

THE UNIVERSITY OF MARYLAND GUIDE TO PEDIATRIC HIV CARE

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PLEASE NOTE

This version replaces prior versions. All information subject to change. Readers are advised to consult with experts in pediatric HIV or the authors of this Guide.

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EVALUATION AND CARE OF THE HIV-INFECTED CHILD

I. Approach to care

Successful HIV care provides continuity of family-centered and developmentally appropriate care in a multidisciplinary program that coordinates efforts across institutional lines. The importance of each of these qualifiers cannot be overstated:

- A. Successful: Although there are many intangible benefits to a successful program, objective measures must be monitored- and achieving goals for these measures is not going to happen without accruing the intangibles. The most critical objective outcomes are cases of transmission prevented, at-risk individuals screened, infected patients retained in care, proportion of patients meeting medical criteria for treatment who have an undetectable viral load, and mortality.
- B. Family-centered. HIV places tremendous burdens on the family, and HIV flourishes in the setting of social disarray, so those most likely to be infected are often the least prepared to respond to the challenge. Success depends on supporting the difficult task of caring for infected family members and on helping to build functional family units.
- C. Continuity. HIV is a complex, chronic illness often associated with psychosocial difficulties and the target of intense fear and stigma. Understanding and responding to medical and psychosocial issues requires the institutional memory and trust gained when care is provided by a stable familiar set of individuals.
- D. Developmentally appropriate.

II. Diagnosis of HIV in the older child or adolescent

A. Serology

1. ELISA and Western blot. For children and adolescents over 18 months of age, standard HIV serology is sensitive and specific for the diagnosis of HIV in most but not all cases. First, a screening ELISA is performed against a mix of HIV-1 (and in some cases, HIV-2) antigens. This screen is highly sensitive for antibodies to HIV, but may not be specific (about 2% false positive). If the ELISA is positive, then a Western blot is done. This determines which antigens the antibodies are recognizing. Criteria are established for negative, indeterminate, and positive Western. Two out of three of the following bands must be positive for a positive result: p24, gp41, and gp120/160; most positives will have multiple additional bands. Bands may be seen at p17, p24, p55, or p66 in people not infected with HIV.
2. Rapid blood or saliva tests. These are very useful in several settings: 1. In emergent situations such as pregnant woman of unknown status in labor or to test source case for health care worker with needle stick injury. 2. Any testing setting where patient may not return for results (very common). 3. Where sample transport and reliable result reporting are problematic. Rapid tests may be sensitive and specific (data for specific tests should be checked), but not perfect. A positive result on a rapid test should be confirmed by standard ELISA and WB. A positive rapid test is sufficient evidence of HIV to justify any emergent HIV-related treatment. In resource-limited high-prevalence settings, algorithms confirming positive rapid results with a different rapid test may be sufficient for diagnosis, but such an algorithm should be tested, using WB, prior to implementation.
3. False negative or indeterminate results in infected patients may occur in several settings:
 - a) Early after infection. The incubation period for viremia is 1-2 weeks and for antibodies to appear, 2-4 weeks. As the antibody response develops, an increasing number of bands appear on the WB (usually starting with p24). The large majority of infected adults will have diagnostic serology 3 months after infection. Very rarely, it may take longer, up to 6 months.
 - b) In rapidly progressive or advanced disease, especially in children, partial or complete seroreversion may occur. These patients are obviously ill and have high viral loads.
 - c) Infants (and rarely adults) diagnosed within a few weeks of infection and treated immediately with effective HAART may never develop an antibody response. This is not a diagnostic issue, because these cases have all been diagnosed by virologic methods.
 - d) Agammaglobulinemia of any cause.
 - e) Infection with HIV-2 (rare in U.S.; endemic at much lower rate than HIV-1 in West Africa, Angola, Mozambique) may or may not be ELISA positive, depending on the kit used. HIV-1 groups N or O (extremely rare in U.S., rare in West Africa) may not have diagnostic serology.
4. Evaluation of indeterminate results. For low-risk individual (e.g. blood donor), no evaluation is indicated. For high-risk individual either determining the HIV viral load (which will be high if indeterminate serology is due to very recent infection or to advanced disease) or repeating

serology in 3 months is reasonable, depending on clinical urgency.

5. Infants of seropositive mothers are always born seropositive. Uninfected infants will eventually serorevert (50% by 10 months, 100% by 18 months). Serology is of no use in a young infant except to determine if a young infant of an unavailable mother is HIV exposed (and then is reliably seropositive only for about 3-7 months if uninfected).

B. Virologic testing

Except for the circumstances noted above that limit serologic testing, virologic methods that directly detect viral RNA or cDNA are not advised for diagnosis in children over 18 months of age. See discussion of infant diagnostic testing for details of virologic methods.

III. Initial evaluation and management of the newly diagnosed HIV-infected child or adolescent

- A. Complete history, including PMH, FH, SH (including risk behaviors), ROS.
- B. Physical exam, including neurologic exam and pelvic exam in sexually active adolescents
- C. Laboratory evaluation
 1. Confirming HIV elisa and western blot
 2. Quantitative HIV RNA PCR (Plasma viral load)
 3. HIV Genotyping
 4. CBC, lymphocyte subsets (at least CD3/CD4)
 5. Electrolytes, BUN, creatinine, liver and pancreatic enzymes, cholesterol, triglycerides
 6. Toxoplasma titer, CMV titer
 7. Hepatitis B sAb and sAg, Hepatitis C Ab, RPR
 8. U/A, (Urine β HCG)
 9. In sexually active females: urine or cervical chlamydia & GC, wet mount, and cervical PAP
- D. Other investigations
 1. PPD
 2. CXR
 3. (Psychometrics, cranial imaging as indicated)
 4. (Ophthalmology exam, depending on CD4 count)
 5. (Dental exam)
 6. Evaluation of any presenting complaints as indicated
- E. Counseling re: risk of transmission, psychosocial issues, referral for psychological counseling or patient support group
- F. Assess need and readiness for antiretroviral therapy (See Principles of Antiretroviral Therapy)

IV. Pediatric HIV classification

Table 1. Pediatric HIV Classification (<13 years old)		
Symptom categories		
Class	Severity	Symptoms attributed to HIV
N	None	None
A	Mild	2 or more: Adenopathy, hepatomegaly, splenomegaly, dermatitis, parotitis, recurrent sinusitis or otitis
B	Moderate	Hematologic (Hgb <8, ANC <1000, or platelets <100,000) for >30 d; meningitis, bacteremia, >2 mo thrush at >6 mo old, cardiomyopathy, symptomatic CMV with onset at <1mo old, recurrent or chronic diarrhea, hepatitis, invasive HSV, recurrent oral HSV, recurrent or severe shingles, leiomyosarcoma, LIP, nephropathy, nocardiosis, fever > 1 month, toxo with onset at < 1 mo old, disseminated VZV
C	Severe	Recurrent (within 2 yr period) invasive bacterial infection (excluding otitis media, line sepsis, superficial abscess), esophageal or lower respiratory candida, disseminated coccidio, extrapulmonary cryptococcus, cryptosporidium or isospora lasting > 1 mo, CMV onset at > 1 mo old (except liver, spleen, nodes), encephalopathy, persistent or invasive HSV at >1 mo old, disseminated histo, kaposi's, brain or B cell lymphoma, disseminated mycobacteria, PCP, PML, CNS toxo onset at >1 mo old, wasting syndrome [=FTT and (chronic diarrhea or fever)]

Table 1 (continued). Immunologic categories

Class	Suppression	< 12 months	1-5 years	6-12 years	≥13 years
1	None	≥ 1500 and ≥ 25%	≥1000 and ≥25%	≥500 and ≥25%	≥500 and ≥28%
2	Moderate	750-1500 or 15-24%	500-999 or 15-24%	200-499 or 15-24%	200-499 or 14-28%
3	Severe	<750 or <15%	<500 or <15%	<200 or <15%	<200 or <14%

Notes: CD4 values that result in change must be confirmed. Use more severe of absolute or % class. Classification cannot be revised upwards. Prefix E = exposed (infection not confirmed). SR = seroreverter (not infected). Pediatric classification: MMWR 43:RR-12 1994. Adolescent and adult classification: MMWR 41:RR-17 1992.

V. Approach to follow up and care

Although true for any complex chronic illness, it is especially important that HIV care be conducted within an organized program that has these characteristics:

- A. Continuity: To the extent possible, the patient should see the same physician and staff at each visit. Prenatal, pediatric, and adult care transitions must be coordinated.
- B. Multidisciplinary: A multidisciplinary team, made up of individuals with pediatric HIV-specific expertise in within their discipline, must function as a unit. HIV medicine, nursing, social work, mental health (including substance abuse), pharmacy, and laboratory are all key disciplines.
- C. Patient and family oriented. This includes sensitivity to developmental issues as they relate to issues such as disclosure of diagnosis to children, adolescent issues, and transition to adult care.

VI. Prophylaxis against opportunistic infections and immunization

See MMWR 1999; 48:RR-10 (available at <http://www.hivatis.org/>); MMWR 1995; 44:RR-4 (Pediatric PCP). Viral load is an independent risk factor for opportunistic infection and may also be considered.

Table 2. Prophylaxis indications according to CD4 count (Per CDC. Parentheses indicate additional reasonable considerations.)

Age	PCP	MAC
6wk-4 months	All exposed infants	<750 (None)
4-12 months	All HIV infected or unknown	<750 (<10%)
12-24 months	< 500 or <15%	<500 (<10%)
2- 5 years	<500 or <15%	<75 (<10%)
≥6 years	<200 or <15%	<50 (<10%)
Any	Prior hx of PCP	MAC requires continued treatment unless immune reconstituted

Table 3. Prophylaxis options

Infection	Priority of options			
	1	2	3 or 4	3 or 4
PCP	TMP/SMX 75 mg/m ² (5 mg/kg) bid 3X/week or 75 mg/m ² qd [Adult: 1 SS (80 mg) or 1 DS (160 mg) qd or 1 DS 3X/week]	Dapsone 2 mg/kg qd (Adult: 100 mg qd or 50 mg bid)	Pentamidine 300 mg aerosolized q 2-4 wk (Adult: same) (Pentamidine 4 mg/kg IV q 2-4 wk has been used but not preferred)	Atovaquone 30 mg/kg qd with food (Adult: 1500 mg qd)
MAI	Azithromycin 5 mg/kg qd or 20 mg/kg q wk (Adult: 250 mg qd or 1200 mg q week) or Clarithromycin 7.5 mg/kg bid (Adult: 500 mg bid)	Rifabutin 5 mg/kg qd (Adult 300 mg qd)		

- A. **Discontinuation of prophylaxis:** Prophylaxis against PCP and MAI may be discontinued after CD4 count has been above the prophylaxis range for 3-6 months *and* will be maintained, i.e., viral load is repeatedly undetectable on a regimen that will be continued.
- B. **TMP/SMX intolerance:** Cutaneous reactions to TMP/SMX are less common if drug is gradually introduced and may not recur on rechallenge.
- C. **Bacterial prophylaxis:** Consider bacterial prophylaxis if ≥ 2 bacteremias or frequent otitis, sinusitis, pneumonia. Regimen may include PCN, amoxicillin, TMP/SMX daily, or a macrolide. IVIG was shown to decrease bacterial infections only in children not taking TMP/SMX; antibiotics are simpler, cheaper, and probably at least as effective. Children with HIV should receive BOTH pneumococcal polysaccharide vaccine (Pneumovax, Pnu-immune) and pneumococcal conjugate vaccine (Prenvar). Prenvar is not labeled for use over 60 months of age, but its use may be considered in the older child with HIV. Pneumococcal polysaccharide vaccine should be given at 2 years of age and repeated 3-5 years after the first dose. Pneumococcal polysaccharide and conjugate vaccines should not be given simultaneously; separate by at least 6-8 weeks.

Age (months) of first dose	Primary doses (6-8 weeks apart)	Booster dose (s)
2-6	3	1 at 12-15 months of age
7-11	2	1 at 12-15 months of age + 1 at 24 months of age
12-23	2	1 at 24 months of age
24-59	2	0

- D. **Tuberculosis:** PPD ≥ 5 mm should be considered positive in HIV-infected child, but even this definition is insensitive in the setting of HIV. Anergy testing adds no useful information. BCG can cause regional adenitis or disseminated disease; however, in areas of TB endemicity, benefits of BCG vaccination of HIV-exposed infants outweigh risks. BCG should not be given to children with severe immunosuppression. In areas endemic for TB, it is common in women with HIV and is readily transmitted to newborn; HIV-infected women in TB-endemic areas should be screened for TB.
- E. **Fungal prophylaxis:** Consider fluconazole prophylaxis in infant/toddler with history of esophagitis. For chronic thrush topical therapy (nystatin, amphotericin, or clotrimazole troche for older child) preferred over systemic. Use secondary prophylaxis after histoplasmosis, coccidiomycosis, or cryptococcosis.
- F. **Viral prophylaxis: Varicella:** Oral acyclovir 40-80 mg/kg/d p.o. for 7 days or duration of potential exposure. VZIG (or IVIG) within 4 days of VZV exposure is effective but expensive and inconvenient. Treat varicella promptly with 80 mg/kg/d p.o. (max 3200 mg/d) or 1500 mg/m²/d IV. HIV infected children class N1 or A1, should receive 2 doses of VZV vaccine 12 weeks apart. Results of a study of VZV vaccine in children with lower classification but who are doing well on therapy are pending. VZV-naive household contacts should be given VZV vaccine to prevent transmission of wild-type VZV to patient.
Measles: IVIG for exposure. Do not give vaccine to class 3 patients unless immune reconstituted.
Influenza: Consider vaccine for immunologic class 1-2, especially if significant pulmonary disease
- G. **Toxoplasmosis:** Severely immunosuppressed toxo serology positive child may be at risk. TMP/SMX is preferred for PCP and effective for toxo prophylaxis; alternate is dapsone + pyrimethamine + folate.
- H. **Immunizations:** All current AAP recommendations for routine immunizations apply to children with HIV except as noted above; consider delaying immunizations if immunosuppressed and immune reconstitution is expected

PRINCIPLES OF ANTIRETROVIRAL THERAPY

See *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, Report of the NIH Panel to Define Principles of Therapy of HIV Infection*, and *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, all available at <http://www.aidsinfo.nih.gov/guidelines/>.

I. Decide whom to treat.

Vertically transmitted HIV progresses more rapidly in infants and children than does HIV acquired as an adult. Approximately 10 years after infection, 50% of adults will have AIDS, whereas 50% of children will have AIDS by 3 years of age and 25% by 12 months without effective treatment. CNS damage is common in infants with HIV. Viral load and CD4 counts are not as predictive of outcome in the first year of life as they are later. Clinical variables (especially weight loss or anemia), CD4 count, and viral load are independent predictors of disease progression and all should be considered in making treatment recommendations. Criteria favoring treatment must be balanced against anticipated problems with treatment. Finally, a decision to embark on treatment is not irreversible- if problems with treatment are more severe than anticipated, suspension of treatment may be considered. U.S. guidelines for antiretroviral therapy in children are outlined in Table 5. The following should guide treatment decisions:

- A. Treatment is indicated for most or all HIV-infected infants less than 6-12 months of age regardless of clinical, immunologic or virologic status.
- B. HIV-infected children over 12 months of age should be candidates for treatment if any of the following conditions are met. Because CD4 and viral load are independent predictors of clinical events, they should be considered together in assessing relative need for treatment.
 1. Recent symptoms attributable to ongoing HIV infection
 2. Significant immune suppression. All class 3 children and, generally, children in the lower half of class 2 CD4 range should be treated.
 3. Viral load suggests that disease progression may occur. Disease progression is rare in children >30 months of age with VL < 15,000 copies/ml. Any child with VL > 100,000 copies/ml should be treated and treatment should be considered if VL > 50,000 c/ml.
- C. Initiation of treatment should be delayed in the stable HIV-infected child if nonadherence is expected to jeopardize the success of treatment. A plan to address adherence problems and then begin antiretroviral therapy should be initiated.
- D. Current WHO guidelines for HAART in children in resource-limited settings are summarized in Box 1. The major differences between these and U.S. guidelines are the absence of viral load criteria and that treatment of infants without symptoms is not recommended.

Table 5. US Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (Dated 20 Jan 2004)

Age	Clinical category and CD4	Viral load	Recommendation
<12 months	Clinical category A, B, or C OR CD4 < 25%	Any	Treat
	Clinical category N AND CD4 >/= 25%	Any	Consider treatment
≥ 1 year	Clinical category C OR CD4 < 15%	Any	Treat
	Clinical category A or B OR CD4 15-25%	>50,000-100,000	Consider treatment
	Clinical category N AND CD4 >/= 25%	<50,000-100,000	Many experts would defer therapy and closely monitor clinical, immune and viral parameters

Box 1. WHO guidelines for HAART in resource-limited settings

WHO guidelines for HAART in seropositive child aged < 18 months

If HIV virologically proven (+DNA PCR or viral load), initiate HAART if:

- WHO Paediatric Stage III
- WHO Paediatric Stage II, especially if CD4<20%
- WHO Paediatric Stage I and CD4 <20%

If HIV PCR/VL not available:

- WHO Paediatric Stage II or III *and* CD4<20%
- Repeat serology at 18 months of age to prove HIV infection
- Stop HAART if not HIV-infected.

