex**	CD4 <50 cells/mm^3	Azithromycin 1200 mg/wk Clarithromycin 500 mg bid
Varicella	Chickenpox /shingles exposure + susceptible (no history of disease and varicella seronegative)	VZIG 5 vials (6.25 mL) IM <96 h post exposure

* SS= Single strength tablet, DS=Double Strength Tablet

† Dose adjusted for concurrent PI/NNRTI

‡ Rifabutin reduces levels of clarithromycin by 50% (consider Azithromycin if RBT is used)

	Alternatives	Comment
	Dapsone 100 mg/d ***or*** Dapsone 50 mg/d + pyrimethamine 50 mg/wk + leucovorin 25 mg/wk ***or*** Dapsone 200 mg + pyrimethamine 75 mg + leukovorin 25 mg/wk ***or*** Aerosol pentamidine 300 mg/mo ***or*** Atovaquone 1500 mg/d ***or*** TMP-SMX 1 DS* 3x /wk	**Immune reconstitution recommendations:** Discontinue primary & secondary prophylaxis if CD4 >200 cells/mm^3 for ≥3 mos. **Restart Prophylaxis:** Restart prohpylaxis if CD4 decreases to <200 cells/mm^3
	TMP-SMX 1 SS* qd, ***or*** Dapsone 50 mg/d + pyrimethamine 50 mg/wk + Leucovorin 25 mg/wk ***or*** Dapsone 200 mg/wk + pyrimethamine 75 mg/wk + Leucovorin 25 mg/wk ***or*** Atovaquone 1500 mg/d ± pyrimethamine 25 mg/d + Leucovorin 10 mg/d	**Immune reconstitution recommendations:** Discontinue if CD4 >200 cells/mm^3 for ≥3 mos **Restart Prophylaxis:** CD4 decreases to <100-200 cells/mm^3
	Rifabutin† 300 mg/d ***or*** Azithromycin 1200 mg/wk + Rifabutin† 300 mg/d	**Immune reconstitution recommendations:** Discontinue if CD4 >100 cells/mm^3 for ≥3 mo **Restart prophylaxis** CD4 decreases to <100 cells/mm^3
		Acyclovir has been removed from OI prophylaxis guidelines due to lack of documented efficacy

Adult OI Table 1. 2001 USPHS/IDSA Guidelines for Prevention of Opportunistic Infections (Cont'd.)

Pathogen	Indication	First Choice
Generally Recommended		
S. pneumoniae	All Patients with CD4 >200 cells/mm^3	Pneumovax
Hepatitis B	Susceptible- (anti-HBc or Anti HBs negative)	HBV vaccine series
Influenza	All Patients	Influenza vaccine
Hepatitis A	Susceptible– (anti-HAV neg) and risk: MSM, IDV, chronic liver disease inducing chronic HBV or HCV	Hepatitis A vaccine series

	Alternatives	Comment
	None	**Immune reconstitution:** Consider reimmunization if CD4 increases to >200 cells/mm^3 and initial immunization was given when CD4 <200 cells/mm^3.
	None	
	Rimantadine 100 mg bid Amantadine 100 mg bid Oseltamivir 75 mg qd	
	None	

Adult OI Table 2. Treatment of Opportunistic Infections

Infection/Organism	Treatment
Bartonella	**Preferred:** • Erythromycin 500 mg qid po or IV, or • Doxycycline 100 mg bid po or IV. **Alternative:** • Azithromycin 600 mg qd po or • Clarithromycin 500 mg bid po
Candida – Thrush	**Preferred:** • Clotrimazole troches 10 mg po 5x/d, or • Nystatin susp 5 mL qid or pastilles 4-5x/d, or • Fluconazole 100 mg qd po, or • Itraconazole oral susp 200 mg qd
Candida – Esophagitis	**Preferred:** • Fluconazole 100 mg qd (up to 400 mg) qd po or IV x 14-21d, ***or*** • Itraconazole oral soln 200 mg qd po.
Candida – Vaginitis	**Preferred:** • Topical azole x 7d, or • Topical naftifine x 7-14d, or • Topical boric acid x 14d, or • Itraconazole 200 mg bid x 1d or 3d, or • Fluconazole 150 mg x 1 po
Cryptosporidiosis	HAART
Cryptococcosis – Meningitis	**Preferred:** Amphotericin B 0.7 mg/kg qd IV plus flucytosine 25 mg/kg qid po x 2 weeks
Cytomegalovirus - Retinitis	**Preferred:** • Intraocular ganciclovir implant + valganciclovir 900 mg qd po (preferred for immediate vision threatening lesion), ***or*** • Ganciclovir 5 mg/kg bid IV x 14-21 d, then 5 mg/kg/d IV, ***or*** • Valganciclovir 900 mg bid po x 14-21 d, then 900 mg qd po, ***or*** • Foscarnet 60 mg/kg q8h IV or 90 mg/kg q 12h IV x 14-21 d; then 90-120 mg/kg IV qd, ***or*** • Cidofovir 5 mg/kg q 7d IV x 2 then 5 mg/kg q 14d IV.

