

APPENDIX E: ANTIRETROVIRAL DRUG PHARMACOKINETIC AND TOXICITY DATA IN HUMAN PREGNANCY AND RECOMMENDATIONS FOR USE FOR TREATMENT OF PREGNANT WOMEN WITH HIV INFECTION #

ARV DRUG	FDA PREGNANCY CLASS ^v	PHARMACOKINETICS IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE FOR TREATMENT OF HIV-INFECTED WOMEN DURING PREGNANCY
<i>NRTI/NRTIs</i>			See text for discussion of potential maternal and infant mitochondrial toxicity.	
RECOMMENDED AGENTS				
Zidovudine (AZT, ZDV)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination ARV regimens in pregnancy based on efficacy studies and extensive experience; should be included in treatment regimen unless significant toxicity or d4T use.
Lamivudine (3TC)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with 3TC in pregnancy in combination with AZT, 3TC plus AZT is the recommended dual NRTI backbone for treatment of pregnant women.
ALTERNATE AGENTS				
Didanosine (ddI)	B	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together.	Alternate NRTI for dual nucleoside backbone of combination regimens. ddI should be used with d4T only if no other alternatives are available.
Emtricitabine (FTC)	B	No studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine (d4T)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together.	Alternate NRTI for dual nucleoside backbone of combination regimens. d4T should be used with ddI only if no other alternatives are available.

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				Do not use with AZT due to potential for antagonism.
Abacavir (ABC)	C	Phase I/II study in progress.	Hypersensitivity reactions occur in ~5-8% of non-pregnant persons, a much smaller percentage is fatal and usually associated with re-challenge; rate in pregnancy unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen.
INSUFFICIENT DATA TO RECOMMEND USE				
Tenofovir (TDF)	B	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased foetal growth and reduction in foetal bone porosity within 2 months of starting maternal therapy. Clinical studies in humans (particularly children) show bone demineralisation with chronic use; clinical significance unknown.	Due to lack of data on use in human pregnancy and concern regarding potential foetal bone effects, TDF should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
NOT RECOMMENDED				
Zalcitabine (ddC)	C	No studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity.	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available.
NNRTIs				
RECOMMENDED AGENTS				
Nevirapine (NVP)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence human teratogenicity. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with	NVP should be initiated in pregnant women with CD4+ T cell counts of >250/mm ³ who do not require therapy for own health only if the benefit

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			CD4+ T cell counts of >250/mm ³ when first initiating therapy; unclear if pregnancy increases risk.	clearly outweighs the risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts; if used, monitor closely for liver toxicity in first 18 weeks of therapy. Women who enter pregnancy on NVP regimens and are tolerating well may continue therapy, regardless of CD4+ T cell count.
NOT RECOMMENDED				
Efavirenz (EFV)	D	No studies in human pregnancy.	Significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving EFV during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure; 4 case reports of neural tube defects in humans after first trimester exposure; relative risk unclear.	Use of EFV should be avoided in the first trimester, and women of childbearing potential must be counselled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of childbearing potential. Use after the second trimester of pregnancy can be considered if other alternatives not available and if adequate contraception can be assured postpartum.
Delavirdine (DLV)	C	No studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity.	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available.
PIs			Hyperglycaemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs; see	

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			text.	
RECOMMENDED AGENTS				
Nelfinavir (NFV)	B	Adequate drug levels are achieved in pregnant women with NFV 1,250mg b.i.d.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant. NFV dosing at 750mg t.i.d produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant adults, NFV-based regimens had a lower rate of viral response compared to LPV/r- or EFV-based regimens, but similar viral response compared to ATV- or NVP-based regimens.
Saquinavir (SQV)-soft gel capsule [SGC] (Fortovase®)/ritonavir	B	Adequate drug levels are achieved in pregnant women with SQV-SGC 800mg boosted with RTV 100mg b.i.d. Recommended adult dosing of SQV-SGC 1,000mg <i>plus</i> RTV 100mg may be used. No pharmacokinetic data on SQV-hard gel capsule [HGC]/ritonavir in pregnancy, but better GI tolerance in non-pregnant adults.	Well-tolerated, short-term safety demonstrated for mother and infant. Inadequate drug levels observed in pregnant women when SQV-SGC given alone at 1,200 mg t.i.d.	Given pharmacokinetic data and moderate experience with use in pregnancy, RTV-boosted SQV-SGC can be considered a preferred PI for combination regimens in pregnancy.
ALTERNATE AGENTS				
Indinavir (IDV)	C	Two studies involving 18 women receiving IDV t.i.d showed markedly lower serum drug levels during pregnancy compared to those postpartum, although HIV viral suppression was seen.	Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinaemia in the neonate, but minimal placental passage. Use of IDV during pregnancy without RTV-boosting not recommended.	Alternate PI to consider if unable to use NFV or SQV-SGC/r, but would need to give IDV as RTV-boosted regimen to achieve adequate levels during pregnancy. Optimal dosing for RTV-boosted IDV in pregnancy is not known.

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Lopinavir/Ritonavir (LPV/r)	C	Phase I/II safety and pharmacokinetic study in progress using LPV 400mg and RTV 100mg b.i.d.	Limited experience in human pregnancy.	Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result not observed, consider increasing dose in consultation with a specialist with expertise in HIV in pregnancy.
Ritonavir (RTV)	B	Phase I/II study in pregnancy showed lower serum drug levels during pregnancy compared to postpartum.	Minimal experience in human pregnancy.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose RTV “boost” to increase levels of second PI.
INSUFFICIENT DATA TO RECOMMEND USE				
Amprenavir (APV)	C	No studies in human pregnancy.	Oral solution contra-indicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolised during pregnancy.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use of capsules during pregnancy. Oral solution contra-indicated.
Fosamprenavir (f-APV)	C	No studies in human pregnancy.	No experience in human pregnancy.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.
Atazanavir (ATV)	B	No studies in human pregnancy.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinaemia in the neonate, although transplacental passage of other PI's has been low.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.
Tipranavir	C	No studies in human pregnancy	No experience in human pregnancy	Data are insufficient regarding the safety and pharmacokinetics in pregnant to recommend

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				use during pregnancy.
<i>Fusion Inhibitors</i>				
INSUFFICIENT DATA TO RECOMMEND USE				
Enfuvirtide	B	No studies in human pregnancy.	No experience in human pregnancy.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.

This table represents information abstracted from *Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy - February 24th, 2005*, a supplement to the *United States Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States - February 24th, 2005* (both documents available at <http://www.aidsinfo.nih.gov/guidelines>). The reader is encouraged to consult these documents for a more detailed discussion of the safety and toxicity of individual ARVs in pregnancy.

[√]FDA Pregnancy Categories:

A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the foetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).

B: Animal reproduction studies fail to demonstrate a risk to the foetus and adequate and well-controlled studies of pregnant women have not been conducted.

C: Safety in human pregnancy has not been determined, animal studies are either positive for foetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the foetus.

D: Positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X: Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

*Triple NRTI regimens including ABC have been less potent virologically compared to PI-based HAART regimens. These regimens should be used only when an NNRTI or PI-based HAART regimen cannot be used (e.g. due to significant drug interactions). A study evaluating use of AZT/3TC/ABC among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development.