WHO guidelines for HAART in HIV seropositive child aged > 18 months

- WHO Paediatric Stage III
- WHO Paediatric Stage II, especially if CD4<15%
- WHO Paediatric Stage I and CD4 <15%

II. Establish goals for each patient.

- A. **THE GOAL FOR ALL PATIENTS SHOULD BE TO MAINTAIN HIV REPLICATION BELOW THE LIMIT OF DETECTION BY VIRAL LOAD ASSAY.** Maintaining the viral load below detection achieves three essential goals: Prevention of disease progression, optimizing opportunity for recovery, and prevention of antiretroviral resistance. A viral load < 50 copies/ml is associated with stable, long-term suppression and no development of drug resistance. This should be the goal of therapy.
- B. **Temporary partial suppression of viral replication.** Antiretroviral therapy that significantly reduces viral load but does not maintain an undetectable viral load can provide meaningful clinical benefit and may be acceptable as a temporary measure in selected patients. **However, treatment that brings the plasma viral load down but not to undetectable levels will select for further antiretroviral resistance, and may thereby limit future treatment options.** Withholding treatment in a stable patient in whom a fully suppressive regimen is not currently feasible may, in the long run, be preferable to incompletely suppressive therapy.

III. Individualize treatment plans.

In addition to virologic and clinical considerations, plans must consider issues such as side effects, drug interactions, patient convenience and acceptability, and drug availability and cost. Timing of the onset of treatment or treatment changes can be more flexible in the older child with stable clinical status.

IV. Assess and prepare family for adherence to regimen.

Because the major causes of treatment failure are a combination of nonadherence and intolerance, a comprehensive assessment of adherence and tolerance issues should be instituted for all children for whom treatment of HIV or a change in treatment is contemplated. Comprehensive evaluation should include nursing, social, behavioral, and psychological assessments.

- A. Assess prior adherence, preferably with an objective measure such as prescription refill records.
- B. Note all phases of medication administration including obtaining, storing, and administering medications. Identify who is responsible and how dosing is performed. Assess social stability and readiness to complete dosing process.
- C. Identify behavioral barriers to adherence and formulate plan to maximize adherence.
 1. *Teaching pill-swallowing.* If using capsules will facilitate dosing and child cannot readily swallow

capsules, children from about 3 years of age can be pill-trained. The best candidates are children who have not had unpleasant experiences with pills and who do not have behavioral problems, especially with medication taking. Training should be done by someone other than the family or others who may have difficulty maintaining emotional neutrality or who are authority figures for the patient. It is important that parents (who should probably not be present) and trainer not give any signals that pill-taking will be difficult or unpleasant. In a relaxed environment the child is given gradually increasing sizes of placebos, starting very small. Encourage the child to drink the pill down with a swallow of water, and then move to larger sizes (without indicating to the child that the pill is bigger). Encouragement should be provided with minimal extrinsic rewards (behavior motivated by extrinsic rewards tends to extinguish if rewards are not maintained). If the child cannot progress to the largest size, end with success at a smaller size and adjourn to try again at a later date. If successful, the skill needs to be maintained by daily pill-taking. If antiretrovirals are not started immediately, other medication taken as a capsule or a placebo (e.g. vitamin) can be given (and a trial period at home prior to starting antiretrovirals may be advisable).

2. *Medication refusal.* Once a child starts on antiretrovirals, he or she cannot be allowed to refuse medication; the child should not be allowed any other activity until the dose is taken.

D. Intensive family education and medication training and other indicated interventions should have made satisfactory progress prior to initiation of new treatment.

V. Choice of treatment.

Long-term suppression of viral replication and maintenance of antiretroviral sensitivity can only be achieved with combinations of currently available antiretrovirals, known as highly active antiretroviral therapy (HAART). Choice of drugs is guided by:

- A. Viral load. Higher pretreatment viral loads predict greater risk of treatment failure; these patients should receive more potent regimens. Failure rates increase for most regimens tested in clinical trials if the baseline viral load is > 100,000 copies/ml. Exceptions are more potent regimens, such as 2 NRTIs plus either EFV or LPV/r. Immunologic or clinical status does not predict virologic response.
- B. Drug sensitivity
 1. *Treatment history.* The patient's lifetime treatment history must be reviewed to determine if resistant strains may be present. Whether prior treatment selected for resistance depends on the level of viral replication during the period of exposure, the duration of exposure, and the ease with which HIV becomes resistant to a particular drug. Potential cross-resistance must also be considered. Treatment history from mother or other source case should be reviewed.
 2. *Resistance testing.*
 - a) *Genotyping.* Genotyping is performed by sequencing (of RT PCR products from virus in plasma) the regions of the reverse transcriptase and viral protease genes that include sites of known mutations associated with resistance. The viral load needs to be at least 1,000-2,000 to get a sequence, but sensitivity varies considerably. The sequence is compared to a wild type consensus and mutations associated with resistance are reported. **The clinical usefulness of the results is highly dependent on the database of mutation-resistance correlations used for interpretation. Comparison of the genotype with a large database of genotype-phenotype correlations (the so-called virtual phenotype) yields a very good predictor of response (assuming enough matching genotypes in the database).** A summary of the effect of mutations of known significance is given in Figure 1.
 - b) *Phenotyping.* Viral RNA from plasma is reverse transcribed and cDNA of reverse transcriptase and viral protease genes is inserted into a laboratory strain. This is then cultured in the presence of different concentrations of the drug of interest and the level of drug producing a 50% inhibition of viral growth is determined and compared to wild-type control. Results are reported as a fold-change as compared to wild type. The fold-change in sensitivity is compared to standards for each drug (preferably determined from clinical trials) to categorize sensitivity versus resistance. Viral load minimum for results is about 500 copies/ml; results can sometimes be obtained with lower viral loads.
 - c) *Clinical use and interpretation of resistance testing.* Genotyping is generally quicker and cheaper than phenotyping and of comparable accuracy for predicting treatment response. If there are multiple mutations or unusual combinations of mutations, interpretation of the genotype is more difficult and a phenotype should also be done. **Standard resistance testing methods can only detect viral strains predominating in the plasma at the time the sample is drawn. Wild-type drug sensitive virus often replicates faster than drug-resistant virus and overgrows drug-resistant virus when drugs are stopped. However, previously selected resistant strains remain "archived" as a minor population of**

virions or as latent provirus (integrated into host cell DNA). If the selective pressure of drug exposure resumes, these strains will rapidly re-emerge. Therefore, the failure to detect resistance does not necessarily mean that resistance is not present. Detection of resistant virus by genotyping or phenotyping is most sensitive if the sample is taken under the selective pressure of drug exposure. Exceptions may occur if the patient is initially infected with resistant virus. Because no wild type virus is present, resistant virions may persist, although there is the possibility of back-mutation. Resistance testing must be combined with a life-long treatment history and review of any previous resistance testing in order to assess all possible latent resistant virus.

- d) *When to use resistance testing.* Resistance testing should be done whenever drug sensitivity is not known. This includes:
 - a. *Recently infected* persons, including young infants. The prevalence of drug resistance in newly transmitted HIV is rising.
 - b. *Treatment failure.* Even if nonadherence was the initial cause of treatment failure, the subsequent growth of virus in the presence of partially suppressive drug levels may have bred resistance. A sample should be taken immediately before stopping the failing regimen.
 - e) When not to use resistance testing: when there has not been selective pressure for years (although some mutations which do not affect viral fitness as much may be persistently detectable).
- C. *Drug interactions.* See the Formulary for details on each drug.
- D. *Genetic barrier to resistance.* Avoid combinations with common resistance mutations. For example, use of 2 NNRTIs is of no benefit because of high degree of cross-resistance among currently available NNRTIs. Conversely, certain mutations to one drug may cause hypersensitivity to another drug; combinations of such drug pairs provide an additional genetic barrier to resistance. See Figure 1 and Table 7 for summaries of resistance patterns, recommended combinations, and combinations that are not advised due to common resistance patterns.
- E. *Adherence. Nonadherence is the major cause of treatment failure. Maximizing potential for adherence in each individual case should be a major consideration in designing a regimen.*
 1. *Pill burden.* In general, adherence improves as the number of dosings per day decreases from 4/day to 2/day; adherence to daily (q.d.) regimens is only marginally better than b.i.d. in most cases. Adherence also declines with very large number of pills, but once the pill burden is down to a few pills, further decrease is less important.
 2. *Tolerance and safety.* Many acute side effects rapidly diminish, but the patient must be informed about what to expect and be supported. Long-term side effects may jeopardize adherence over time.
 3. *Palatability.* Palatability is the major drug-related impediment to adherence in children, especially if they cannot swallow capsules whole. If there is any doubt, palatability should be tested in clinic with drug samples. (Because of rapid selection for resistance, do not give single doses of NNRTI drugs.)
- F. *Consequences of failure.* Consider the consequences of failure of a treatment plan. Will resistance have developed by the time failure is detected, such as for the NNRTIs? Are the potential side effects readily reversible? Every plan should have a back-up plan. Even if there is a chance of failure due to inadequate potency or to reversible side-effects, as long there are no irreversible consequences (such as resistance or permanent injury) and other options are preserved, it is reasonable to try an option that otherwise is attractive and switch to the back-up plan if there is a problem.
- G. *Initial antiretroviral treatment regimens.* Many specific regimens have been shown in trials to maintain an undetectable viral load in many or most subjects. These results should be used as a guideline, but the number of possible regimens is too immense to ever evaluate formally. **Any regimen that is based on sound virologic and pharmacologic principles and which is appropriate for the individual patient is acceptable.** Preferred and alternate regimens for treatment-naïve patients are described in Table 7.
- H. *Salvage therapy for the treatment-experienced patient.* Treatment must be guided by assessment of resistance: by history, review of all prior resistance-testing results, and repeat resistance testing. Because recombination of resistant strains probably occurs readily in vivo, treatment should be directed at any and all possible combinations of previously observed genotypes. If a regimen of 3-4 drugs to which full sensitivity has been preserved cannot be constructed, then it is reasonable to use larger numbers of drugs with intermediate levels of efficacy. Using 5 or more drugs in this fashion is known as mega-HAART, and the approach can be successful, although complexity and toxicity of the regimen can limit efficacy. In some situations, a fully suppressive regimen cannot be constructed and the patient will

not tolerate being off therapy. Continuing partially suppressive therapy in such circumstances can be of clinical benefit, especially if resistance to chosen drugs decreases viral fitness (such as the 3TC-associated RT M184V mutations).

- I. ***Viral fitness and drug hypersensitivity.*** In general, resistance mutations decrease the replication capacity (fitness) of the virus in the absence of drug. Continuing therapy to which high-level resistance has developed may thereby result in lower viral load and clinical improvement. However, continued drug exposure in the face of resistance selects for compensatory mutations that correct the loss of replication capacity associated with resistance. Some mutations, notably reverse transcriptase M184V selected by 3TC and causing high-level resistance to that drug, can cause increased sensitivity to other drugs or reverse resistance. In the case of M184V, sensitivity to ZDV, TDF, and to a lesser extent D4T is increased and resistance may be reversed. Because 3TC remains effective against archived wild-type virus and 3TC-resistant virus can be hypersensitive to ZDV or TDF, continuing 3TC in the face of high-level resistance can be of benefit, as shown in clinical studies.
- J. ***Presenting options.*** If more than one option presents a good choice for full suppression with acceptable safety, then the various options and their relative merits should be presented to the family to elicit their judgment regarding relative value of various factors. For example, one family may accept a more frequent dosing schedule in return for better palatability, while another may opt for convenience. Avoid technical explanations; present options in terms of what the patient and family are likely to experience.

VI. Preventing resistance.

If virus replicates in the presence of drug, resistance will develop. Resistance to antiretrovirals can occur only if virus is replicating. Emergence of viral resistance depends on the level of viral replication, duration of exposure to drug, and genetic barrier to resistance. For some drugs a single point mutation confers high-level resistance, for others multiple mutations must be present. Rapidity of development of resistance, in the order of time to resistance from shortest (days to weeks) to longest (months to years): 3TC, NNRTIs > PIs (except LPV/r) > ZDV, DDI, ABC, D4T > LPV/r. The following guidelines will help prevent resistance:

- A. The most common cause of resistance is nonadherence.
- B. The next most common cause of resistance is failure to prescribe an adequately potent regimen, taking into account pre-existing resistance and baseline viral load.
- C. Avoid combining drugs with overlapping resistance patterns.
- D. If the expected decay of viral load does not occur or if virus re-emerges after being undetectable, the possibilities of nonadherence and/or drug resistance should immediately be considered and addressed. It may be best to stop treatment if the viral load does not decay rapidly towards nondetectable, in order to prevent resistance while the cause of an inadequate response is investigated.
- E. Stepwise selection for further resistance mutations will continue if a partially effective treatment program is continued. Although such a regimen may provide clinical benefit, such benefit will come at the cost of further resistance and cross-resistance.
- F. Do not add (or substitute) a single drug to a failing regimen.
- G. Additions may be made to intensify a regimen that has substantially reduced the viral load (i.e. by >2 logs) but not quite to undetectable levels.
- H. Substitutions may be made to a successful regimen to improve patient tolerance.
- I. Because resistance can develop very rapidly if there is not adherence to the entire regimen, NNRTIs should be used with caution in patients with a history of nonadherence or new patients without a record of adherence.

VII. Monitor treatment and modify plans.

- A. ***Intensive follow up is necessary to support and educate the family and to monitor adherence, tolerance, and viral response during the critical initial period of a treatment program. Follow up including viral load monitoring should be scheduled at least every 2 weeks initially, then every month until the viral load is repeatedly undetectable. Thereafter visits can be every 2-3 months if there are no medical or adherence issues.***
- B. Assessment should include objective measures of adherence such as pharmacy refill records and pill counts. Guardians should be asked specifically about medication intolerance, dosing difficulties, or inconvenience. Guardians frequently will not report non-adherence, but nonadherent guardians may report dosing difficulties and may be unable to describe the regimen in detail.
- C. ***The initial viral load response is an excellent predictor of long-term response. The viral load should drop about 1 log (10-fold) in the first week, and 2 logs by 2-3 weeks after initiation of HAART. This is followed by a slower phase decline that may continue for months.*** In general, viral load should be <400 by 2-3 months and <50 copies by 6 months, but while the log of the viral load drop is independent of baseline viral load, the time to reach <400 and <50 copies/ml targets depends on the initial viral load. (The reproducibility of viral load assays is about 2-fold, and so some error within this

range can be expected, including *transient* very low-level detectable viremia in person who has recently achieved an undetectable viral load.) ***If the viral load is not decaying as expected, immediately evaluate adherence and consider the possibility of drug resistance.*** Treatment may need to be suspended while evaluation is in progress, in order to avoid further development of resistance. If nonadherence is ruled out and the viral load has been brought down to low but not undetectable levels the regimen should be intensified (by addition of a drug or substitution with more potent drugs).

VIII. Managing treatment failure.

- A. Defining treatment failure. The goal of antiretroviral therapy is to achieve and maintain viral load below the limit of detection. Treatment failure is the failure, at any point, to follow the expected rate of virologic decay and to maintain an undetectable viral load once achieved. Continued symptoms of HIV or delay in reconstitution of CD4 counts are **NOT** failures of antiretroviral therapy and are not reasons to alter therapy. Continued viremia, even with clinical and immunologic improvement, **IS** antiretroviral therapy failure and will eventually lead to clinical and immunologic failure.
- B. Immediately confirm failure with a repeat viral load.
- C. Assess adherence with an objective method.
- D. Reassess regimen potency
 1. Does the potency of the regimen match the baseline viral load?
 2. Could there have been undetected pre-existing resistance? Could resistance have emerged on therapy (due to nonadherence or to inadequate initial potency)?
 3. If either pre-existing resistance or newly emergent resistance are possibilities, **obtain resistance testing.**
- E. Outline treatment options using principles of resistance assessment and choice of treatment described above.
- F. Do not embark on a new treatment until the causes of failure are identified and a new plan is formulated. However, continuation of a virologically failing regimen should be avoided.

Table 6. Available antiretrovirals (see Formulary for details)

Drug Class	Generic Name	Trade Name	Abbreviation
Nucleoside reverse transcriptase inhibitors	Zidovudine	Retrovir ^{1,2}	ZDV, AZT
	Lamivudine	Epivir ^{1,2,3}	3TC
	Stavudine	Zerit	D4T
	Didanosine	Videx, Videx-EC	DDI
	Abacavir	Ziagen ^{2,3}	ABC
	Zalcitabine	HIVID	DDC
	Emtricitabine	Emtriva ⁴	FTC
Nucleotide reverse transcriptase inhibitor	Tenofovir	Viread ⁴	TDF
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Viramune	NVP
	Efavirenz	Sustiva	EFV
	Delavirdine	Rescriptor	DLV
Protease inhibitors	Nelfinavir	Viracept	NFV
	Ritonavir	Norvir	RTV, r (low dosage)
	Saquinavir	Fortovase, Invirase	SQV
	Indinavir	Crixivan	IDV
	Amprenavir	Agenerase	APV
	Lopinavir/ritonavir	Kaletra	LPV/r
	Atazanavir	Reyataz	ATV
Fusion inhibitor	Enfuvirtide	Fuzeon	T-20

¹Also available as Combivir (ZDV/3TC combination, CBV)

²Also available as Trizivir (ZDV/3TC/ABC combination, TZV)

³Also available as Epzicom (3TC/ABC combination)

⁴Also available as Truvada (TDF/FTC combination)

Table 7. Preferred and alternate antiretroviral combinations for initial therapy of treatment-naïve children.