	Comment
	Duration: ≥3 months; lifelong if relapse
	Fluconazole refractory: • Itraconazole oral soln 200 mg qd po, ***or*** • Ampho B 0.3 mg/kg/d IV **Relapsing disease:** Chronic fluconazole only if recurrences are frequent or disabling
	Duration: Continue azole with disabling or recurrent infection **Fluconazole-refractory:** • Caspofungin 70 mg x 1, then 50 mg qd IV x 7 d, ***or*** • Ampho B 0.3-0.7 mg/kg qd IV
	High opening pressure: • >200 mm: Drain CSF until 50% OP ***or*** • <200 mm: Repeat daily prn **Renal failure or Ampho B intolerance:** Lipid formulation amphotericin 4 mg/kg IV qd + flucytosine 25 mg/kg qid po x 2 weeks **Consolidation therapy:** Fluconazole 400 mg po qd x 8 weeks or until CSF cultures are sterile **Alternative-consolidation:** Itraconazole 200 mg bid po **Maintenance therapy:** Fluconazole 200 mg qd po **Alternative-maintenance:** • Ampho B 1 mg/kg/wk IV (if multiple relapses on azole or intolerance to azoles) • Itraconazole 200 mg qd po (if intolerant or failure with Fluconazole)
	Duration: Implant– change q 6-8 mo. **Systemic:** continue until inactive disease + CD4 >100 cells/mm^3 x 3-6 mo. **Immune recovery uveitis:** Periocular steroids or short course oral prednisone.

Adult OI Table 2. Treatment of Opportunistic Infections (Cont'd.)

Infection/Organism	Treatment
Cytomegalovirus – Colitis, Esophagitis, Pneumonia	**Preferred:** Valganciclovir (oral), ganciclovir (IV), foscarnet (IV) above doses for CMV retinitis x 14-21d
Cytomegalovirus – Neurologic Disease	**Preferred:** Ganciclovir + foscarnet above doses for CMV retinitis
Hepatitis B Virus	**Patients Requiring Tx for HIV but not HBV †** • Include (3TC or FTC) + TDF at standard doses in HAART regimen to avoid HBV flare. Note: 3TC, FTC, and TDF should not be used as the only anti-HIV drugs. **Patients Requiring Tx for HIV and HBV †** HAART plus: **Preferred:** • TDF 300 mg qd *plus* - Either 3TC 150 mg bid po ***or*** - FTC 200 mg qd **Alternative:** • Entecavir 0.5-1.0 mg qd with/without - 3TC 150 mg bid po ***or*** - FTC 200 mg qd ***or*** - TDF 300 mg qd Note: 3TC, FTC, and TDF should not be used as the only anti-HIV drugs. **Patients Requiring TX for HBV *but not* HIV †** • Adefovir 10 mg qd ***or*** • Entecavir .5 mg qd ***or*** • Peginterferon alfa 2b 180 mg SQ qw
Hepatitis C Virus	**Preferred:** Peginterferon alfa 2b 1.5 mcg/kg(or Peginterferon alfa 2a 180 mcg/kg SQ q wk) + ribavirin. Genotype 1: <75 kg - ribavirin 1000 mg; >75 kg ribavirin 1200 mg qd. Genotype 2/3: ribavirin 400 mg bid po. All therapy given for 48 weeks.
Herpes Simplex Virus – Moderate or Severe Mucocutaneous	**Preferred:** Acyclovir 5 mg/kg q8h IV, then: • Famciclovir 500 mg bid po, ***or*** • Acyclovir 400 mg 4-5x/d po when lesions begin to regress and continue until lesions healed.

† The CDC/IDSA guidelines for HBV have been updated by the author to reflect recent data.

	Comment
	Maintenance: Consider after relapse
	All patients: counseling to avoid alcohol and HBV prevention; hepatitis A vaccine to all susceptible patients; and referral for evaluation for HBV treatment. **Duration of Therapy:** ≥1 year or 6 mo. post HBeAg loss/HBe antibody gain
	Contraindication to Ribavirin: Peginterferon alone
	Acyclovir-resistant HSV: Foscarnet 120-200 mg/kg qd IV in 2-3 daily doses

Adult OI Table 2. Treatment of Opportunistic Infections (Cont'd.)

Infection/Organism	Treatment
Herpes Simplex – Keratitis	**Preferred:** Trifluridine 1% ophthalmic soln 1 drop q2h up to 9 drops/d ≤21d
Herpes Simplex – Encephalitis	**Preferred:** Acyclovir 10 mg/kg q8h IV x 14-21d
Microsporidia	**Preferred:** HAART
Mycobacterium avium	**Preferred:** Clarithromycin 500 mg bid po + ethambutol 15 mg/kg qd po ± Rifabutin 300 mg qd po for severe disease.* **Alternative to Clarithromycin:** Azithromycin 500-600 mg qd po **Third/fourth drug:** ciprofloxacin 500-750 mg bid po, levofloxacin 500 mg qd po, or moxifloxin 400 mg qd po or Amikacin 10-15 mg/kg qd IV
Mycobacterium tuberculosis	See Adult OI Table s 5-7 starting on page 68.

* Rifabutin reduces levels of clarithromycin by 50% (consider azithromycin if rifabutin is used).

	Comment
	Enterocytozoon bieneusi: Fumagillin 60 mg qd po **Microsporidia other than *E. bieneusi*:** Albendazole 400 mg bid po until CD4 >200 cells/mm^3 **Disseminated disease:** Itraconazole 400 mg qd po + albendazole with Trachipleistophora or Brachiola
	Duration: Lifelong unless: • 12 mo treatment, ***and*** • asymptomatic, ***and*** • CD4 >100 cells/mm^3 x 3-6 mo.

Adult OI Table 2. Treatment of Opportunistic Infections (Cont'd.)

Infection/Organism	Treatment
Pneumocystis jiroveci **(formerly carinii)**	**Preferred:** • TMP-SMX (15-20 mg TMP and 75-80 mg SMX) /kg q 6-8h po or IV, ***or*** • TMP-SMX 2 DS tid (TMP 5 mg/kg/tid) x 21d (14 days with rapid response + toxicity) **Alternative-Severe disease:** Pentamidine 3-4 mg/kg/d IV **Alternative-moderate or mild disease:** • Dapsone 100 mg qd + TMP 5 mg/kg tid, ***or*** • Primaquine 15-30 mg qd + clindamycin 600-900 mg IV q 6-8h (or clindamycin 300-450 mg po q 6-8hr), ***or*** • Atovaquone 750 mg bid po Duration of therapy=21 days.
Salmonella	**Preferred:** Ciprofloxacin 500-750 mg bid po (or gatifloxacin, moxifloxacin) **Alternative:** • TMP-SMX po or IV, ***or*** • Ceftriaxone, ***or*** • Cefotaxime
Toxoplasmosis	**Preferred-Acute:** Pyrimethamine 200 mg x 1 po, then 50 mg (<60 kg) or 75 mg (>60 kg) qd po + sulfadiazine 1 g (<60 kg) or 1.5 g (>60 kg) qid po + leucovorin 10-20 mg qd po x ≥6 weeks. **Alternative-Acute:** • Pyrimethamine + leucovorin (as above) +: ◦ Clindamycin 600 g q6h po or IV, ***or*** ◦ Atovaquone 1500 mg bid po, ***or*** ◦ Azithromycin 900-1200 qd po • TMP-SMX 5 mg/kg bid IV or po, ***or*** • Atovaquone 1.5 g bid po ± sulfadiazine 1-1.5 g q6h po, ***or*** • **Miscellaneous:** ◦ Pyrimethamine + leucovorin + clarithromycin 500 mg bid po ◦ 5 FU + Clindamycin; ◦ Dapsone + pyrimethamine + leukovorin ◦ Minocycline/doxycycline + either pyrimethamine or sulfadiazine or clindamycin **Preferred-Maintenance:** • Continue half dose indicated above for pyrimethamine + Sulfadiazine or clindamycin or TMP-SMX, ***or*** • Pyrimethamine 50 mg qd po + leucovorin 15 mg qd po + sulfadiazine 1 g q12h 3x/week.

	Comment
	Hypoxia (Pa02 <70 mm Hg or A-a 02 gradient >35 mm Hg): • **Prednisone:** 40 mg bid days 1-5, 40 mg qd days 6-10, then 20 mg qd days 11-21, ***or*** • IV methylprednisolone as 75% prednisone dose.
	NOTE: **Mild gastroenteritis only:** Treat 7-14d **CD4 <200 cells/mm^3 ± bacteremia:** Treat ≥4-6 weeks **Relapse:** Treat several months or until immune reconstitution

Adult OI Table 3. Immune Reconstitution Syndrome
(Adapted from: Hirsch HH, et al. *Clin Infect Dis* 2004;38:1159)

Common Features

- MAC accounts for 1/3 of all reported cases.
- Usually occurs at 1-8 weeks post HAART initiation.
- Baseline CD4 count is usually <50 cells/mm^3 and increases 2-4 fold in ≤12 months.
- May occur while treating OI or at time of OI clinical stability.
- Usual treatment is continued ART, antimicrobial therapy agents for the OI, and NSAIDS and/or steroids.
- Rapid reduction in viral load.