Preferred		
NNRTI-based HAART	ZDV/3TC/EFV	EFV teratogenic in primates Low barrier to resistance: avoid if adherence potential questionable Pharmacokinetic and safety data in infants <3 years old are pending.
PI-based HAART	ZDV/3TC/LPV/r	LPV/r pharmacokinetic and safety data in infants <6 months old are pending
Alternatives		
NNRTI-based HAART	NVP + 2 NRTI	NVP may not be as potent as EFV. NVP hepatic toxicity in adults; whether toxicity occurs at similar rate in children is not known.
PI-based HAART	NFV + 2 NRTI	NFV probably not as potent as ritonavir-boosted PI options, but well-tolerated and powder or crushed pills more palatable than other PI liquids.
	ATV±r + 2 NRTI	ATV under investigation in children but may emerge as attractive option for initial therapy.
	IDV/r + 2 NRTI	Under study in children.
	APV/r + 2 NRTI	APV liquid should not be used in children <4 years old.
	SQV/r or SQV/RTV + 2 NRTI	See Formulary for SQV + RTV options.
NRTI-based HAART	ZDV/3TC/ABC	Less potent than other options; do not use if VL>100,000. Good option for more potent NRTI arm of NNRTI- or PI- based regimen.
	ZDV/3TC/ABC/TDF	Not formally tested, but simple, well tolerated, and theoretically should be potent and durable. TDF may cause bone mineral loss in children; avoid pending further data. Pediatric TDF formulation not available.
Options for young infants		
3-drug options	ZDV/3TC/NFV	NFV powder in formula; infants require high dosage
	ZDV/3TC/NVP	
	ZDV/3TC/RTV	RTV no longer used in older children except as booster
	ZDV/3TC/LPV/r	LPV/r under study in infants < 6 months of age
	ZDV/3TC/EFV	Dosage of EFV in children < 3 not well established
4-drug options	ZDV/3TC/NVP/NFV	Similar regimen (D4T instead of ZDV) well-studied and effective
	ZDV/3TC/ABC + PI or NNRTI	ABC not labeled for use < 3 months of age
Alternative NRTI Combinations (with NNRTI or PI)		
Studied in children	ZDV/DDI	ZDV hinders selection of DDI resistance due to hypersensitivity
	D4T/3TC	
Studied in adults only	ABC/3TC	Overlapping resistance, but effective in clinical trial
	ZDV/ABC	
Effective but concerns in children	TDF/3TC or TDF/FTC	Preliminary data suggest bone mineral loss with TDF in children. 3TC/FTC resistance (M184V mutation) causes hypersensitivity to TDF so TDF generally should be used with 3TC or FTC
Combinations to avoid		
Do not use	ZDV/D4T	Pharmacologically antagonistic
	NVP/EFV	No benefit; increased toxicity
	3TC/FTC	No data, no theoretical benefit
	DDC	Toxicity and low potency leave no role for this drug
	Hydroxyurea	Formerly used to enhance DDI effect, but too toxic
	D4T/DD I	Synergistic toxicity, especially in pregnant women
Avoid	ABC/3TC/TDF or ABC/TDF	ABC/3TC/TDF fails as a HAART regimen, with emergence of K65R mutation giving resistance to all 3 drugs. Inclusion of ZDV would probably prevent K65R from emerging, due to hypersensitivity to ZDV.
	ABC/DDI	Both drugs select for K65R and L74V mutations. Inclusion of ZDV might prevent emergence of these mutations due to hypersensitivity.
	DDI/TDF	Both drugs select for K65R mutation. Inclusion of ZDV might prevent emergence of this mutation due to hypersensitivity.
Once-daily drugs		
FDA-approved once daily (in adults only except EFV and DDI-EC also in children)		ABC, APV/r, ATV/r, DDI-EC, 3TC, FTC, TDF

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV AND MANAGEMENT OF THE HIV-EXPOSED INFANT

I. Voluntary counseling and HIV testing of pregnant women

See U.S. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs During Pregnancy for Maternal Health and Reduction of Perinatal Transmission of Human Immunodeficiency Virus Type 1 in the United States at <http://www.aidsinfo.nih.gov/guidelines/>.

- A. All pregnant women should be offered testing for HIV infection. HIV testing should be presented as part of the set of routine screens recommended for *all* pregnant women (similar to STS, red cell antibodies, or glucose), and the clinician should avoid assessments of perceived risk.
- B. Testing may be repeated at term in women continuing to engage in high-risk behavior.

II. Management of HIV in pregnancy

- A. The urgency of protecting the fetus means that the woman must quickly be engaged as a full partner in her care. For several reasons- including the usual stresses of pregnancy, a new diagnosis of HIV, a high prevalence of substance abuse, social isolation exacerbated by the stigma of HIV, risk of domestic violence or abandonment, problems with access to prenatal care or willingness to engage in prenatal care- **HIV infected pregnant women should be followed very closely in a supportive multidisciplinary environment.** Pregnant HIV-infected women should be seen in consultation with specialists in HIV, preferably with experience in management of HIV in pregnancy.
- B. The newly diagnosed HIV-infected woman should be evaluated thoroughly for disease status, complications, and comorbid conditions, as for any new HIV diagnosis. The process of HIV education, support, and treatment should not be delayed until after parturition.
- C. Track infected pregnant women to ensure that they or their infants are not lost to follow up.
- D. Follow up should include assessment of adherence to therapy. The best measure of adherence is the viral load assay, which should be performed frequently. Failure to achieve and maintain an undetectable viral load on therapy should be addressed promptly.

III. Antiretroviral treatment and prophylaxis

- A. Table 8 describes the risk of transmission of HIV from mother to child without intervention. Risk is related to the maternal viral load, but is still significant in *untreated* women with very low or nondetectable viral loads. Obstetric factors, most strongly duration of rupture of membranes, also increase risk of transmission. *Because a significant proportion of infant infections occur prior to labor and delivery, interventions to prevent mother-to-child transmission should begin by the second trimester.* The efficacy of interventions to prevent mother-to-child transmission depends on the **timing** and **intensity** of treatment. *HAART begun early in the second trimester and continued to maintain an undetectable viral load through labor and delivery almost eliminates the risk of mother-to-child transmission of HIV (Table 8).*

Exposure	Transmission risk (%)	Cumulative risk (%)
1st trimester	<1	<1
2nd trimester	2	2
3rd trimester	5	7
Labor & delivery	12-14	19-21
24 months breastfeeding	12-18	31-39

- B. The pregnant woman newly diagnosed with HIV should be thoroughly evaluated as for any other new diagnosis of HIV. The process of HIV education, support, and treatment should not be delayed until after parturition.
- C. Scenarios relevant to pregnancy and HIV include:
 1. HIV-infected women who may become pregnant. Antiretroviral therapy, if indicated, should be formulated to consider the possibility of conception while on therapy. EFV should be avoided due to the possibility of early teratogenicity.
 2. Pregnant women who are receiving antiretroviral therapy. Generally, therapy should continue, with modifications as appropriate. Consideration may be given to suspending therapy in the first trimester to avoid drug exposure, although benefits of such a measure may not outweigh risks.
 - a) If current therapy is not maintaining an undetectable viral load, then adherence assessment and resistance testing should be performed and treatment reformulated to optimize efficacy.

- and fetal safety
- b) Women receiving antiretroviral therapy and maintaining an undetectable viral load may be continued on the same therapy unless pregnancy poses a contraindication (such as EFV in the first trimester or the combination of D4T and DDI at any time during gestation). Consideration may also be given to stopping HAART if pregnancy is diagnosed early, and resuming the same regimen after the first trimester. A supervised withdrawal and reinstatement of therapy is not likely to select for resistance. Whether the benefits of treatment interruption outweigh risks is not known.
 - c) Inclusion of ZDV in the regimen is preferred, unless it is contraindicated or unlikely to be effective. There is no evidence or compelling argument that ZDV has efficacy superior to alternatives, especially if there is documented resistance.
3. Pregnant women whose clinical status meets criteria for initiating antiretroviral therapy. Women who need therapy for indications of their own health should receive HAART according to adult guidelines, modified as indicated for pregnancy (<http://www.aidsinfo.nih.gov/guidelines/>). Delaying initiation of therapy until after the 1st trimester may be considered.
 4. Pregnant women whose clinical status does not meet usual criteria for antiretroviral therapy for the woman's own health. **If the maternal clinical status does not meet guidelines for treatment based on maternal indications, HAART should be offered on the basis of the proven benefit in minimizing maternal-fetal transmission.** For most women, treatment should consist of 3-drug HAART designed to achieve and maintain an undetectable viral load up through parturition. ZDV should be included as part of the regimen, if possible. If the pretreatment viral load is <1000 copies/ml, prophylaxis with 1-2 NRTI (usually ZDV with or without 3TC) may be considered, although there may be residual risk of transmission. Treatment may be delayed until the end of the first trimester, in order to reduce the theoretical risk to the fetus, without greatly compromising efficacy.
- D. Treatment should be continued during labor as tolerated.
- E. Various non-HAART regimens have been evaluated for use in settings where resources limit availability of HAART. These are summarized in Table 9. In general, the longer and more intensive the regimen, especially at term, the more effective. Also note that if mother received ZDV during pregnancy, intrapartum NVP does not appear to be necessary if neonatal NVP given.
- F. Choice of antiretroviral drugs for pregnant women is complicated by the known and unknown risks of ARV in pregnancy. Considerations include:
1. The level of experience with various ARVs in pregnancy should influence choice of ARV. The most experience is with ZDV and should be included whenever possible. 3TC, NVP, NFV have been studied and there is increasing use of LPV/r and ABC.
 2. The combination of D4T + DDI in pregnancy is associated with lactic acidosis, hepatic steatosis, and death (at or after term).
 3. EFV causes a high incidence of severe birth defects (anencephaly, anophthalmia, cleft palate) in rhesus monkeys exposed in utero to therapeutic levels, and one similar case has been reported in humans. Because these defects develop very early in gestation, EFV should be avoided in women who might become pregnant.
 4. There have been reports of fatal mitochondrial pathology (primarily CNS symptoms) in infants exposed to ZDV + 3TC continuously from mid-pregnancy through 6+ weeks of age. Review of experience with exposure to ZDV monotherapy or in combination with 3TC during pregnancy followed by neonatal ZDV monotherapy has not revealed similar cases, although changes in mitochondria due to fetal exposure can be detected. In utero exposure to ZDV, 3TC, D4T, and especially to DDI is associated with prolonged elevated lactic acid levels in the infant. The risk of transmission of HIV from a mother whose viremia was well controlled during pregnancy is very low, and so nucleoside exposure after delivery should be limited to ZDV monotherapy in most cases.
 5. An early report showing increased incidence of premature delivery in mothers receiving protease inhibitors was not confirmed in larger series.
 6. Protease inhibitors are associated with insulin resistance and hyperglycemia, which could contribute to gestational diabetes.
 7. Some antiretrovirals, especially protease inhibitors, can cause nausea or vomiting, especially in the first week of treatment, and could exacerbate morning sickness or abdominal discomfort in pregnant women.
 8. A registry of antiretroviral use in pregnancy (<http://www.apregistry.com/>) has not revealed an increased risk of all birth defects or any consistent pattern of teratogenicity associated with exposure to commonly used antiretrovirals, but data for many are limited. Reports to the registry of

all pregnancy outcomes after antiretroviral exposure are encouraged.

Table 9. Rates of transmission of HIV from mother to child with various interventions	
Intervention (IP = intrapartum)	% HIV+ at 1 month
None	~18-22
Neonatal NVP or ZDV	13-21, 9.3-16.6
Neonatal ZDV/3TC or ZDV/NVP	14.2-15.3
Intrapartum/neonatal NVP	10.4-11.9
Intrapartum/neonatal ZDV	10-20
Intrapartum/neonatal ZDV/3TC	7.9-8.9
ZDV start 36-37 wk + IP + neonatal	9.6-15.1
ZDV start 35 wk + IP + neonatal	8.6-10.4
ZDV start 23-28 wk + IP + neonatal	4.3-8.3
ZDV/3TC start 36, 34, 23 wk	5.9, 2.8, 1.6
ZDV start 34 wk + IP ZDV/NVP neonatal NVP	4.3%
ZDV start 34 wk + IP ZDV + neonatal NVP	3.7%
ZDV 28 wk + IP NVP +/- neonatal NVP	1.1-2.0
HAART 34 wk	3.6
HAART starting early 2 nd trimester	<1

G. Transplacental passage of antiretrovirals. In general, NRTIs and NNRTIs cross the placenta well; protease inhibitors show little transplacental passage. Antiretroviral treatment has efficacy for preventing mother-to-child transmission out of proportion to the effect on maternal viral load, probably due to a prophylactic effect of having drug in the fetus at the time of viral exposure. This implies that antiretrovirals with better transplacental passage are preferred (although considerations of fetal toxicity would favor drugs not crossing the placenta). In practice, the fetus will maintain effective levels of 2-3 drugs depending on whether a PI or an NNRTI, respectively, is used with 2 NRTI in a HAART regimen.

H. Antiretroviral prophylaxis during labor

1. Oral ARV drugs should be continued as long as tolerated during labor.
2. ZDV should be given during labor unless contraindicated. The original study of ZDV in pregnancy (ACTG 076) used intravenous ZDV 2 mg/kg over 1 hour, followed by 1 mg/kg/h until delivery. Other studies done in developing countries have used 300 mg p.o. every 3 hours (with a loading dose of 600 mg for the first dose if mother not receiving ZDV during pregnancy).
3. Regimens using single dose NVP in women who receive no other antiretrovirals or who have been on ZDV monotherapy during pregnancy may result in resistance in mothers and in infants failing prophylaxis and increased failure rates with subsequent NVP-containing HAART. Preliminary evidence indicates that a week of ZDV/3TC after single dose NVP greatly reduces the risk of resistance.

I. **HIV transmission and mode of delivery.**

1. Elective Cesarean section prior to onset of labor or rupture of membranes (at 38 weeks gestation) reduces the risk of vertical transmission of HIV from women on no antiretrovirals or on ZDV monotherapy. **Elective Cesarean section is not likely to have measurable additional benefit**

in women receiving HAART and maintaining a very low or undetectable viral load; the transmission risk in women successfully treated with HAART is extremely low. Cesarean delivery should probably be reserved for women not receiving highly active antiretroviral therapy or in whom virologic control has not been achieved. This approach emphasizes medical, rather than surgical, prophylactic measures [see JAMA 281:1946 (1999)].

2. For the woman presenting late in gestation or not achieving virologic control by late in gestation, alternatives include intensive efforts to treat with HAART until vaginal delivery at term, or giving HAART until a scheduled C section at 38 weeks. The preferred alternative would likely depend on individual consideration of the likelihood of quickly achieving adherence to HAART.

IV. Antiretroviral prophylaxis of the HIV-exposed infant

- A. Results from clinical trials suggest that the intensity and duration of infant antiretroviral prophylaxis required to prevent transmission depends on the intensity of maternal prophylaxis. ZDV for 6 weeks is the standard, but one trial directly comparing 3 days and 6 weeks of infant ZDV (in women treated with ZDV from 28 or 35 weeks gestation) showed no difference in transmission risk.
- B. Infants born to mothers who received HAART and had an undetectable viral load at term are at low risk of infection. U.S. guidelines recommend a 6-week course of ZDV; shorter courses may be recommended in other settings.
- C. Infants of mothers who received little or no antiretroviral prophylaxis should be considered for more intensive neonatal prophylaxis. There are no regimens of proven high efficacy in this situation (see Table 9). A reasonable option is a short course of combination antiretroviral therapy; such prophylaxis should consist of drugs that have been studied in newborns, such as ZDV + 3TC + 1-2 doses of NVP (depending on whether mother received NVP).
- D. Initiation of antiretroviral prophylaxis more than 48-72 hours after infection is unlikely to be effective.
- E. Neonatal prophylaxis and drug resistance
 1. Treatment with HAART that achieves and maintains an undetectable viral load is known not to lead to development of resistance. ZDV monotherapy in the last trimester is also not likely to lead to resistance. Single-dose NVP prophylaxis results in NVP resistance in about half of infants failing prophylaxis.
 2. Women with HIV that has developed resistance during prior attempts at therapy can pass resistant virus to the infant. The maternal HIV resistance status should be considered in planning maternal and neonatal prophylactic regimens.