Agent	Clinical Features	Treatment
M. avium	Adenitis, pulmonary infiltrates, liver granuloma, mediastinitis, osteomyelitis, cerebritis, skin	ART, antibiotics, ± NSAIDS or steroids.
M. tuberculosis	Pneumonia, ARDS, adenitis, hepatitis, CNS TB, renal failure, epididymitis	ART, anti-TB meds, NSAIDS ± steroids.
M. leprae	Cutaneous	ART, dapsone.
Cryptococcus	Meningitis, palsy, hearing loss, abscess, mediastinitis, adenitis	ART, azole, steroids.
P jirovecii	Pneumonia	ART, anti-PCP meds, steroids.
HBV and HCV	Hepatitis flare	ART, ? d/c interferon or anti-HBV agents.
JC virus	CNS lesions-inflammation (MRI)	ART, steroids.
HSV	Chronic erosive ulcers, encephalitis	ART, antivirals, steroids.
Varicella	Zoster flare	ART, antivirals.
CMV	Vitritis, cytoid macular edema, uveitis, vitromacular traction	ART, steroids, vitrectomy, IVIG.
KS	Tracheal mucosal edema, obstruction	d/c ART, steroids.
HPV	Inflamed warts	Steriods, surgery.

Adult OI Table 4. Latent TB and HIV Co-Infection

Candidates For Tuberculosis Test (TST):

- All HIV-infected patients without prior positive test upon entry into HIV care.
- Repeat testing annually for HIV-infected patients at risk of acquiring TB who have no prior positive tests.
- All HIV-infected patients with prior negative skin test who are discovered to be contacts of pulmonary cases.

Indications For Treatment of Latent Tuberculosis Infection (*MMWR* 2000;49 RR-6)

- Positive PPD (≥5 mm induration) plus no prior completed prophylaxis or treatment for TB disease.
- Recent contact with TB case (Recent contacts who are initially TST negative should have TST repeated 12 weeks after last exposure to TB case. Those placed on prophylaxis should be discontinued if PPD negative at 12 weeks.)
- History of inadequately treated TB that healed

Treatment of Latent TB

- Rule out active TB based on symptoms and chest x-ray
- **Preferred Regimens:**
    - INH 300 mg + pyridoxine 50 mg qd for 9 months (270 doses in ≤12 months); or
    - INH 900 mg + pyridoxine 100 mg 2x/wk by directly observed therapy for 9 months (76 doses in ≤12 months)
- **MDR-TB Exposure:** Expert consultation is recommended for persons who are likely to be infected with INH and RIF (multidrug) resistant-TB and at high risk of reactivation.

Monitoring Therapy

- Contact monthly to review sx suggesting hepatitis.
- LFTs (ALT and bilirubin) at baseline, 1 mo., 3 mo., and with symptoms of hepatitis. D/C INH if asymptomatic and ALT increases to ≥5x ULN or if symptomatic and ALT increases to ≥3x ULN.

Treatment of Tuberculosis Disease
(American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis *Am J Respir Crit Care Med* 2003;167(4):603.)

Adult OI Table 5. Treatment of Drug-Susceptible Active Tuberculosis

Phase 1 (8 weeks)	Phase 2*: regimen, doses, minimal duration
INH, RIF, PZA, EMB 8 weeks • 7 d/wk for 8 wks (56 doses); **or** • 5 d/wk for 8 wks (40 doses)	• INH/RIF 7 d/wk for 18 wks (126 doses); **or** • INH/RIF 5 d/wk for 18 wks (90 doses); **or** • INH/RIF 2x/wk for 18 wks (36 doses).
INH, RIF, PZA, EMB 2 wk/6 week 7 d/wk, for 2 wks (14 doses), then 2x/wk for 6 wks (12 doses).	INH/RIF 2x/wk for 18 wks (36 doses)
INH, RIF, PZA, EMB 8 weeks 3 x/wk for 8 wks (24 doses)	INH/RIF 3x/wk for 18 wks (54 doses)
INH, RIF, EMB 8 weeks • 7 d/week for 8 wks (56 doses) • 5 d/week for 8 wks (40 doses)	• INH/RIF 7 d/wk for 31 wks (217 doses); **or** • INH/RIF 5 d/wk for 31 wk (155 doses); **or** • INH/RIF 2x/wk for 31 wks (62 doses).