V. Evaluation and management of the HIV-exposed infant

- A. HIV-exposed infants should be followed closely in a supportive environment to ensure compliance with antiretroviral and PCP prophylaxis, to perform viral diagnostics, to start early treatment if HIV is confirmed, and to counsel the family.
- B. History. Initial evaluation of the HIV-exposed infant should include:
 1. Maternal HIV diagnostic history. Resolve any uncertainties about the maternal diagnosis.
 2. Other maternal conditions that may affect the infant, including hepatitis B, hepatitis C, and syphilis testing status.
 3. Life-long maternal treatment history and resistance testing history.
 4. Treatment history and virologic response during the pregnancy.
 5. Intrapartum and neonatal prophylaxis.
 6. Neonatal HIV PCR results.
 7. The existence of any maternal siblings and their HIV diagnostic status. From the maternal diagnostic history, an earliest date of maternal infection can be determined if there is a clear history of a negative HIV test. Otherwise, *all maternal siblings of the exposed infant should be considered exposed and potentially infected, regardless of apparent good health- HIV can remain undiagnosed in a congenitally infected child through adolescence and beyond, until presenting with catastrophic complications.*
 8. A complete social assessment, including the mother's HIV care status. Women will often bring their child in for care while neglecting their own care and need assistance or encouragement in seeking care.
- C. Timing of HIV infection and incubation period. Among non-breastfed infants eventually found to be infected, about a third have a positive virologic test on the first day of life. The large majority of the rest develop detectable HIV around 2-4 weeks of age. All HIV-exposed infants not receiving treatment have detectable virus by 2 months of age. Maternal HAART and neonatal prophylaxis with ZDV may temporarily suppress virus to below the limit of detection, but rapid viral rebound can be expected as soon as ZDV is discontinued.
- D. Virologic testing. All infants of HIV-seropositive mothers have passive HIV antibodies. Testing for HIV

- infection of the infant must use virologic methods, which include RT PCR (reverse-transcribed PCR, the standard viral load assay, which detects viral RNA in plasma), or NASBA (nucleic acid sequence-based amplification, which also detects viral RNA and is used as a viral load assay). RNA methods may be slightly more sensitive (detecting infection slightly earlier), but either DNA or RNA methods are acceptable and the choice of method should be driven by considerations of cost, sample handling issues, and the availability and reliability of local laboratories (some laboratories have had problems with low-level false positive RT PCR). HIV culture has no advantage and many disadvantages over PCR techniques, and p24 assays are not sensitive. Sensitive assays for reverse transcriptase enzymatic activity have not been sufficiently tested for infant diagnosis. DNA detection on filter paper blood spots is less sensitive than standard methods, but offers advantages of ease of sample collection and shipping.
- E. Testing schedule. At the University of Maryland, PCR for HIV is recommended at birth, 4 weeks, 8 weeks, and 4 months of age. If PCR was not done at birth, it is usually done at the initial outpatient visit at 2 weeks. The standard viral load assay is performed on 1-2 ml of blood in an EDTA (purple top) tube. HIV infection can reasonably be excluded in a non-breastfed infant with negative results from a minimum of 2 PCRs after 1 month of age, including 1 PCR after 4 months of age. The same schedule using DNA PCR is equally acceptable.
- F. Serologic tests for HIV in infants. Maternal IgG antibodies to HIV cross the placenta, leading to positive serologic tests in exposed infants. Half of seropositive, uninfected infants become seronegative by 10 months, but all are not negative until 18 months. Rarely, infants with rapidly progressive disease may become seronegative. HIV-infected Infants started on HAART in early infancy often become seronegative. If virologic tests (such as PCR) are performed according to recommendations, serologic tests for HIV in infants are unnecessary except:
1. To determine if a newborn infant of a mother of unknown HIV status is exposed. This may arise if the mother refused testing for herself or an infant is abandoned. Serology on the newborn discloses mother's HIV status. A serologic test to screen for HIV exposure is part of the initial metabolic screen for all babies born in New York State.
 2. To confirm virologic testing. Serologic testing at 18 months has been recommended in order to confirm virologic results. However, if virologic testing has been done according to recommendations, it is not absolutely necessary.
- G. There is no reason to perform CD4 counts in HIV-exposed infants if virologic testing is available.
- H. ZDV given during pregnancy and to the newborn usually causes mild anemia. The hemoglobin should be monitored; occasionally ZDV may need to be stopped before 6 weeks because of progressive anemia. The anemia resolves rapidly after discontinuation.
- I. Hepatitis C testing. Most people in the U.S. with a history of injection drug use are hepatitis C seropositive (of which about half have ongoing infection) and a large proportion has hepatitis B. The risk of vertical transmission of hepatitis C from seropositive mothers is about 3% from HIV-uninfected mothers and 12% from HIV-infected mothers. Transmission only occurs if the mother has hepatitis C viremia, but often the maternal hepatitis C viral load has not been determined. If a history of needle use is known or suspected and hepatitis C serology on the mother is not available, then it should be performed on the newborn to look for passively acquired antibody. Infants exposed to hepatitis C should have 2 hepatitis C PCRs performed after 1 month of age. Serology may be done at 18 months of age.
- J. PCP prophylaxis. Infants with HIV infection have a very high incidence of *Pneumocystis jirovecii* (formerly *carinii*) pneumonia. TMP/SMX (Bactrim) has been recommended for all HIV-exposed infants, to begin at 6 weeks of age and continue until HIV infection has been ruled out (i.e. when the final PCR is done at 4 months of age). The initiation of TMP/SMX may be delayed until 8 weeks to allow for recovery from ZDV-induced anemia if PCR was negative at 4 weeks of age. (In practice, an infant with negative PCRs at birth and 4 weeks of age is unlikely to have HIV infection and extremely unlikely to have severe manifestations of disease by the time repeat PCR is done at 2 months. However, decisions to withhold, delay, or discontinue TMP/SMX prophylaxis should consider the possibility that the child will not return for follow up as scheduled.)
- K. Infants with a positive PCR should be called back immediately for confirmatory diagnostic testing along with baseline laboratories (viral load, CD4 count, hematology and chemistries). HIV infection is confirmed with 2 positive virologic tests. Infants with HIV infection should be started on antiretroviral therapy as soon as possible. This will require that the family be educated regarding the infant's needs and be supported as they contemplate the diagnosis and begin therapy. See treatment guidelines below. PCP prophylaxis should be started by 6 weeks of age in infected infants and continued until the viral load is repeatedly nondetectable and the CD4 count is normal.

VI. HIV transmission and infant feeding

- A. HIV transmission and breastfeeding. There is about a 10-18% additional risk of HIV transmission from breastfeeding.
 1. Risk is highest in early infancy, but continues throughout the period of breastfeeding.
 2. Risk is related to the maternal viral load, mastitis (clinical or subclinical), and milk viral load.
 3. In situations where breast milk substitute feeding is not acceptable, feasible, affordable, sustainable and safe and carries a very high mortality and a women chooses to breastfeed, exclusive breastfeeding should be supported. Exclusive breastfeeding minimizes risk of diarrheal disease and carries a lower (but still significant) risk of HIV transmission than mixed feeding
- B. In some resource-limited situations, feeding with breast milk substitute can be difficult and has considerable morbidity and mortality. A counseling process should assess whether substitute feeding is acceptable, feasible, affordable, sustainable, and safe. Women in these settings must be able to make an free and informed decision regarding feeding their infant.
- C. Women not breastfeeding need access to affordable nutritionally complete breast milk substitute and support for its safe use. Breastfeeding women should be educated and supported to exclusively breastfeed, particularly not giving any milk substitutes.
- D. Preliminary results indicate that 3TC or NVP prophylaxis giving twice daily to nursing infants may reduce the risk of post-natal HIV transmission. Another study comparing breastfeeding + ZDV versus formula feeding + placebo showed less HIV transmission in the formula-fed group, but no difference in 18 thon HIV-free survival. There was no breastfeeding + placebo group, to directly determine the effect of ZDV. Other trials of prevention of HIV transmission from breastfeeding are planned or ongoing. At this point, antiretroviral prophylaxis of infants may be considered promising but unproven.
- E. It is not known if HAART to the nursing mother reduces the risk of HIV transmission, but such an effect is likely. In one study, ZDV/3TC/NVP results in 88% of women having no detectable free virus in their milk (as compared to 36% of untreated women). Significant levels of 3TC and NVP are found in the blood of infants nursing from mothers receiving these drugs.

WEB RESOURCES FOR PROFESSIONALS AND HIV-AFFECTED FAMILIES

<http://www.pedhivaids.org/>

The National Pediatric and Family HIV Resource Center. Information for families with children infected with HIV.

<http://www.hivatis.org/>

The HIV/AIDS Treatment Information Service. US government website with treatment, guidelines for adult, pediatric, pregnant woman, other information for professionals and public.

<http://www.hivmedicationguide.com/>

Antiretroviral drug interaction data. Extensive, well-referenced, up-to-date, user friendly.

<http://www.iasosociety.org/>

Website of the International AIDS Society. Search for International AIDS Conference and IAS Conference on HIV Pathogenesis and Treatment abstracts.

<http://www.retroconference.org/>

Website of the annual Conference on Retroviruses and Opportunistic Infections. Search past CROI abstracts.

<http://hivdb.stanford.edu/>

HIV sequence and drug resistance/genotype site.

<http://www.hivresistanceweb.com/>

HIV drug resistance information. Appears not to have been updated in past year.

<http://www.who.int/3by5/en/>

Website of the WHO's "3 by 5" program for expansion of antiretroviral therapy to resource-limited settings.

<http://www.synergyaids.com/>

Website of the US Agency for International Development's programs for expansion of HIV prevention and treatment services to resource-limited settings.

<http://www.Hopkins-aids.edu>

The web site of the Johns Hopkins adult HIV program.

<http://www.cdc.gov/hiv/pubs/facts.htm>

The HIV section of the federal Centers for Disease Control and Prevention website.

<http://pubmed/>

The National Library of Medicine's free service for searching the entire world's medical literature.

<http://hivinsite.ucsf.edu/>

The website of the University of California at San Francisco's HIV program.

Figure 1. Resistance patterns of antiretrovirals. Compiled from several sources.

Nucleoside Reverse Transcriptase Inhibitors						
Mutation	ZDV	DDI	D4T	3TC FTC	ABC	TDF
M41L						
E44D						
A62V						
K65R	IS					
D67N						
T69D/N/S						
T69ins ¹						
K70R						
L74V	IS					IS
V75T/M/A/I					?	?
F77L						
Y115F						
F116Y						
V118I						
Q151M						
M184V ²	IS		IS			IS
L210W						
T215Y/F						
K219Q/E/N						
	Intermediate/high level resistance					
	Low level resistance					
	Contributes to resistance					
?	Unknown					
IS	Increased susceptibility M184V may reverse ZDV or TDF resistance					
1)	S insertion. In combination with other mutations causes high-level resistance to all NRTI.					
2)	M184V causes high level 3TC or FTC resistance					

Non-Nucleoside Reverse Transcriptase Inhibitors			
Mutation	NVP	DLV	EFV
A98G			
L100I			
K101E			
K101P			
K103N			
K103R			
V106A			
V106M			
V106I			
V108I			
V179D/E			
Y181C/I			*
Y188C			
Y188L			
Y188H			
G190A/S		IS	
P225H		IS	
M230L			
P236L			
Y318F			
	High level resistance		
	Intermediate resistance		
	Low level resistance		
	No resistance		
?	Unknown		
IS	Increased susceptibility		
	Low level resistance in vivo, but associated with failure		
*			

Protease Inhibitors							
Codon	SQV	IDV	RTV	NFV	APV	LPV*	ATV
10							
20							
24							
30							
32							
33							
36							
46							
47							
48							
50L	IS	IS	IS	IS	IS	IS	
50V							
53							
54							
63							
71							
73							
77							
82							
84							
88	?						
90							
93							?
	Causes resistance						
	Major resistance mutation-may require other mutations for high-level resistance						
	Contributes to resistance- may require other mutations to be significant						
	Accessory mutation- may contribute to resistance if other mutations present						
	No resistance						
?	Unknown						
IS	Increased susceptibility						
*LPV requires 4-10 mutations for resistance							

PEDIATRIC ANTIRETROVIRAL FORMULARY

Notes:

1. Dosages approved for marketing and other well-established dosages are given. Other dosage regimens for which there are some supportive data are noted with question mark (?). All dosages are for the oral route except as noted.
2. Check adult dosages for maximum pediatric dosage.
3. Interactions table: First column is co-administered drug; second column is ratio of AUC (area under time-concentration curve) of ARV given in combination/given alone; third column is ratio of AUC of co-administered drug given in combination with ARV/given alone. AUCs may be over dosing interval or to infinity. Generally, effects less than 20% are not included. Fold-changes in C_{min} (which may be therapeutically important, especially for NNRTIs and PIs) are generally greater than fold-changes in AUC.
4. Several interrelated complications are associated with HIV infection or its treatment. These include peripheral lipodystrophy, dyslipidemias, insulin resistance, and bone mineral loss. Evidence associating these complications with specific drugs varies. The protease inhibitors except ATV are associated with dyslipidemias and insulin resistance. D4T is associated with lipodystrophy, dyslipidemia, and insulin resistance. Other causal associations with specific drugs are less clear. Visceral fat accumulation has been associated with HIV treatment, but it is not clear whether this is a separate entity or represents coexisting obesity and peripheral lipodystrophy.
5. RTV boosting of protease inhibitors. Low-dosage RTV (abbreviated r or rtv) is used to inhibit metabolism of protease inhibitors, producing lower dosage and/or greater exposure of co-administered PI. Low-dosage RTV does not have significant antiviral activity. RTV boosting often reverses effects of third drugs or food on co-administered PI pharmacokinetics. Low-dosage RTV may have profound effect on PK of multiple drugs; see information for RTV.
6. Drug interaction data mostly from HIV negative adults; effects in children with HIV may differ.
7. Pregnancy risk category definitions.
 - A. Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
 - B. No evidence of risk in humans. Either animal findings show risk, but human findings do not, or, if no adequate human studies have been performed, animal findings are negative.
 - C. Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk, or lacking as well. However potential benefits may justify the potential risk.
 - D. Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
 - X. Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

Zidovudine (Retrovir/AZT/ZDV)					
Nucleoside reverse transcriptase inhibitor					
Dosage		Formulation		Adverse effects	
<u>Premature neonate</u> (<34 wk): 1.5 mg/kg IV or 2 mg/kg p.o. q 12 hr IV then increase to q 8 hr at 2 weeks (for >30 wk EGA) or 4 weeks (for <30 wk EGA)		<u>Syrup:</u> 10 mg/ml (240ml, stable, mildly unpleasant taste) <u>Cap:</u> 100 mg (#100) <u>Tab:</u> 300 mg (#60) <u>IV:</u> 10 mg/ml (20ml)		Common: anemia, GI intolerance, neutropenia, fatigue, headaches, insomnia, myalgia. MCV always increases. Uncommon: myopathy, myositis, cardiomyopathy, hepatitis, SEVERE OR FATAL LACTIC ACIDOSIS (presents as fatigue, tachypnea, abdominal pain, vomiting), hepatic failure, fingernail discoloration.	
<u>Term neonate</u> <u>(prophylaxis):</u> 2 mg/kg q 6 hr or 4 mg/kg q 12 hr or 1.5 mg/kg q 6 hr IV		Stable 15-25 C <u>Fixed combinations</u> <u>Combivir tabs:</u> 300 mg ZDV + 150 mg 3TC <u>Trizivir tabs:</u> 300 mg ZDV + 150 mg 3TC + 300 mg ABC			
<u>Child:</u> 160 (120-180) mg/m ² po tid (120 mg/m ² q 6 hr IV) ? 240 mg/m ² bid					
<u>Adult:</u> 200 mg tid or 300 mg bid					
<u>Intrapartum prophylaxis:</u> 2 mg/kg IV over 1 h then 1mg/kg/h IV (300 mg po q 3 hr has been used in resource-poor setting with similar efficacy.)					
Pharmacology					
Absorption: 90% (but 1st pass metabolism of 30%). Not changed by food. Metabolism: glucuronidation Excretion: glucuronide in urine					
Interactions: AUC ratio (combined /alone) of ZDV or co-administered drug.					
Co-admin. Drug	ZDV AUC	Co-admin. Drug AUC	Co-admin. Drug	ZDV AUC	Co-admin. Drug AUC
Amprenavir	1.31	1	Methadone	1.43	
Atovaquone	1.31		Nelfinavir	0.65	
Fluconazole	1.74		Nevirapine	0.75	
fAPV	1.31		Probenicid	2.06	
Ganciclovir	1.20		Rifampin	0.47	
3TC	1.39	1	Ritonavir	0.75	
			Valproate	1.80	
No significant effect of on ZDV: ABC, ATV, DDI, DLV, EFV, FTC, IDV, SQV, dapsone, rifabutin, TMP/SMX Simultaneous clarithromycin dosing may decrease ZDV- separate doses. Inducers of glucuronidation such as phenobarbital, DPH, or carbamazepine may decrease ZDV level. ZDV inhibits D4T activation: Do not use ZDV and D4T concurrently. Anemia or neutropenia may be worsened when coadministered with other drugs sharing these toxicities.					