INH = Isoniazide, RIF = Rifampin, PZA = Pyrazinamide, EMB = Ethambutol
* Patients with cavitation at baseline and positive cultures at 2 months should receive 31 week continuation phase for total of 9 months.

Adult OI Table 6: Special Considerations for TB Treatment with HIV Co-Infection

Identical for general population except:

- Always treat TB first in untreated patients with dual infection. Problems with initiating therapy simultaneously is high pill burden (6-7 meds) including many with ADRs including hepatitis and the risk of immune reconstitution syndrome.
- Usually delay initiating HAART based on CD4 count: CD4 <50 cells/mm^3– delay ≥2 wks, CD4 50-200 cells/mm^3– delay ≥8 wks, CD4 200-350 cells/mm^3– delay until TB treatment completed.
- **CD4 <100 cells/mm^3:** Continuation phase should be daily or 3x/week.
- **Positive cultures at 2 months:** "Strongly consider" 7 month continuation phase (total 9 mo.).
- In absence of prior HIV therapy and CD4 <350 cells/mm^3: delay antiretroviral drugs for 4-8 weeks.
- RIF may be used with 2 NRTIs + EFV or RTV + SQV (*Invirase* or *Fortovase*). With other PIs and NNRTIs use rifabutin.
- Rifabutin combined with other PIs and NNRTI requires dose adjustment of both. See Drug Table 7 (www.cdc.gov/nchstp/tb/).
- When starting NNRTI or PI in patient receiving RIF, substitute rifabutin 2 weeks prior to NNRTI or PI to give a 2 week washout period for RIF.
- **Paradoxical reaction:** Frequency in 7-36%; clinical features– high fever; increased adenopathy, CNS lesions, pulmonary infiltrates and pleural effusions. Treatment is symptomatic; if severe give prednisone 1 mg/kg and reduce steroid dose at 1-2 weeks.

Adult OI Table 7. Doses of Antituberculosis Drugs– First Line Drugs

Drug	7 or 5 days/wk	2x/wk	3x/wk
INH*	5 mg/kg (300)*†	15 mg/kg (900)*†	15 mg/kg (900)*†
RIF	10 mg/kg (600)*	10 mg/kg (600)*	10 mg/kg (600)*
Rifapentene	-	10 mg/kg (600)*	-
PZA (wt)			
40-55 kg	1 gm	2.0 gm	1.5gm
56-75 kg	1.5 gm	3.0 gm	2.5 gm
76-90 kg	2.0 gm	4.0 gm	3.0 gm
EMB (wt)			
40-55 kg	800 mg	2,000 mg	1,200 mg
56-75 kg	1,200 mg	2,800 mg	2,000 mg
76-90 kg	1,600 mg	4,000 mg	2,400 mg

*Usual dose in mg in parentheses.

† INH should be given with pyridoxine. Dose at 25 mg on for each day INH is given.

Adult OI Table 8. Treatment of Hepatitis C
(Recommendations of the American Association for Study of Liver Disease [*Hepatology* 2004;39:1147])

Indications for Screening: HIV Infection

Background: Experience with HIV/HCV co-infection shows optimal response with pegylated interferon plus ribavirin but reduced rates of sustained viral response (undetectable HCV RNA at 24 weeks post treatment) with genotype one of 14-29% [Chunk,RT *N Engl J Med* 2004;351:451; Torrani FJ *N Engl J Med* 2004;351:438]compared to rates of 45-50% in absence of HIV [Fried MW *N Engl J Med* 2002;347:973]. Rate of sustained viral response (SVR), the goal of therapy ranges 60-75% with treatment for 48 weeks with non-1 genotypes.

Pretreatment Evaluation

- Counsel patient on risks and benefits – if patient refuses therapy most of the work-up is unnecessary.
- Lab tests: CBC, ALT, AST, and creatinine.
- HIV status: CD4 count, viral load, OI (nearly all published experience is with stable HIV and CD4 >200 cells/mm^3 and mean CD4 >500 cells/mm^3.
- HCV status: HCV genotype, HCV viral load, liver biopsy (if unavailable, contraindicated, or refused may elect to treat without).
- Patient status: assess co-morbidities including psychiatric disease, substance abuse, cardiopulmonary disease, renal disease.

Indications to Treat

1. HCV RNA >50 IU/mL,
2. Liver biopsy showing fibrosis score ≥2,
3. No contraindication to interferon or ribavirin, and
4. Stable HIV infection, preferably with CD4 >200 cells/mm^3.

Regimen

- All genotypes treated with pegylated interferon and ribavirin x 48 weeks
- Peginterferon alfa 2a (Pegasys) 180 mcg or alfa 2b (Peg-Intron) – 1.5 mcg/kg SC qw x 48 weeks
- **Ribavirin:** 800-1200 mg qd in divided doses x 48 weeks

Follow-up

- Reinforce birth control for now and 6 months post treatment
- **Lab Tests:** CBC + ALT at wks 2 & 4, then at 4-8 wk intervals
- **HCV:** Quantitative HCV RNA at 12 wks-continue if undetectable or decreased by 2 $\log_{10}$ IU/mL. Retest at end of treatment and 6 mos post treatment (wk 72) to determine SVR.*
- Neuropsychiatric evaluation monthly ± SSRI & consultation.
- **Thyroid:** TSH at 3 + 6 month intervals.
- **HIV:** CD4 count and viral load every 3-4 months.

* Failure to achieve no detectable HCV or a 2 $\log_{10}$ IU/mL decrease at 12 weeks indicates failure

Guidelines for Sexually Transmitted Disease Co-Morbidity

CDC Guidelines for the Treatment of Sexually Transmitted Diseases
Available on the CDC web site at: http://www.cdc.gov/nchstp/dstd/dstdp.html

The following are additional sources of information and guidance:

- State or Local Health Department Case consultations, disease reporting, and may be able to provide hardcopy of STD Treatment Guidelines.
- STD/HIV Prevention Training Centers
  Check the web site: http://depts.washington.edu/nnptc/ for a list of the PTCs

STD/HIV Table 1. Sexually Transmitted Disease Identification and Treatment*

Condition	Identification/Screening	Diagnosis
Urethritis	• Patient self-report sx • Review of hx at follow- up visits, including contact with other case.	Confirm Urethritis and test for Gonorrhea and Chlamydia
Gonorrhea	• Patient self-report sx • Review of hx at follow- up visits, including contact with other case. • Many infections are asymptomatic in men and women: consider urinary NAAT for GC & CT in sexually active men and women	Gram stain and/or culture (or other specific test) of urethral or cervical swabs. Urine NAAT tests are valid for urethral infections and may be more acceptable to patients.
Chlamydia	• Patient self-report sx • Review of hx at follow- up visits, including contact with other case. • Most infections are asymptomatic • Routine cervical tests for sexually active women <25 yrs. Consider routine NAAT urine test for GC & CT in sexually active women >25 yrs and men. • Consider repeat test annually or more often, especially if high risk behavior or prior positive test.†	Culture (or other specific test). Urine PCR/LCR tests are valid for urethral infections and may be more acceptable to patients.
Syphilis	• Patient self-report sx • Contact to case. • Screen at initial visit • Repeat screen annually	• RPR(or VDRL) **PLUS** FTA-ABS if positive • Darkfield exam or DFA of lesion material or exudates (primary syphillis).

* CDC STD treatment guidelines updated by authors to reflect latest research data.

† Screening interval depends upon community prevalence, outcome of women's previous screening tests, and individual risk.

	Treatment
	For non-gonococcal urethritis treat for Chlamydia
	Urethral, endocervical, rectal: ceftriaxone 125 mg IM x 1 (also for **pharyngeal**), ciprofloxacin‡ 500 mg po x 1 (also for **pharyngeal**), ofloxacin‡ 400 mg po x 1, levofloxacin‡ 250 po x 1; **or** cefixime 400 mg po x 1, **PLUS** azithromycin 1 gm po x 1 or doxycycline‡ 100 mg po bid x 7 days **Alternative:** Spectinomycin 29 m IM x 1
	Disseminated GC: Patients with disseminated GC infections are most appropriately treated in the hospital. Consult full-text of the guidelines for treatment recommendations.
	azithromycin 1 gm po x 1 **or** doxycycline* 100 mg po bid x 7 days **Alternatives:** erythromycin base 500 mg po qid x 7d; erythromycin ethylsuccinate 800 mg po qid x 7d; ofloxacin 300 mg po bid x 7d, or levofloxacin 500 mg po qd x 7d
	See table: STD/HIV Table 2. Management of Syphillis Co-Infection: Summary

‡ Tetracycline, fluoroquinalones contraindicated in pregnancy.

STD/HIV Table 1. Sexually Transmitted Disease Identification and Treatment*

Condition	Identification/Screening	Diagnosis
Herpes Simplex	• Patient self-report sx • Review of hx at follow-up visits • Most common cause of genital ulcer disease in the US and the world • Many infections are asymptomatic unless history is targeted	Patients with lesions suspected to be herpes should be evaluated to rule out syphilis. Virologic Tests: Culture, DFA Serology for HSV-2
Trichomonas	Malodorous yellow-green discharge	Wet mount or culture
Pelvic inflammatory disease	Endometritis, salphingitis	Uterine, adenexal, or cervical motion tenderness

* CDC STD treatment guidelines updated by authors to reflect latest research data.