Lamivudine (EpiVir/3TC) Nucleoside reverse transcriptase inhibitor						
Dosage	Formulation	Adverse effects	Pharmacology			
<u>Neonate <30 d:</u> 2 mg/kg bid <u>Child (> 1 month old):</u> 4 mg/kg bid <u>Adult:</u> 150 mg bid 300 mg qd	<u>Solution:</u> 10 mg/ml (240 ml, stable at RT, tastes good) 5mg/ml (EpiVir HBV) <u>Tab:</u> 100 (EpiVir HBV) 150 mg (#60) 300 mg (#30) <u>Fixed combinations</u> <u>Combivir tabs:</u> 300 mg ZDV + 150 mg 3TC <u>Trizivir tabs:</u> 300 mg ZDV + 150 mg 3TC + 300 mg ABC <u>Epzicom tabs</u> 600 mg ABC + 300 mg 3TC	Uncommon: ↑liver enzymes, SEVERE OR FATAL LACTIC ACIDOSIS (presents as fatigue, tachypnea, abdominal pain, vomiting), ?nausea, ?headache, ?rash, ?peripheral neuropathy, ?pancreatitis, See note re: potential toxicity in perinatal section above.	Absorption: 66% bioavailable; unaffected by food Metabolism: Minimal Excretion: Unchanged in urine Interactions: AUC ratio (combined /alone) of 3TC or co-administered drug.			
			Co-admin. Drug	3TC AUC	Co-admin. Drug AUC	Co-admin. Drug AUC
			ZDV	1	1.39	TMP/SMX 1.43 1
			No significant interaction either way with ABC, APV, EFV, fAPV, NFV, TDF, No significant effect on 3TC: NVP, ribavirin			

Didanosine (Videx, Videx-EC, DDI) Nucleoside reverse transcriptase inhibitor								
Dosage	Formulation	Adverse effects	Pharmacology					
<u>Videx</u> Neonate < 90 days: 50 mg/m ² bid <u>Child:</u> 90-120 mg/m ² bid <u>Adult >60 kg:</u> 200-250 mg bid <u>Adult <60 kg:</u> 125-167 mg bid Take on empty stomach >30 min before or >2 hr after meal. <u>Videx EC</u> <u>Adult > 60 kg:</u> 400 mg qd 250 mg qd with TDF <u>Adult < 60 kg:</u> 250 mg qd 200 mg qd with TDF Take on empty stomach; may be taken with light meal when given with TDF	<u>Videx (buffered)</u> <u>Tablets:</u> 25, 50, 100, 150, 200 mg (#60; chew or disperse in water; take 2 tabs at once to get sufficient buffer). <u>Suspension:</u> 10mg/ml (2, 4g bottles, suspended in antacid; 30d @ 4C). Shake well. Tastes like antacid. <u>Videx EC caps:</u> Caps with enteric coated beads: 125 mg, 200 mg, 250 mg, 400 mg All stable RT	Common: pancreatitis, peripheral neuropathy (? less common in children, more likely with advanced disease). Uncommon: abdm pain, diarrhea (buffered formulations), emesis, liver toxicity, SEVERE OR FATAL LACTIC ACIDOSIS (presents as fatigue, tachypnea, abdominal pain, vomiting), retinal depigmentation, rash. Note: Tabs contain Na, Mg, Ca. DDI toxicity is enhanced by hydroxyurea or D4T COMBINATION OF D4T AND DDI IN LATE PREGNANCY PRESENTS HIGH RISK OF ACIDOSIS AND HEPATIC STEATOSIS WITH HIGH MATERNAL AND FETAL MORTALITY	Absorption: Buffered formulation: 42%; inhibited ~50% by food. Videx EC: AUC ↓19% by food. Metabolism: Extensive Excretion: 20-50% in urine Interactions: AUC ratio (combined /alone) of DDI or co-administered drug. Note: this table does not include effects of buffered DDI on absorption of other drugs (see comments).					
			Co-admin. Drug	DDI AUC	Co-admin. Drug AUC	Co-admin. Drug	DDI AUC	Co-admin. Drug AUC
			ATV	1.26	0.89	Allopurinol	2.2	
			TDF	1.48 (fasted) 1.60 (fed)	1	Ganciclovir	1.5-2.2	0.9
			Simultaneous dosing of buffered DDI may decrease absorption of: ketoconazole, ciprofloxacin (& other fluoroquinolones), itraconazole, quinolones, tetracyclines, IDV, DLV, dapsone, RTV, ATV, NFV, LPV/r, tenofovir (decreased 32%). May take buffered DDI simultaneously with ZDV, D4T, EFV, NVP, APV Methadone decreases absorption of DDI buffered tablets No effect on DDI (except see note on buffered DDI): azithromycin, TMP/SMX, fluconazole, itraconazole, foscarnet, methadone, ranitidine, ribavirin, rifabutin, RTV No effect of DDI (except see note on buffered DDI) on: dapsone, fluconazole, itraconazole, foscarnet, IDV, ribavirin, rifabutin, RTV, SQV Warning: Coadministration with drugs associated with pancreatitis or peripheral neuropathy may increase these risks.					

Stavudine (Zerit, D4T) Nucleoside reverse transcriptase inhibitor								
Dosage	Formulation	Adverse effects	Pharmacology					
<u>Infant, Child:</u> 1 mg/kg bid (up to weight of 30kg)	<u>Solution:</u> 1 mg/ml (200 ml, 30 days @ 4C, mildly unpleasant taste)	Common: headache, GI, rash, lipodystrophy, insulin resistance, hypercholesterolemia. peripheral neuropathy (more likely with advanced disease; rare in children) Uncommon: hepatic toxicity, pancreatitis, SEVERE OR FATAL LACTIC ACIDOSIS (risk greater with D4T than with other NRTIs; presents as fatigue, tachypnea, abdominal pain, vomiting).	Absorption: 75% bioavailable; unaffected by food Metabolism: minimal Excretion: unchanged in urine					
<u>Adult 30-60 kg:</u> 30 mg bid	Unreconstituted powder stable RT. Solution 4 C X 30 d	THE COMBINATION OF D4T AND DDI IN LATE PREGNANCY APPEARS TO PRESENT A HIGH RISK OF ACIDOSIS AND HEPATIC STEATOSIS WITH HIGH MATERNAL AND FETAL MORTALITY	Interactions: AUC ratio (combined /alone) of D4T or co-administered drug.					
<u>Adult >60 kg:</u> 40 mg bid	<u>Caps:</u> 15, 20, 30, 40 mg (#60) Stable RT An extended-release formulation (D4T-XR) was approved by FDA but has not been marketed.		Co-admin. Drug	D4T AUC	Co-admin. Drug AUC	Co-admin. Drug	D4T AUC	Co-admin. Drug AUC
			IDV	1.25	1			
			No effect on D4t: clarithromycin, DDI, FTC, IDV, NVP, ribavirin D4T has no effect on: DDI, FTC, NFV, NVP, TDF ZDV inhibits D4T activation: Do not use ZDV and D4T concurrently. Co-administration of drugs associated with peripheral neuropathy may increase this risk.					

Emtricitabine (Emtriva, FTC) Nucleoside reverse transcriptase inhibitor			
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology
<u>Child > 2 years (?):</u> 120-140 mg/m ² or 6 mg/kg	<u>Tablets:</u> 200 mg (#30) Stable at room temperature <u>Fixed combination:</u>	Common: Hyperpigmentation of palms or soles. Other reported symptoms with FTC in combination with other ARVs showed no increase in any symptoms over comparator regimens. Common complaints included: asthenia, headache, GI upset, rash.	Absorption: Rapid; unaffected by food. Metabolism: Minor. No effect on P450 or UGT. Excretion: Glomerular filtration + tubular secretion. Unchanged drug >> metabolites in urine >> feces. T ½ ~10 h in children.
<u>Adult:</u> 200 mg qd	<u>Truvada tablets</u> 300 mg TDF + 200 mg FTC (#30)	Severe or fatal lactic acidosis with hepatic steatosis (presenting as fatigue, tachypnea, abdominal pain, vomiting, hepatomegaly) has been reported in patients treated with FTC in combination with other NRTIs. Severe exacerbation of hepatitis has been observed after stopping FTC in patients with hepatitis B. Pregnancy category: B.	No significant interaction with: D4T, TDF, ZDV, IDV, famciclovir.

Abacavir (Ziagen, ABC) Nucleoside reverse transcriptase inhibitor					
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology		
<u>Neonate:</u> ?2 mg/kg bid	<u>Solution:</u> 20 mg/ml (tastes mildly unpleasant)	Common: Hypersensitivity reaction (3%): [Fever, malaise or hypotension, GI symptoms (emesis, pain, diarrhea), respiratory (cough, dyspnea), rash. Symptoms worsen after each successive dose. May have ↑transaminases, ↑CK, ↑creatinine, lymphopenia thrombocytopenia, Onset few days-6 wk after starting drug. May be life-threatening. Rechallenge may result in severe or fatal reaction within hours. Once ABC is stopped for suspected hypersensitivity, it should not be restarted. A medication guide and warning card should be provided to the patient.]	Absorption: 83%, unaffected by food. Metabolism: dehydrogenation or glucuronidation; t _{1/2} =1.5 hr; no adjustment for renal failure Excretion: metabolites in urine and feces		
<u>Infant 1-3 months:</u> ? 8 mg/kg bid	Stable RT		Interactions: AUC ratio (combined /alone) of ABC or co-administered drug.		
<u>Child > 3 months:</u> 8 mg/kg bid	<u>Tabs:</u> 300 mg	Not as part of hypersensitivity syndrome: nausea, vomiting, rash	Co-admin. Drug	ABC AUC	Co-admin. Drug AUC
<u>Adult:</u> 300 mg bid 600 mg qd (given as coformulation with 3TC; pharmacology supports qd dosing in other combinations)	<u>Fixed combinations</u> <u>Trizivir tabs:</u> 300 mg ZDV + 150 mg 3TC + 300 mg ABC <u>Epzicom tabs</u> 600 mg ABC + 300 mg 3TC		Uncommon: fatigue, headache, ?↑ALT, AST, or CPK.	Ethanol	1.41
	Stable RT	Severe lactic acidosis (presenting as fatigue, tachypnea, abdominal pain, vomiting) is associated with other NRTIs, but ABC is probably not as likely to cause this or other signs of mitochondrial toxicity.	No significant interaction with: APV, 3TC, TDF, methadone Inducers of glucuronidation such as phenobarbital, DPH, rifampin, or carbamazepine may decrease level of ABC. RTV may slightly lower ABC levels. Comment: CSF:plasma = 0.30.		

Zalcitabine (HIVID, ddC) Nucleoside reverse transcriptase inhibitor
This drug has a high incidence of toxicity (particularly peripheral neuropathy), weak antiretroviral activity, and a resistance pattern virtually identical to DDI. There is no longer a therapeutic role for this drug.

Hydroxyurea (Droxia, HU)
HU has been used with DDI to increase the effect of DDI and for its immune modulating effect. However, it increases DDI toxicity. At this point its use in antiretroviral therapy of children should be limited to controlled trials.

Tenofovir (Viread, TDF) Nucleotide reverse transcriptase inhibitor								
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology					
<p><u>Child 6-16 years:</u> ? 210 mg/m² qd (when given with LPV/r, which probably increases TDF levels)</p> <p><u>Adults:</u> 300 mg qd</p>	<p><u>Tablets:</u> 300 mg (#30) Stable at room temp.</p> <p><u>Fixed combination:</u></p> <p><u>Truvada</u> 300 mg TDF + 200 mg FTC (#30)</p>	<p>Common: None in adults. Early studies in children suggest TDF may cause significant bone mineral loss.</p> <p>Uncommon: GI upset, renal tubular toxicity, acute renal failure, bone mineral loss. Severe exacerbation of hepatitis has been observed after stopping TDF in patients with hepatitis B.</p> <p>Pregnancy category: B.</p>	<p>Absorption: 25% in fasted state. AUC increased 40% with full meal; light meal has no effect. Metabolism: No P450 metabolism. Excretion: Glomerular filtration and renal tubular secretion. T_{1/2} = 17 hr. Interactions: AUC ratio (combined /alone) of TDF or co-administered drug.</p>					
			Co-admin. Drug	TDF AUC	Co-admin. Drug AUC	Co-admin. Drug	TDF AUC	Co-admin. Drug AUC
			ATV	1.24	0.75	DDI-EC, fasted, 2 hr before TDF		1.48 ¹
			ATV/r		0.75	DDI-EC + TDF, simultaneous with food		1.6 ¹
			DDI (buffered, 1 hr before TDF)	1	1.44	LPV/r	1.32	1
			<p>¹DDI-EC 250/TDF 300 mg gave same AUC as 400 mg DDI-EC alone under these conditions. No significant interaction with: ABC, adefovir, EFV, FTC, IDV, 3TC TDF has no effect on: Methadone, oral contraceptives, RTV</p>					

Efavirenz (Sustiva, EFV)

Non-nucleoside reverse transcriptase inhibitor

Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology																																																											
<p><u>Child > 3 years:</u> 600X(wt in kg/70)^{0.7} mg qd This formula gives: 10-15 kg: 200 mg qd 15-20 kg: 250 mg qd 20-25 kg: 300 mg qd 25-32.5 kg: 350 mg qd 32.5-40 kg: 400 mg qd >40 kg: 600 mg qd</p> <p>or 15 mg/kg qd</p> <p>Preliminary data in children <3 suggest proportionately higher dosages will be needed.</p> <p><u>Adult:</u> 600 mg qd</p>	<p><u>Capsules:</u> 50,100, 200 mg Capsules easily opened and contents (water insoluble) added to jelly, food, or drink; drug has minimal taste.</p> <p><u>Tablets:</u> 600mg</p> <p>Stable RT</p>	<p>Common: Various CNS complaints [impaired concentration, somnolence, insomnia, change in activity level, abnormal dreams tend to resolve in a few weeks (dosing in A.M. or qhs, depending on symptoms, may help); depression may persist in patients with pre-existing depression; CNS side effects correlate with drug levels, which correlate with CYP2D6 genotype: 20% of African-Americans and 3% of European-Americans are slow metabolizers]; rash (~20%)- onset days-few weeks after starting, usually mild and resolves without discontinuation, can be severe including Stevens-Johnson (1-2%); elevation of total and HDL cholesterol.</p> <p>Uncommon: ↑transaminases</p> <p>WARNING: EFV is highly teratogenic in non-human primates, producing severe brain/face/eye defects early in embryogenesis. Use with extreme caution in women of childbearing potential.</p>	<p>Absorption: ~50% regardless of food except ↑ with high fat meal. Metabolism: Substrate/inhibitor for CYP 3A4> 2B6; inducer of 3A4; inhibitor of 2C9, 2C19, 3A4, 2B6. t_{1/2}=40-55 hr Excretion: metabolites in urine and stool</p> <p>Interactions: AUC ratio (combined /alone) of EFV or co-administered drug.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>EFV AUC</th> <th>Co-admin. Drug AUC</th> <th>Co-admin. Drug</th> <th>EFV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>APV</td> <td>1.16</td> <td>0.64-0.76</td> <td>LPV/r</td> <td>0.84</td> <td>0.75</td> </tr> <tr> <td>ATV</td> <td></td> <td>0.26</td> <td>Methadone</td> <td></td> <td>0.43</td> </tr> <tr> <td>Atorvastatin</td> <td>1</td> <td>0.57</td> <td>NFV</td> <td>1</td> <td>0.62*</td> </tr> <tr> <td>Clarithromycin</td> <td>1</td> <td>0.61</td> <td>Pravastatin</td> <td>1</td> <td>0.60</td> </tr> <tr> <td>Ethynil estradiol</td> <td>1</td> <td>1.37</td> <td>Rifabutin</td> <td>1</td> <td>0.62**</td> </tr> <tr> <td>IDV</td> <td>1</td> <td>0.54-0.67</td> <td>SQV-SGC</td> <td>0.78</td> <td>0.38</td> </tr> <tr> <td>Levofloxacin</td> <td>0.74</td> <td>1</td> <td>Simvastatin</td> <td>1</td> <td>0.42</td> </tr> <tr> <td></td> <td></td> <td></td> <td>Rifampin</td> <td>0.78</td> <td></td> </tr> </tbody> </table> <p>*Active M8 metabolite of NFV was unchanged. **Increase rifabutin dosage 50%.</p> <p>Because EFV is both inducer and inhibitor of P450 enzymes, effects on drugs metabolized by P450 system are difficult to predict. Check for the potential for interactions before co-administering other drugs. Addition of RTV generally reverses effects of EFV on PI (or other drug) exposure: see information on individual PIs for data and dosing recommendations. No effect on EFV: antacid, azithromycin, fluconazole, fluoxetine, RTV, TDF, ZDV, 3TC EFV has no effect on: azithromycin, fluconazole, paroxetine, rifampin, RTV, TDF, ZDV, 3TC</p>						Co-admin. Drug	EFV AUC	Co-admin. Drug AUC	Co-admin. Drug	EFV AUC	Co-admin. Drug AUC	APV	1.16	0.64-0.76	LPV/r	0.84	0.75	ATV		0.26	Methadone		0.43	Atorvastatin	1	0.57	NFV	1	0.62*	Clarithromycin	1	0.61	Pravastatin	1	0.60	Ethynil estradiol	1	1.37	Rifabutin	1	0.62**	IDV	1	0.54-0.67	SQV-SGC	0.78	0.38	Levofloxacin	0.74	1	Simvastatin	1	0.42				Rifampin	0.78	
Co-admin. Drug	EFV AUC	Co-admin. Drug AUC	Co-admin. Drug	EFV AUC	Co-admin. Drug AUC																																																									
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Levofloxacin	0.74	1	Simvastatin	1	0.42																																																									
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Nevirapine (Viramune, NVP)