(Cont'd.)

	Treatment
	Episodic therapy of recurring infection: **Genital:** Acyclovir 200 mg po 5x per day for 5 days, ***or*** 400 mg po tid for 5 days, ***or*** 800 mg po bid for 5 days; famciclovir 125 mg po bid for 5 days; valacyclovir 1 gm po qd for 5 days, ***or*** 500 mg po bid for 3-5 days, **Suppression:** acyclovir 400 mg po bid; famciclovir 250 mg po bid; ***or*** valacyclovir 500 mg po qd, or 1 gm po qd HSV in HIV-coinfected patients with low CD4 counts show flares that are more severe, more common, more likely to be disseminated and more likely to involve acyclovir-resistant HSV. Many patients require IV acyclovir (15-30 mg.kg/day) or foscarnet for acyclovir-resistant HSV.
	Metronidazole 2 gm x 1 **Alternative:** Metronidazole 500 mg bid x 7d
	Oral: Ofloxacin 400 mg po bid x 14d or levofloxacin 500 mg po qd x 14d **Outpatient parenteral/oral:** cefoxitin 2 gm or ceftriaxone 250 mg IM x 1 plus doxycycline 100 mg po bid x 14d

STD/HIV Table 2. Management of Syphilis Co-Infection: Summary*

Form	Treatment	LP†
Primary and Secondary syphilis	Initial: Benzathine penicillin G 2.4 mil units IM x 1 **Pen. Allergic** - doxycycline 100 mg po bid x 14 days Re-treatment Benzathine penicillin G 2.4 mil units IM x 3 (weekly)	Neuro sx Treatment failure
Early latent (<1 yr)	Initial: Benzathine penicillin G 2.4 mil units IM x 1 Pen. allergic- doxycycline 100 mg po bid x 14 days Re-treatment Benzathine penicillin G 2.4 mil units IM x 3 (weekly)	All HIV-infected patients
Late latent (>1 yr or unknown duration)	Benzathine penicillin, 2.4 mil units IM weekly for 3 wks Pen. allergic– doxycycline 100 mg po bid x 28 days ‡	All HIV-infected patients
Late syphilis (tertiary, not neurosyphilis)	Benzathine penicillin, 2.4 mil units IM weekly for 3 wks Pen. allergic– doxycycline 100 mg po bid x 28 days ‡	All patients
Neurosyphilis (or ocular syphilis)	Aq penicillin G, 18-24 mil units/day x 10-14 days administered as 3-4 million units IV q 4 hr ***or*** Procaine penicillin 2.4 million units IM qd + probenecid 500 mg po qd x 10-14 days Some recommend benzathine penicillin, 2.4 million units IM weekly x 3 weeks after completion of IV course. Penicillin allergy: desensitization required.	Required

* CDC STD treatment guidelines updated by authors to reflect latest research data.

† Some experts recommend CSF examinations of all syphilis-HIV co-infected patients before treatment, regardless of stage, and modification of treatment accordingly. Consultation with an expert may be appropriate.

	Follow-up VDRL/RPR	Expectation VDRL/RPR	Indications to Re-treat
	HIV: 3, 6, 9, 12 & 24 mos	Four-fold decrease at 6 mos	Titer increases four-fold and CSF negative. Titer fails to decrease four-fold at 6-12 mos. Symptoms persist or recur
	6, 12, 18, & 24 mos	Four-fold decrease at 12 to 24 mos.	Titer increases four-fold Titer of >1:32 fails to decrease four-fold at 12-24 mos Develops signs or sx of syphilis
	6, 12, 18, & 24 mos	Four-fold decrease in titer at 12-24 mos (lower initial titers may remain unchanged)	Titer fails to decrease four-fold at 12-24 mos. Increase titer by four-fold at any time after 3 mos.
	6 & 12 mos	As above Granulomatous lesions should heal	As above Documentation of T. pallidum or other histologic feature of late syphilis
	Every 6 mos. until negative	CSF WBC decrease at 6 mos and CSF normal at 2 yr	CSF WBC fails to decrease at 6 mos or if CSF VDRL is still positive. Persisting signs and symptoms.

‡ Alternatives to penicillin have not been sufficiently evaluated in HIV infected persons and cannot be considered first-line therapy. If required, there needs to be close clinical monitoring. If adherence cannot be insured, desensitization and tx with penicillin is recommended.