Non-nucleoside reverse transcriptase inhibitor

Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology																																						
<p><u>Perinatal prophylaxis:</u> Maternal: 200 mg X 1 at onset of labor, repeat at 48 hr if still in labor Newborn: 2 mg/kg X 1 24-72 hr after birth if mom got NVP >2 hr before birth. 4 mg/kg X 1 at birth if mom did not get NVP >2 hr before birth</p> <p><u>Pediatric:</u> (Multiple dosing regimens exist; these are author's recommendations.)</p> <p><u>Newborn 15-30 d old:</u> 5 mg/kg qd X 14 d, then 120 mg/m² bid X 14 d, then 200 mg/m² bid</p> <p><u>Child 1 month-4 years:</u> 120 mg/m² qd X 2 wks, then 200 mg/m² bid</p> <p><u>Child 4-8 years:</u> 120 mg/m² qd X 2 wks, then 150 mg/m² bid</p> <p><u>Child >8 years:</u> 120 mg/m² qd X 2 wks, then 120-150 mg/m² bid</p> <p><u>Adult:</u> 200 mg qd X 2 wks, then 200 mg bid</p>	<p><u>Suspension:</u> 10 mg/ml (shake well, store at room temperature)</p> <p><u>Tabs:</u> 200 mg scored (#100) (Moderately bitter)</p>	<p>Common: Rash (8% adults, 19% infants/children. Usually mild and drug can be continued or held and restarted. If fever, mucosal lesions, joint complaints, erythema multiforme, or Stevens-Johnson occur, stop drug.) Uncommon: Increased LFTs; SEVERE HEPATITIS OR LIVER FAILURE (Risk is 0.9% for women with CD4 < 250, 11.0% for women with CD4 > 250, 2.3% for men with CD4 < 400, and 6.3% for men with CD4 > 400. Usually occurs in first 6 weeks but may occur up to 18 weeks after starting NVP. May also have rash or fever. The incidence of severe hepatic toxicity in children is unknown, but AST > 250 occurred 14% of children. Monitor liver enzymes when initiating treatment and always use 14-day qd treatment lead-in. Use with caution in liver disease or with other hepatotoxic drugs); fever, nausea, headache, ? pancreatitis.</p>	<p>Absorption: >90%, unaffected by food or antacid Metabolism: Hydroxylation by cytochrome P450 CYP3A, then glucuronidation. Substrate/inhibitor for CYP 3A4 and 2B6; inducer of 2B6 > 3A4. Excretion: Metabolites in urine</p>																																						
			<p>Interactions: AUC ratio (combined /alone) of NVP or co-administered drug.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>NVP AUC</th> <th>Co-dmin. Drug AUC</th> <th>Co-admin. Drug</th> <th>NVP AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>LPV/r</td> <td>~1</td> <td>0.71</td> <td>Ketoconazole</td> <td></td> <td>0.37</td> </tr> <tr> <td>Clarithromycin</td> <td>1.26</td> <td>0.70</td> <td>Methadone</td> <td></td> <td>0.48</td> </tr> <tr> <td>Ethynil estradiol</td> <td></td> <td>0.81</td> <td>Rifampin</td> <td>0.63-0.69</td> <td>~1</td> </tr> <tr> <td>Norethindrone</td> <td></td> <td>0.82</td> <td>Zidovudine</td> <td></td> <td>0.75</td> </tr> <tr> <td>IDV</td> <td>1</td> <td>0.74</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>No effect on NVP: DDI, NFV, rifabutin NVP has no effect on: DDI, NFV, rifabutin, RTV Because NVP is both inducer and inhibitor of P450 enzymes, effects on drugs metabolized by P450 system are difficult to predict. Check for the potential for interactions before co-administering other drugs. NVP has pharmacologic properties similar to EFV- see data for EFV. Addition of RTV generally reverses effects of NVP on PI (or other drug) exposure: see information on individual PIs for data and dosing recommendations.</p>						Co-admin. Drug	NVP AUC	Co-dmin. Drug AUC	Co-admin. Drug	NVP AUC	Co-admin. Drug AUC	LPV/r	~1	0.71	Ketoconazole		0.37	Clarithromycin	1.26	0.70	Methadone		0.48	Ethynil estradiol		0.81	Rifampin	0.63-0.69	~1	Norethindrone		0.82	Zidovudine		0.75	IDV	1	0.74
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Delavirdine (Rescriptor, DLV) Non-nucleoside reverse transcriptase inhibitor								
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology					
<u>Infant, child:</u> 16 mg/kg bid <u>Adult:</u> 400 mg tid 600 mg bid	<u>Tabs:</u> 200 mg (bitter) (original 100 mg tab has been withdrawn from market) Stable RT	Common: Rash (Usually mild and drug can be continued or held and restarted. If fever, mucosal lesions, joint complaints, erythema multiforme, or Stevens-Johnson occur, stop drug.) Uncommon: ? Headache, fatigue, GI	Absorption: 85%, minimal ↓ by fat intake; ↓ with antacid or H2 blockers Metabolism: Substrate for 3A4>>2D6, 2C9; inhibitor of 3A4, 2C9, 2C19, 2D6 Excretion: Metabolites in urine and feces Interactions: AUC ratio (combined /alone) of DLV or co-administered drug.					
			Co-admin. Drug	DLV AUC	Co-admin. Drug AUC	Co-admin. Drug	DLV AUC	Co-admin. Drug AUC
			IDV ²	1	1.4	Rifabutin	0.2	
			NFV	0.6	2.0 ¹	Rifampin	0.05	
			RTV		1.7	Antacid	0.6	
			SQV		5.0	Clarithromycin	1.44	2.0
			DDI (buffered)	0.8	0.8	Fluoxetine	1.5	
			APV or fAPV	0.39-0.53	1.3-2.3	LPV/r	-7-0.75	1.24
			Ketoconazole	1.5 ³		RTV	1.19	1.6-1.8
			¹ AUC of NFV active metabolite 0.5. ² No effect of food on IDV if given with DLV. ³ C _{min} No interaction: fluconazole, ZDV, TMP/SMX					

Nelfinavir (Viracept, NFV) Protease inhibitor																																																																																			
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology																																																																																
<p>Infant: No FDA-approved dosage < 2 years. <u>0-6 weeks of age:</u> ?40 mg/kg bid (highly variable levels) <u>2-9 months of age:</u> ?60-75 mg/kg bid ?40-50 mg/kg tid (these dosages result in levels slightly lower than adult norms.)</p> <p><u>Child 2-13 years:</u> 25-35 mg/kg tid 45-55 mg/kg bid ?30 mg/kg bid with RTV bid</p> <p>Adult: 750 mg tid 1250 mg bid</p> <p>NFV MUST BE TAKEN WITH A MEAL (OR IN FORMULA). Absorption in fasted state is very poor.</p> <p><u>Adult dosage for concurrent use with other PI or NNRTI:</u> ? 500-750 mg bid with RTV 400 mg bid ? 750 mg bid with LPV/r 400 mg bid</p>	<p><u>Powder:</u> 50 mg/1.25 ml (1 gm) scoop (200 mg/level teaspoon) (#144 scoops/bottle); reconstitute immediately prior to administration in water, milk, formula, Ensure, pudding, ice cream, etc; avoid acidic food or juice (will make taste more bitter). Powder is sweet and gritty. Contains phenylalanine.</p> <p><u>Tablets:</u> 250 (#300), 625 (#120) mg (readily dissolve in water or can be crushed and administered with pudding). Tablets are chalky, faintly bitter.</p>	<p>Common: Diarrhea, hypercholesterolemia Uncommon: Nausea, vomiting, asthenia, ? ↑transaminases, ? ↑CPK, ?headache, ? Abdominal pain, ?rash, ?other.</p> <p>PIs have been associated with: insulin resistance, hyperglycemia, diabetes, ↑triglycerides, ↑cholesterol, spontaneous bleeding in hemophiliacs.</p> <p>Pregnancy category: B.</p>	<p>Absorption: Highly variable, depending on food intake. Exposure with 625 mg tablet is ~25% higher than same dosage as 250 mg tablets. 250 mg tablets and powder are equivalent. Metabolism: Substrate for 3A4>>2C19(M8), P-gp; Inducer of: UGT, 2C9 (?) P-gp; Inhibitor of: 3A4 (nelfinavir autoinduction), 1A2, 2B6. Major metabolite (M8) has equivalent <i>in vitro</i> antiviral activity; NFV and M8 levels often not affected in parallel. Excretion: Multiple metabolites in feces.</p> <p>Interactions: AUC ratio (combined /alone) of NFV, M8, or co-administered drug.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>NFV AUC</th> <th>M-8 AUC</th> <th>Co-dmin. Drug AUC</th> <th>Co-admin. Drug</th> <th>NFV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>IDV</td> <td>1.83</td> <td></td> <td>1.51</td> <td>Ethynil estradiol</td> <td></td> <td>0.53</td> </tr> <tr> <td>RTV</td> <td>2.52</td> <td></td> <td>1</td> <td>Norethindrone</td> <td></td> <td>0.82</td> </tr> <tr> <td>RTV + NVP</td> <td>1²</td> <td></td> <td></td> <td>Methadone</td> <td>1.6¹</td> <td>0.53</td> </tr> <tr> <td>SQV-SGC</td> <td>1.18</td> <td></td> <td>2.7-4.9</td> <td>Phenytoin</td> <td>1</td> <td>0.71</td> </tr> <tr> <td>SQV-HGC</td> <td></td> <td></td> <td>5</td> <td>Ketoconazole</td> <td>1.35</td> <td></td> </tr> <tr> <td>LPV/r</td> <td>1.07</td> <td>3.5</td> <td>0.73</td> <td>Rifabutin</td> <td>0.68-1</td> <td>3³</td> </tr> <tr> <td>ZDV</td> <td>1</td> <td></td> <td>0.65</td> <td>Rifampin</td> <td>0.17</td> <td></td> </tr> <tr> <td>EFV</td> <td>1.2</td> <td>0.6-1.0</td> <td>0.9</td> <td>Azithromycin</td> <td>0.85</td> <td>2.1</td> </tr> <tr> <td>DLV</td> <td>2.07</td> <td></td> <td>0.69</td> <td>Atorvastatin</td> <td>~1</td> <td>1.7</td> </tr> <tr> <td>Pravastatin</td> <td>~1</td> <td>~1</td> <td>0.53-0.65</td> <td>Simvastatin</td> <td>~1</td> <td>6</td> </tr> </tbody> </table> <p>¹C_{min} ²NFV + M8, as compared to NFV/RTV ³Rifabutin at a half usual dosage (150 mg qd) + NFV gave rifabutin AUC 1.8 X rifabutin 300 mg qd AUC. No significant interaction with: ZDV, 3TC, NVP, APV, D4T, mefloquin NFV has no effect on: fAPV No effect on NFV: DDI NFV increases APV C_{min}, but not AUC. Do not use: amiodarone, quinidine, ergot derivatives, pimozone, midazolam, triazolam. Other CYP3A inducers [e.g. phenobarbital, phenytoin, carbamazepine, rifabutin, rifampin, dexamethasone, hypericum (St. John's wort)] may ↓ levels of PI. Other drugs for which data are not available may affect NFV metabolism or may be affected by NFV. See Table at end of formulary for other drugs with potentially significant interactions.</p>				Co-admin. Drug	NFV AUC	M-8 AUC	Co-dmin. Drug AUC	Co-admin. Drug	NFV AUC	Co-admin. Drug AUC	IDV	1.83		1.51	Ethynil estradiol		0.53	RTV	2.52		1	Norethindrone		0.82	RTV + NVP	1 ²			Methadone	1.6 ¹	0.53	SQV-SGC	1.18		2.7-4.9	Phenytoin	1	0.71	SQV-HGC			5	Ketoconazole	1.35		LPV/r	1.07	3.5	0.73	Rifabutin	0.68-1	3 ³	ZDV	1		0.65	Rifampin	0.17		EFV	1.2	0.6-1.0	0.9	Azithromycin	0.85	2.1	DLV	2.07		0.69	Atorvastatin	~1	1.7	Pravastatin	~1	~1	0.53-0.65	Simvastatin	~1	6
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Indinavir (Crixivan, IDV) Protease inhibitor																																																																							
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology																																																																				
<p>Child >4 years: ?500 mg/m² tid</p> <p>Adult: 800 mg tid</p> <p>Take unboosted IDV on empty stomach or with light snack</p> <p>RTV-boosting: ? 800 mg bid with RTV 100-200 mg bid ?1200 mg qd with RTV 200-400 mg qd May take boosted IDV with a meal.</p> <p>Adult dosage (?) for concurrent use with other PI or NNRTI: 400 mg bid with RTV 400 mg bid 1200 mg bid with NFV 1250 mg bid 600-666 mg bid with LPV/r 400 mg/100 mg bid 800 mg tid with APV 800 mg tid 600 mg tid with DLV 400 mg tid 800 mg bid with RTV 200 mg bid and EFV 600 mg qd 1000 mg tid with EFV 600 mg qd or NVP 200 mg qd</p>	<p>Capsules: 100 mg (#180) 200 mg (#360) 333 mg (#135) 400 mg (#18, 90, 120, 180)</p> <p>(Powder inside capsules is very bitter.)</p> <p>Capsules are sensitive to moisture and should be stored in original container with desiccant. Stable RT.</p>	<p>Common: Nephrolithiasis (monitor U/A and encourage fluid intake; stones might not recur if dosage lowered 25%; more common with RTV-boosted regimens), hematuria, ↑creatinine, ↑indirect bilirubin (10%).</p> <p>Less common: Nausea, headache, dry skin, dry mouth, dry eyes, alopecia, ingrown toenails, abdominal pain, HA, metallic taste, dizziness/fatigue, hepatitis, hepatic failure.</p> <p>PIs have been associated with: insulin resistance, hyperglycemia, diabetes, ↑triglycerides, ↑cholesterol, spontaneous bleeding in hemophiliacs.</p> <p>Pregnancy category: C. PIs generally do not cross placenta well.</p>	<p>Absorption: 65% fasted; food greatly decreases availability of unboosted IDV. Metabolism: Substrate for 3A4, P-gp; Inhibitor of 3A4, UGT1A1 Unboosted IDV is rapidly metabolized; t_{1/2} = 1.8 hr in adults; must be given on q8 hr schedule. Children have more rapid clearance and lower C_{min}. Excretion:</p> <p>Interactions: AUC ratio (combined /alone) of IDV or co-administered drug.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>IDV AUC</th> <th>Co-admin. Drug AUC</th> <th>Co-admin. Drug</th> <th>IDV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>Clarithromycin</td> <td>1.07</td> <td>1.47</td> <td>SQV-HGC¹⁰</td> <td></td> <td>6</td> </tr> <tr> <td>DLV</td> <td>1-1.4¹</td> <td>1</td> <td>SQV-SGC¹⁰</td> <td></td> <td>4.6-7.2</td> </tr> <tr> <td>EFV</td> <td>0.6⁵</td> <td>1</td> <td>St. Johns wort</td> <td>0.46</td> <td></td> </tr> <tr> <td>Ethynil estradiol</td> <td></td> <td>1.25</td> <td>Itraconazole⁹</td> <td>1</td> <td></td> </tr> <tr> <td>Ketoconazol⁶</td> <td>1.6</td> <td></td> <td>ZDV</td> <td>1</td> <td>1.2-1.4</td> </tr> <tr> <td>Norethindrone</td> <td></td> <td>1.26</td> <td>fAPV</td> <td></td> <td>1.3</td> </tr> <tr> <td>Rifabutin²</td> <td>0.67</td> <td>2.7</td> <td>Ascorbic acid</td> <td>0.86</td> <td></td> </tr> <tr> <td>Rifampin</td> <td>0.08⁸</td> <td></td> <td>Sildenafil</td> <td></td> <td>4.4</td> </tr> <tr> <td>RTV 100 mg</td> <td>2.7^{3,7}</td> <td></td> <td>APV</td> <td>0.62-0.78</td> <td>1.26-1.64</td> </tr> <tr> <td>RTV 200 mg</td> <td>3.6⁴</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>			Co-admin. Drug	IDV AUC	Co-admin. Drug AUC	Co-admin. Drug	IDV AUC	Co-admin. Drug AUC	Clarithromycin	1.07	1.47	SQV-HGC ¹⁰		6	DLV	1-1.4 ¹	1	SQV-SGC ¹⁰		4.6-7.2	EFV	0.6 ⁵	1	St. Johns wort	0.46		Ethynil estradiol		1.25	Itraconazole ⁹	1		Ketoconazol ⁶	1.6		ZDV	1	1.2-1.4	Norethindrone		1.26	fAPV		1.3	Rifabutin ²	0.67	2.7	Ascorbic acid	0.86		Rifampin	0.08 ⁸		Sildenafil		4.4	RTV 100 mg	2.7 ^{3,7}		APV	0.62-0.78	1.26-1.64	RTV 200 mg	3.6 ⁴				
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<p>¹No effect of food if co-administered with DLV. ²Rifabutin at ½ usual dosage (150 mg/d) + IDV gave rifabutin AUC 1.5 X rifabutin 300 mg qd AUC. ³IDV 800 mg/RTV 100 mg bid compared to IDV 800 tid. C_{min} ratio = 11. ⁴IDV 800 mg/RTV 200 mg bid compared to IDV 800 tid. C_{min} ratio = 24. ⁵IDV 800 mg/RTV 100 mg bid/EFV 600 qd versus IDV 800 mg/RTV 100 mg bid gives IDV AUC ratio = 0.75 (use 200 mg RTV if IDV resistance). ⁶IDV 600 tid/ketoconazole 400 mg X1 gave IDV AUC 0.82 X AUC of IDV 800 tid ⁷IDV 600 mg/LPV 400 mg/RTV 100 mg bid IDV AUC = 3.5X AUC of IDV 800 mg tid. ⁸0.13-0.18 with IDV/r (i.e. RTV not adequate to overcome rifampin effect). ⁹IDV 600 mg tid + itraconazole compared to IDV 800 mg tid ¹⁰ Antiretroviral effect of SQV and IDV may be antagonistic- avoid. No significant interaction with: INH, methadone, D4T, TMP/SMX, 3TC, atovaquone, mefloquine, methadone, pravastatin, TDF, ZDV IDV has no effect on: No effect on IDV: cimetidine, DDI (1 hr before IDV), DLV, fluconazole, quinidine, azithromycin, Carbamazepine reduces IDV levels 4-25%. RTV boosting may affect drug interactions: refer to RTV interactions if IDV is boosted with RTV. Other drugs for which data are not available may affect IDV metabolism or may be affected by IDV. See Table at end of formulary for other drugs with potentially significant interactions.</p>																																																																							