Occupational Post-Exposure Prophylaxis (PEP)

Source	Type of Exposure			
	Percutaneous		Mucocutaneous	
	Not Severe[1]	More Severe[2]	Small Volume[3]	Large Volume[4]
HIV Positive				
Low risk[5]	2 drugs	≥3 drugs	2 drugs	2 Drugs
High risk[6]	3 drugs	≥3 drugs	≥3 Drugs	≥3 drugs
Source unknown				
–	None or 2 drugs[7]	None or 2 drugs[7]	None or 2 drugs[7]	None or 2 drugs[7]

[1] Solid needle or superficial injury etc.

[2] Large bore hollow needle, deep injury or visible blood on needle/device

[3] Few drops

[4] Major splash

[5] HIV positive and asymptomatic viral load <1500 c/mL

[6] HIV positive and symptomatic, AIDS, acute retroviral syndrome or known high viral load; if HIV resistance is a concern – get expert consultation

[7] PEP is optional based on discussion of risk: benefit

Risk for HIV Transmission

Exposure: Percutaneous injury with sharp object or exposure to mucous membranes or nonintact skin (skin that is abraded, chapped or with dermatitis).

Source:
- Percutaneous injury: 0.3% (3/1000)
- Mucocutaneous exposure: 0.09% (9/10,000)
- Increased risk: Device (needle) with visible blood, needle placed in artery or vein, deep injury, large volume, high viral load

Relative risk (without prophylaxis)
- Established risk with occupational exposure: Blood or bloody body fluid
- Theoretical risk: CSF; pleural pericardial., peritoneal, amniotic and vaginal fluids; semen
- Not potentially infectious: Urine, stool, nasal secretions, sputum, tears, vomitus (if not bloody)

Efficacy of PEP
- Efficacy of AZT monotherapy prophylaxis estimated at 80% in retrospective case control series
- Recorded prophylaxis failures (US): 6

Regimens: Initiate as soon as possible after exposure and continue 4 weeks

- Recommended drugs:

2 Drug Regimen	3 Drug Regimen
3 TC or FTC *plus* AZT, d4T or TDF	Two nucleocides *plus* Preferred: LPV/r Alternatives: ATV, FPV, IDV/r, SQV/r or NFV*

*Consider EFV if PI– resistance in source and HCW has no pregnancy risk

- Not recommended: ABC, DLV, ddC, DDI/d4T, NVP

Adverse reactions

- Reported frequency: 17-47%
- Most frequent: Nausea– 27%, malaise and fatigue– 23%

Pregnancy: Avoid EFV and ddI/d4T– Caution with IDV/r

Expert consultation

- Delayed PEP to >24-36 hrs
- Unknown source
- Pregnancy or breastfeeding
- Resistant HIV strain in source
- Toxicity management

Monitoring

- **Source** – rapid HIV test preferred if serostatus is unknown
- **Re-evaluate** HCW at 72 hours
- **HCW serology testing for HIV:** Baseline, 6 weeks, 12 weeks and 6 months; if HCV seroconversion add a 12 month serologic test for HIV
- **Tests for HIV** (P24 Ag or HIV PCR) in HCW are not routinely recommended due to high rates of false positives; these tests should be done if there are symptoms compatible with the acute retroviral syndrome
- **Report any seroconversion** to CDC at 1-800-893-0485
- **Toxicity monitoring**
    1. CBC and LFT at baseline an at 2 weeks
    2. PIs– Blood glucose at baseline and 2 weeks
    3. IDV– Urinanalysis
    4. Warn to report: Rash, fever, back or abdominal pain, dysuria, blood in urine and symptoms of hyperglycemia
- **HCW warnings**
    1. Avoid blood or tissue donations
    2. Avoid pregnancy and breastfeeding especially in first 6-12 weeks
    3. Warn about drug toxicities, drug interactions and need to complete 4 week course

Resources for PEP

- **PEPline:**
  http://www.ucsf.edu/hivcntr/Hotlines/PEPline
  Telephone: 1-888-448-4911
- **HIV Pregnancy registry:**
  http://www.apregistry.com/index.htm
  Telephone: 1-800-258-4263
  email– registry@nc.crl.com
- **CDC (HCW serconversions):**
  Telephone – 1-800-893-0485
- **HIV/AIDS Treatment Information Service:**
  http://aidsinfo.nih.gov

The Johns Hopkins AIDS Service

- The Moore Clinic (410) 955-1725
- The Garey Lambert Research Center
- AIDS Clinical Trials Unit
- Website: *http://www.hopkins-aids.edu/*
- HIV Guide: *http://hopkins-hivguide.org/*
- The Hopkins HIV Report
- The Medical Management of HIV Infection
- Center for Clinical Global Health Education
  http://www.ccghe.jhmi.edu