Saquinavir (SQV-SGC, FTV = Fortovase; SQV-HGC, INV = Invirase)

Protease inhibitor

Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology 33																																																						
<p><u>N.B.</u> SQV must be boosted with RTV (or LPV/r) coadministration. Invirase formulation is preferred. FTV formulation given without boosting requires very large dosage and does not yield levels as high as boosted INV.</p> <p><u>Child:</u> Boosted SQV has not been studied in children; surface-area scaled dosages may be used with caution.</p> <p><u>Adults:</u> Preferred: 1000 mg SQV with 100 mg RTV bid</p> <p>Other boosted regimens: 1000 mg SQV with 400 mg/100 mg LPV/r bid 400 mg SQV with 400 mg RTV bid ? 800 mg SQV with 750 mg NFV tid ? 1200 mg SQV with 1250 mg NFV bid ? 1600 mg SQV with 100 mg RTV qd ? 1200 mg SQV with 400 mg ATV qd ? 800 mg SQV with 600 mg DLV bid</p> <p>Take with food, although boosted SQV absorption depends less on food intake.</p> <p><u>Unboosted FTV adult dosage (do not use unboosted FTV in children):</u> 1200 mg FTV t.i.d. Must take with full meal including fat.</p>	<p><u>Invirase</u> <u>Hard gelatin capsules:</u> 200 mg (#270, store at 15-30 C)</p> <p><u>Tablets</u> 500 mg tablet</p> <p><u>Fortovase soft gelatin capsules:</u> (The soft gel caps may come off the market.) 200 mg (#180, refrigerate, stable at 25C for 3 months). Liquid inside capsule can be removed, but tastes very bitter.</p>	<p>Common: Nausea, abdominal pain, diarrhea. Less common HA, paresthesia, rash, photosensitivity; in combination with ritonavir may cause increased transaminases especially if liver disease. High incidence of hepatitis when used with rifampin: combination of SQV and rifampin is contraindicated.</p> <p>PIs have been associated with: insulin resistance, hyperglycemia, diabetes, ↑triglycerides, ↑cholesterol, spontaneous bleeding in hemophiliacs.</p> <p>Pregnancy category: B. PIs generally do not cross placenta well.</p>	<p>Absorption: Unboosted: INV 4%, FTV is better, both highly food-dependent. RTV boosting greatly improves exposure; this likely in part due to better absorption or less first-pass metabolism. Metabolism: Substrate for CYP 3A4, P-gp. Inhibitor of CYP3A4 Excretion: Biliary (metabolites in feces).</p> <p>Interactions: AUC ratio (combined /alone) of INV, FTV, or co-administered drug.</p> <table border="1" data-bbox="1129 324 1995 771"> <thead> <tr> <th>Co-admin. Drug</th> <th>INV AUC⁵</th> <th>Co-admin. Drug AUC</th> <th>Co-admin. Drug</th> <th>FTV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>RTV</td> <td>20-60</td> <td></td> <td>APV/r</td> <td>0.18⁶</td> <td></td> </tr> <tr> <td>RTV + ATV</td> <td>1.6¹</td> <td></td> <td>APV</td> <td>0.82</td> <td></td> </tr> <tr> <td>DLV</td> <td>5.2</td> <td></td> <td>ATV</td> <td>5.5⁷</td> <td></td> </tr> <tr> <td>LPV/r</td> <td>(²)</td> <td></td> <td>ATV400 + FTV 1200 qd</td> <td>~1¹</td> <td></td> </tr> <tr> <td>IDV³</td> <td>5-8</td> <td></td> <td>RTV 400 + FTV400 bid</td> <td>2.2¹</td> <td></td> </tr> <tr> <td>RTV + rifabutin</td> <td>~1⁴</td> <td></td> <td>RTV 100 + FTV 1000 bid</td> <td>2.8¹</td> <td></td> </tr> <tr> <td>Rifampin + INV/r (Toxic)</td> <td>~1^{4,8}</td> <td></td> <td>Rifampin + FTV/r (Toxic)</td> <td>~1^{6,8}</td> <td></td> </tr> <tr> <td>EFV + FTV/RTV 400/400 bid</td> <td>~1⁹</td> <td>1</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>¹As compared to INV/r ²C_{min} of INV same as with INV/r. ³IDV & SQV have antagonistic antiretroviral activity in vitro: avoid. ⁴As compared to INV/r. ⁵Only effects in potentially useful boosted regimens are given. ⁶As compared to FTV/r. ⁷As compared to FTV 1200 mg tid. ⁸Data from small number of subjects. ⁹As compared to FTV/RTV 400/400 bid.</p> <p>No effect on FTV: Do not use SQV with EFV or NVP concurrently unless SQV/RTV combination used (no dosage adjustment). RTV boosting will affect drug interactions (generally less induction of SQV metabolism and greater inhibition of metabolism of concomitant drugs). Other drugs for which data are not available may affect SQV metabolism or may be affected by SQV. See Table at end of formulary for other drugs with potentially significant interactions. Other CYP3A inducers [e.g. phenobarbital, phenytoin, carbamazepine, rifabutin, rifampin, dexamethasone, hypericum (St. John's wort)] may ↓ levels of PI.</p>	Co-admin. Drug	INV AUC ⁵	Co-admin. Drug AUC	Co-admin. Drug	FTV AUC	Co-admin. Drug AUC	RTV	20-60		APV/r	0.18 ⁶		RTV + ATV	1.6 ¹		APV	0.82		DLV	5.2		ATV	5.5 ⁷		LPV/r	(²)		ATV400 + FTV 1200 qd	~1 ¹		IDV ³	5-8		RTV 400 + FTV400 bid	2.2 ¹		RTV + rifabutin	~1 ⁴		RTV 100 + FTV 1000 bid	2.8 ¹		Rifampin + INV/r (Toxic)	~1 ^{4,8}		Rifampin + FTV/r (Toxic)	~1 ^{6,8}		EFV + FTV/RTV 400/400 bid	~1 ⁹	1			
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Ritonavir [Norvir, RTV, r (low dosage RTV)]

Pharmacokinetic booster, protease inhibitor

Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology					
<u>Full-dosage RTV:</u> <u>Child:</u> 400-450 mg/m ² bid (use the higher dosage for <2 y.o.) <u>Adult:</u> 600 mg bid Start at about half of full dosage and gradually increase over ~3 days to improve tolerance. Dosing with food improves tolerance. Adult dosage for concurrent use with other PI: 400 mg bid with SQV 400 mg bid ? 400 mg bid with IDV 400 mg bid ? 400 mg bid with LPV/r 400 mg bid <u>Low-dosage RTV as pharmacokinetic booster:</u> RTV is now usually used at low dosage to inhibit metabolism of other PIs, resulting in lower PI dosage and/or higher PI levels. At these low dosages, RTV does not have significant antiretroviral activity. For low-dosage RTV dosages, see dosing information for other PIs.	<u>Syrup:</u> 80 mg/ml (240ml; 30 d @25C, longer @ 4C; contains 43% EtOH, tastes extremely bitter) <u>Capsules:</u> 100 mg (#120; refrigerate)	Common: TASTES BAD, diarrhea, GI upset (abdominal pain, anorexia, emesis), asthenia, circumoral & peripheral paresthesia, taste perversion, Uncommon: Increased transaminase, allergic reactions, PIs have been associated with: insulin resistance, hyperglycemia, diabetes, ↑triglycerides, ↑cholesterol, spontaneous bleeding in hemophiliacs. RTV is a very potent inhibitor of CYP3A4. Delayed clearance and accumulation of co-administered drugs that rely on this cytochrome for metabolism may result in prolonged effect or toxicity. Patients and other physicians should be warned to always check before taking or prescribing other medications. Pregnancy category: B. PIs generally do not cross placenta well.	Absorption: Absolute absorption unknown. Slightly increased by food. Metabolism: Substrate for 3A4 > 2D6, P-gp. Inducer of 1A2, 2C9, 2C19, UGT, 3A4 (auto-induction). Inhibitor of 3A4 > 2D6 > 2C9 > 2C19 > 2A6, 2E1, 2B6; P-gp Excretion: Metabolites and unchanged drug in feces. Interactions: AUC ratio (combined /alone) of RTV or co-administered drug. SEE INFORMATION FOR OTHER PIs AND NNRTIs FOR BOOSTING EFFECT OF RTV.					
			Co-admin. Drug	RTV AUC	Co-admin. Drug AUC	Co-admin. Drug	RTV AUC	Co-admin. Drug AUC
			Clarithromycin	1.1	1.77	Theophylline		0.57
			Desipramine		2.45	ZDV	1	0.75
			Ethynil estradiol		0.60	Atorvastatin		4.4
			Ketoconazole	1.18	3.4	Fentanyl		1.8
			Meperidine		0.38	Mefloquin	0.69	~1
			Meperidine metabolite		1.47	Pravastatin	~1	0.53
			Methadone		0.64	Trazadone		2.4
			Rifabutin		4	Triazolam		14 ¹
			25-O-desacetyl rifabutin metabolite		35	Vardenafil		49
			Rifampin	0.65		Zolpidem		1.27
			Sildenafil		11			
			¹ T _{1/2} . No significant interaction with: DDI (separate dosings). No significant effect on RTV: Clarithromycin, fluconazole, fluoxetine, NVP RTV has no significant effect on: alpraxolam, SMX/TMP, T-20 RTV may slightly lower R-warfarin and slightly raise S-warfarin levels: monitor coagulation. This is not a complete list of potential interactions. RTV is a potent inhibitor of the hepatic P450 system (CYP3A > CYP2D6) and may increase levels of drugs utilizing these pathways resulting in serious or life-threatening consequences depending on degree of inhibition of metabolism, therapeutic index, and number of doses. RTV also induces CYP3A and UGT (uridyl glucuronyl transferase) and may lower the level of certain drugs metabolized by these routes. . See Table for drugs that are CONTRAINDICATED or must be USED WITH CAUTION. Other CYP3A inducers [e.g. phenobarbital, phenytoin, carbamazepine, rifabutin, rifampin, dexamethasone, hypericum (St. John's wort)] may ↓ levels of PI.					

Amprenavir (APV, Agenerase) Protease inhibitor																																																					
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<p><u>Child > 4 years old:</u> Capsules: 20 mg/kg bid Liquid: 22.5 mg/kg bid</p> <p><u>Adult:</u> Capsules: 1200 mg bid Liquid: 1400 mg bid</p> <p>Do not take with high fat meal.</p> <p><u>RTV-boosting:</u> 600 mg bid with RTV 100 mg bid 1200 mg qd with RTV 200 mg qd 1200 mg bid with EFV 600 qd + RTV 200mg bid</p> <p>Adult dosages (?) for concurrent use with other PI or NNRTI:</p> <p>800 mg bid with IDV 800 mg tid 800 mg bid with NFV 750 mg tid 750 mg bid with LPV/r 400 mg bid 1200 mg tid with EFV 600 qd</p>	<p><u>Liquid:</u> 15 mg/ml (240 ml) Liquid contains propylene glycol- not advised for children <4 y.o.</p> <p><u>Capsules:</u> 50 mg (#480) 150 mg (#240)</p> <p>Store caps or liquid at RT; do not refrigerate.</p> <p>Contains vitamin E well in excess of daily requirements.</p>	<p>Common: GI (nausea, vomiting, diarrhea), rash (can be severe including Stevens-Johnson; mild rash may resolve on treatment or not recur with rechallenge; may be less common in children), circumoral paresthesia. Uncommon: Increased transaminases, increased amylase or lipase.</p> <p>APV is a sulfonamide and should be used with caution in patients with sulfonamide allergy.</p> <p>PIs have been associated with: insulin resistance, hyperglycemia, diabetes, ↑triglycerides, ↑cholesterol, spontaneous bleeding in hemophiliacs.</p> <p>Pregnancy category: C. PIs generally do not cross placenta well.</p>	<p>Absorption: Absolute bioavailability not known. Metabolism: Substrate for CYP3A4. Inducer of 3A4, P-gp. Inhibitor of 3A4 Excretion: metabolites in feces > urine.</p> <p>Interactions: AUC ratio (combined /alone) of APV or co-administered drug. See also data for fAPV: very similar effects can be expected.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>APV AUC</th> <th>Co-admin. Drug AUC</th> <th>Co-admin. Drug</th> <th>APV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>ABC</td> <td>1.29</td> <td></td> <td>ZDV</td> <td>1.1</td> <td>1.3</td> </tr> <tr> <td>DLV</td> <td>2.3</td> <td>0.49</td> <td>EFV</td> <td>0.7</td> <td>1.15</td> </tr> <tr> <td>IDV</td> <td>1.3</td> <td>0.7</td> <td>EFV/r</td> <td>0.6¹</td> <td></td> </tr> <tr> <td>Ketoconazole</td> <td>1.3</td> <td>1.4</td> <td>LPV/r</td> <td>1.7</td> <td>0.6</td> </tr> <tr> <td>Rifabutin</td> <td>0.85</td> <td>2.9</td> <td>SQV/r</td> <td></td> <td>0.18</td> </tr> <tr> <td>Rifampin</td> <td>0.18</td> <td>~1</td> <td>SQV</td> <td>0.66</td> <td>0.8</td> </tr> <tr> <td>RTV</td> <td>1.6</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>¹Relative to APV/r AUC.</p> <p>No significant interaction with: clarithromycin, ethinyl estradiol, norethindrone, 3TC, NFV APV has no significant effect on: methadone RTV boosting may affect drug interactions: refer to RTV interactions if APV is boosted with RTV.</p> <p>APV is both an inhibitor and inducer of 3A4: direction of effect may be difficult to predict. See Table at end of formulary for other drugs with potential interactions.</p> <p>Other CYP3A inducers [e.g. phenobarbital, phenytoin, carbamazepine, rifabutin, rifampin, dexamethasone, hypericum (St. John's wort)] may ↓ levels of PI.</p>			Co-admin. Drug	APV AUC	Co-admin. Drug AUC	Co-admin. Drug	APV AUC	Co-admin. Drug AUC	ABC	1.29		ZDV	1.1	1.3	DLV	2.3	0.49	EFV	0.7	1.15	IDV	1.3	0.7	EFV/r	0.6 ¹		Ketoconazole	1.3	1.4	LPV/r	1.7	0.6	Rifabutin	0.85	2.9	SQV/r		0.18	Rifampin	0.18	~1	SQV	0.66	0.8	RTV	1.6				
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Fosamprenavir (fAPV, Lexiva) Protease inhibitor																																																					
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology																																																		
<p><u>Children:</u> No data.</p> <p><u>Adults:</u> <u>No PI resistance:</u> 1400 mg bid</p> <p>1400 mg qd with RTV 200 mg qd</p> <p><u>If PI resistance:</u> 700 mg with RTV 100 mg bid</p> <p>Both RTV-boosted regimens yield much greater drug exposure than unboosted regimen. fAPV/r qd failure rate higher than with fAPV/r bid in treatment-experienced patients.</p>	<p><u>Tablets:</u> 700 mg (#60, room temp)</p>	<p>Common: GI (nausea, vomiting, diarrhea), rash (can be severe including Stevens-Johnson; mild rash may resolve on treatment or not recur with rechallenge; may be less common in children), circumoral paresthesia. Uncommon: Increased transaminases, increased amylase or lipase.</p> <p>APV is a sulfonamide and should be used with caution in patients with sulfonamide allergy.</p> <p>PIs have been associated with: insulin resistance, hyperglycemia, diabetes, ↑triglycerides, ↑cholesterol, spontaneous bleeding in hemophiliacs.</p> <p>Pregnancy category: C. PIs generally do not cross placenta well.</p>	<p>Absorption: Absolute bioavailability not known. Not affected by food. Metabolism: Prodrug is rapidly dephosphorylated to active APV by gut epithelium. APV is substrate for CYP3A4. Inducer of 3A4, P-gp. Inhibitor of 3A4 Excretion: metabolites in feces > urine.</p> <p>Interactions: AUC ratio (combined /alone) of APV or co-administered drug. See also data for APV: very similar effects can be expected.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>APV AUC</th> <th>Co-admin. Drug AUC</th> <th>Co-admin. Drug</th> <th>APV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>Atorvastatin</td> <td>0.73</td> <td>2.3</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Atorvastatin + fAPV/r</td> <td>1</td> <td>2.5</td> <td></td> <td></td> <td></td> </tr> <tr> <td>LPV/r + fAPV/r</td> <td>0.37</td> <td>0.63</td> <td></td> <td></td> <td></td> </tr> <tr> <td>IDV</td> <td>0.62¹</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>SQV</td> <td>0.81¹</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>NFV</td> <td>1.15¹</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Methadone</td> <td>0.7</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>¹As compared to historical data. No effect on fAPV or fAPV/r: EFV, TDF</p> <p>RTV boosting may affect drug interactions: refer to RTV interactions if fAPV is boosted with RTV. Other CYP3A inducers [e.g. phenobarbital, phenytoin, carbamazepine, rifabutin, rifampin, dexamethasone, hypericum (St. John's wort)] may ↓ levels of PI.</p>			Co-admin. Drug	APV AUC	Co-admin. Drug AUC	Co-admin. Drug	APV AUC	Co-admin. Drug AUC	Atorvastatin	0.73	2.3				Atorvastatin + fAPV/r	1	2.5				LPV/r + fAPV/r	0.37	0.63				IDV	0.62 ¹					SQV	0.81 ¹					NFV	1.15 ¹					Methadone	0.7				
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Lopinavir/ritonavir (Kaletra, LPV/r) Protease inhibitor/pharmacokinetic booster coformulation																																																																	
Dosage (as LPV)	Formulation	Adverse effects (see also note 4 above)	Pharmacology																																																														
<p><u>Child > 6 months:</u> 230 mg/m² bid <i>or</i> 7-15 kg: 12 mg/kg bid 15-40 kg: 10 mg/kg bid >40 kg: Adult dosage</p> <p>With NVP, EFV, NFV, APV, or fAPV: 300 mg/m² bid <i>or</i> 7-15 kg: 13mg/kg bid 15-45 kg: 11mg/kg bid >45 kg: adult dose</p> <p><u>Adult:</u> 400 mg (3 caps) bid</p> <p>With NVP, EFV, NFV, APV, or fAPV: 533 mg (4 caps) bid</p> <p>LPV/r dosage not affected by PI other than RTV, NFV, APV, fAPV, but dosage of concomitant PI is affected- see dosage information for other PIs.</p> <p>Take with moderate fat meal; absorption and tolerance poor if fasted.</p>	<p><u>Solution:</u> 80 mg LPV + 20 mg RTV/ ml (160 ml) Tastes extremely bitter. Contains 42% ethanol.</p> <p><u>Capsules:</u> 133.3 mg LPV + 33.3 mg RTV (#180)</p> <p>Refrigerate. May store caps or solution at 25C for 2 months.</p>	<p>Common: TASTES BAD, diarrhea, GI upset (abdominal pain, anorexia, emesis), asthenia, circumoral & peripheral paresthesia, taste perversion, Uncommon: Increased transaminase, allergic reactions, pancreatitis.</p> <p>PIs have been associated with: insulin resistance, hyperglycemia, diabetes, ↑triglycerides, ↑cholesterol, spontaneous bleeding in hemophiliacs.</p> <p>RTV is a very potent inhibitor of CYP3A4. Delayed clearance and accumulation of co-administered drugs that rely on this cytochrome for metabolism may result in prolonged effect or toxicity. Patients and other physicians should be warned to always check before taking or prescribing other medications.</p> <p>Pregnancy category: C. PIs generally do not cross placenta well.</p>	<p>Absorption: Absolute bioavailability not known. Absorption (especially of solution) increased with fat-containing meal. Dosage recommendations assume administration with moderate fat meal. Metabolism: LPV: CYP3A4 (almost exclusively). RTV: Substrate for 3A4 > 2D6, P-gp. Inducer of 1A2, 2C9, 2C19, UGT, 3A4 (auto-induction). Inhibitor of 3A4 > 2D6 > 2C9 > 2C19 > 2A6, 2E1, 2B6; P-gp Excretion: LPV: metabolites in feces > urine.</p> <p>Interactions: AUC ratio (combined /alone) of LPV or co-administered drug.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>LPV AUC</th> <th>Co-admin. Drug AUC</th> <th>Co-admin. Drug</th> <th>LPV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>APV</td> <td>0.62</td> <td>1.7</td> <td>NVP</td> <td>0.75</td> <td>1.08</td> </tr> <tr> <td>Atorvastatin</td> <td>0.90</td> <td>5.9</td> <td>Norethindrone</td> <td></td> <td>0.83</td> </tr> <tr> <td>EFV</td> <td>0.81</td> <td>0.84</td> <td>Pravastatin</td> <td>0.95</td> <td>1.33</td> </tr> <tr> <td>Ethynil estradiol</td> <td></td> <td>0.58</td> <td>Rifabutin 150 qd⁷ (versus 300 qd)</td> <td>1.17</td> <td>3.03⁴ 47⁵ 5.7⁶</td> </tr> <tr> <td>IDV 600 bid with food</td> <td></td> <td>0.91¹</td> <td>Rifampin + LPV/r 400/100</td> <td>0.25</td> <td></td> </tr> <tr> <td>Ketoconazole</td> <td>0.87</td> <td>3.0</td> <td>Rifampin + LPV/r 800/200</td> <td>0.84</td> <td></td> </tr> <tr> <td>Methadone</td> <td></td> <td>0.47</td> <td>Rifampin + LPV/r 400/400</td> <td>0.98</td> <td></td> </tr> <tr> <td>NFV 1000 bid</td> <td>0.73</td> <td>1.07², 3.5^{2,3}</td> <td>RTV 100 + LPV 400/100</td> <td>1.46</td> <td></td> </tr> <tr> <td>Tipranavir</td> <td>0.51</td> <td></td> <td>SQV-SGC 800 bid</td> <td></td> <td>9.6⁸</td> </tr> </tbody> </table>			Co-admin. Drug	LPV AUC	Co-admin. Drug AUC	Co-admin. Drug	LPV AUC	Co-admin. Drug AUC	APV	0.62	1.7	NVP	0.75	1.08	Atorvastatin	0.90	5.9	Norethindrone		0.83	EFV	0.81	0.84	Pravastatin	0.95	1.33	Ethynil estradiol		0.58	Rifabutin 150 qd ⁷ (versus 300 qd)	1.17	3.03 ⁴ 47 ⁵ 5.7 ⁶	IDV 600 bid with food		0.91 ¹	Rifampin + LPV/r 400/100	0.25		Ketoconazole	0.87	3.0	Rifampin + LPV/r 800/200	0.84		Methadone		0.47	Rifampin + LPV/r 400/400	0.98		NFV 1000 bid	0.73	1.07 ² , 3.5 ^{2,3}	RTV 100 + LPV 400/100	1.46		Tipranavir	0.51		SQV-SGC 800 bid		9.6 ⁸
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Ethynil estradiol		0.58	Rifabutin 150 qd ⁷ (versus 300 qd)	1.17	3.03 ⁴ 47 ⁵ 5.7 ⁶																																																												
IDV 600 bid with food		0.91 ¹	Rifampin + LPV/r 400/100	0.25																																																													
Ketoconazole	0.87	3.0	Rifampin + LPV/r 800/200	0.84																																																													
Methadone		0.47	Rifampin + LPV/r 400/400	0.98																																																													
NFV 1000 bid	0.73	1.07 ² , 3.5 ^{2,3}	RTV 100 + LPV 400/100	1.46																																																													
Tipranavir	0.51		SQV-SGC 800 bid		9.6 ⁸																																																												
<p>¹As compared to IDV 800 mg tid fasting. ²As compared to NFV 1250 mg bid. ³Active NFV M8 metabolite. ⁴Rifabutin ⁵25-O-desacetyl rifabutin active metabolite. ⁶Rifabutin + active metabolite ⁷Rifabutin dosage of 150 mg tid with close monitoring is suggested. ⁸As compared to SQV-SGC 1200 mg tid. LPV has no significant effect on: Desipramine, This is not a complete list of potential interactions. RTV is a potent inhibitor of the hepatic P450 system (CYP3A > CYP2D6) and may increase levels of drugs utilizing these pathways resulting in serious or life-threatening consequences depending on degree of inhibition, therapeutic index, and number of doses. RTV also induces CYP3A and UGT (uridyl glucuronyl transferase) and may lower the level of certain drugs metabolized by these routes. Other CYP3A inducers [e.g. phenobarbital, phenytoin, carbamazepine, rifabutin, rifampin, dexamethasone, hypericum (St. John's wort)] may ↓ levels of PI. See Table for drugs that are CONTRAINDICATED or must be USED WITH CAUTION.</p>																																																																	

Atazanavir (ATV, Reyataz) Protease inhibitor																																																					
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology																																																		
<p>Child: Study of ATV in children is ongoing; adequate levels not achieved without RTV boosting.</p> <p>Adult: 400 mg qd 300 mg with 100 mg RTV qd RTV-boosted regimen gives higher levels and is recommended for treatment-experienced patients.</p> <p>Take with meal</p>	<p>Capsules: 100 mg (#60) 150 mg (#60) 200 mg (#60)</p>	<p>Common: Indirect hyperbilirubinemia (35%), jaundice (9%), fever, dizziness</p> <p>Less common: GI symptoms (nausea, vomiting, diarrhea) appear to be less common than with many other PIs. 1st degree heart block (prolongation of PR interval). Other reported symptoms and laboratory abnormalities are of uncertain association.</p> <p>Rare: 2nd degree heart block and other conduction abnormalities; no 3rd degree heart block. Other PIs (e.g. LPV/r) may have similar effect. Use caution in conditions or with other drugs that may cause heart block, especially if there may be pharmacokinetic interaction.</p> <p>ATV does not cause lipid abnormalities and insulin resistance associated with other PIs. In a switch study from other PI, LDL and total cholesterol on ATV/r were same as in separate ATV study in naive subjects at baseline or on-therapy, suggesting that ATV/r has little or no effect on cholesterol.</p> <p>Pregnancy category: B. PIs generally do not cross placenta well.</p>	<p>Absorption: Increased by food (with fat). Metabolism: Substrate for CYP3A4; inhibitor of 3A4, 1A2, 2C9, UGT1A1. Excretion: Metabolites > unchanged drug in feces > urine.</p> <p>Interactions: AUC ratio (combined /alone) of ATV or co-administered drug.</p> <table border="1"> <thead> <tr> <th>Co-admin. Drug</th> <th>ATV AUC</th> <th>Co-admin. Drug AUC</th> <th>Co-admin. Drug</th> <th>ATV AUC</th> <th>Co-admin. Drug AUC</th> </tr> </thead> <tbody> <tr> <td>Atenolol</td> <td>0.93</td> <td>1.25</td> <td>Rifabutin³</td> <td>1.15</td> <td>2.10, 22.0²</td> </tr> <tr> <td>Clarithromycin</td> <td>1.28</td> <td>1.94</td> <td>SQV-SGC</td> <td></td> <td>5.5⁴</td> </tr> <tr> <td>DDI (buffered, simultaneous)</td> <td>0.13</td> <td>0.98</td> <td>TDF</td> <td>0.75</td> <td>1.24</td> </tr> <tr> <td>Diltiazem</td> <td>1</td> <td>2.25, 2.65¹</td> <td>TDF + ATV/r</td> <td>0.75⁶</td> <td></td> </tr> <tr> <td>EFV</td> <td>0.26</td> <td></td> <td>ATV/r 300/100 + EFV</td> <td>3.4⁵</td> <td></td> </tr> <tr> <td>Ethinyl estradiol</td> <td></td> <td>1.48</td> <td>ATV/r 300/100</td> <td>3.4⁵</td> <td></td> </tr> <tr> <td>Norethindrone</td> <td></td> <td>2.1</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>¹Active diltiazem metabolite. ²25-O-desacetyl rifabutin active metabolite. ³ATV 600/Rifabutin 150 mg qd as compared to rifabutin 300 qd. ⁴SQV-SGC 1200 /ATV 400 qd gives similar SQV exposure as SQV-SGC 1200 tid. ⁵As compared to ATV (unboosted) ⁶As compared to ATV/r APV significantly lowers ATV C_{min}. Increased gastric pH may decrease absorption: do not use proton pump inhibitors or antacids. RTV boosting may affect drug interactions: refer to RTV interactions if ATV is boosted with RTV. No effect on ATV: ketoconazole ATV has no effect on: D4T, ZDV, 3TC No significant interaction with: DDI-EC, DDI given 1 hr before ATV, Other CYP3A inducers [e.g. phenobarbital, phenytoin, carbamazepine, rifabutin, rifampin, dexamethasone, hypericum (St. John's wort)] may ↓ levels of PI.</p>			Co-admin. Drug	ATV AUC	Co-admin. Drug AUC	Co-admin. Drug	ATV AUC	Co-admin. Drug AUC	Atenolol	0.93	1.25	Rifabutin ³	1.15	2.10, 22.0 ²	Clarithromycin	1.28	1.94	SQV-SGC		5.5 ⁴	DDI (buffered, simultaneous)	0.13	0.98	TDF	0.75	1.24	Diltiazem	1	2.25, 2.65 ¹	TDF + ATV/r	0.75 ⁶		EFV	0.26		ATV/r 300/100 + EFV	3.4 ⁵		Ethinyl estradiol		1.48	ATV/r 300/100	3.4 ⁵		Norethindrone		2.1			
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Enfuvirtide (T-20, ENF, Fuzeon)			
Fusion inhibitor			
Dosage	Formulation	Adverse effects (see also note 4 above)	Pharmacology
<p><u>Child 6-16 years:</u> 2 mg/kg sc bid</p> <p><u>Adult:</u> 90 mg sc bid</p> <p>Inject subcutaneously in upper arm, abdomen, or thighs and rotate sites.</p>	<p><u>Lyophilized powder for reconstitution and injection:</u> 108 mg/vial; reconstitute with 1.1 ml sterile water and inject 1 ml sc (90 mg). Supplied as 60 unit dose vials with 60 vials of water, 60 reconstitution syringes, 60 administration syringes, and instructions. Store at room temperature, refrigerate and use reconstituted drug within 24 h.</p>	<p>Common: Injection site reactions (98%, usually with pain, induration, and erythema; may have pruritis, ecchymosis, nodules, or cysts). Uncommon: An increased incidence of bacterial pneumonia (4.7 versus 0.61/100 pt-y) was seen in phase 3 trials of background therapy +/- T-20; eosinophilia; hypersensitivity reaction. Other adverse events not significantly higher in patients receiving T-20.</p> <p>Pregnancy category: B.</p> <p>Dispense with sharps container.</p>	<p>Absorption: 85% Metabolism: Deamidation of C-terminal residue; extensive hydrolysis. Excretion: Unknown (broken down to amino acids and recycled). No significant interaction with RTV, SQV/r, rifampin.</p>

APPENDIX: DRUGS THAT MAY BE AFFECTED BY INHIBITORS OF HEPATIC P450 SYSTEM

RTV (and LPV/r) is a very potent inhibitor of the hepatic P450 system (affecting CYP3A4 > CYP2D6). All the other protease inhibitors and DLV have this effect, in the rough order DLV, IDV, NFV > SQV, APV. THE FOLLOWING DRUGS ARE KNOWN TO UTILIZE THIS SYSTEM FOR METABOLISM. **COADMINISTRATION OF THESE DRUGS WITH RTV OR LPV/r MAY RESULT IN ACCUMULATION OF THESE DRUGS WITH POTENTIALLY SERIOUS OR LIFE-THREATENING CONSEQUENCES** DEPENDING ON DEGREE OF INHIBITION OF METABOLISM, THERAPEUTIC INDEX, AND NUMBER OF DOSES. DLV, IDV, NFV, SQV, and APV may have a similar but lesser effect. **Drugs marked with (*) are CONTRAINDICATED for use with RTV or LPV/r.** All others should be avoided or used with caution. Other drugs not listed may also be affected.

alprazolam
 amiodarone
 amlodipine
 astemizole*
 atorvastatin (use low dosage or substitute pravastatin or fluvastatin)
 bepridil
 birth control pills (lowered estrogen- may be ineffective)
 bupropion
 calcium channel blockers
 cerivastatin (use low dosage or substitute pravastatin or fluvastatin)
 cisapride*
 citalopram
 clarithromycin (dosage adjust if renal failure)
 clorazepate
 clozapine
 cyclosporine (monitor)
 diazepam
 diltiazem
 ergot derivatives*
 estazolam
 ethynil estradiol (lowered levels- BCP may be ineffective)
 felodipine
 flecainide*
 flurazepam
 isradipine
 itraconazole (do not use high dosage)
 ketoconazole (do not use high dosage)
 lidocaine (systemic)
 lovastatin*
 midazolam*
 nocardipine
 nifedipine
 nimodipine
 nisoldipine
 nitrendipine
 pimoziide*
 propafenone*
 propoxyphene
 quinidine
 rapamycin (monitor)
 rifabutin (dose reduce 75%)
 sildenafil (Viagra)
 simvastatin*
 tacrolimus (monitor)
 tamoxifen
 terfenadine*
 triazolam*
 tricyclic antidepressants (monitor)
 verapamil
 zolpidem