



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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What Not to Use (Last updated March 27, 2012; last reviewed March 27, 2012)

Some antiretroviral (ARV) regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

Antiretroviral Regimens Not Recommended

Monotherapy with nucleoside reverse transcriptase inhibitor (NRTI). Single-NRTI therapy does not demonstrate potent and sustained antiviral activity and **should not be used (AII)**. For prevention of mother-to-child transmission (PMTCT), zidovudine (ZDV) monotherapy is not recommended but might be considered in certain unusual circumstances in women with HIV RNA <1,000 copies/mL, although the use of a potent combination regimen is preferred. (See [Perinatal Guidelines](#),¹ available at <http://aidsinfo.nih.gov>.)

Single-drug treatment regimens with a ritonavir (RTV)-boosted protease inhibitor (PI), either lopinavir (LPV),² atazanavir (ATV),³ or darunavir (DRV)⁴⁻⁵ are under investigation with mixed results, and **cannot be recommended** outside of a clinical trial at this time.

Dual-NRTI regimens. These regimens **are not recommended** because they have not demonstrated potent and sustained antiviral activity compared with triple-drug combination regimens (**AI**).⁶

Triple-NRTI regimens. In general, triple-NRTI regimens other than abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) (**BI**) and possibly lamivudine/zidovudine + tenofovir (3TC/ZDV + TDF) (**BII**) **should not be used** because of suboptimal virologic activity⁷⁻⁹ or lack of data (**AI**).

Antiretroviral Components Not Recommended

Atazanavir (ATV) + indinavir (IDV). Both of these PIs can cause Grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly. Therefore, these two PIs **are not recommended** for combined use (**AIII**).

Didanosine (ddI) + stavudine (d4T). The combined use of ddI and d4T as a dual-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis.¹⁰⁻¹³ This combination has been implicated in the deaths of several HIV-infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis.¹⁴ Therefore, the combined use of ddI and d4T **is not recommended (AII)**.

Didanosine (ddI) + tenofovir (TDF). Use of ddI + TDF may increase ddI concentrations¹⁵ and serious ddI-associated toxicities including pancreatitis and lactic acidosis.¹⁶⁻¹⁷ These toxicities may be lessened by ddI dose reduction. The use of this combination has also been associated with immunologic nonresponse or CD4 cell decline despite viral suppression,¹⁸⁻¹⁹ high rates of early virologic failure,²⁰⁻²¹ and rapid selection of resistance mutations.²⁰⁻²² Because of these adverse outcomes, this dual-NRTI combination **is not generally recommended (AII)**. Clinicians caring for patients who are clinically stable on regimens containing ddI + TDF should consider altering the NRTIs to avoid this combination.

Two-non-nucleoside reverse transcriptase inhibitor (2-NNRTI) combinations. In the 2NN trial, ARV-naive participants were randomized to receive once- or twice-daily nevirapine (NVP) versus efavirenz (EFV) versus EFV plus NVP, all combined with d4T and 3TC.²³ A higher frequency of clinical adverse events that led to treatment discontinuation was reported in participants randomized to the two-NNRTI arm. Both EFV and NVP may induce metabolism of etravirine (ETR), which leads to reduction in ETR drug exposure.²⁴ Based on these findings, the Panel **does not recommend using two NNRTIs in combination in any regimen (AI)**.

Efavirenz (EFV) in first trimester of pregnancy and in women with significant childbearing potential.

EFV use was associated with significant teratogenic effects in nonhuman primates at drug exposures similar to those representing human exposure. Several cases of congenital anomalies have been reported after early human gestational exposure to EFV.²⁵⁻²⁶ EFV **should be avoided** in pregnancy, particularly during the first trimester, and in women of childbearing potential who are trying to conceive or who are not using effective and consistent contraception (**AIII**). If no other ARV options are available for the woman who is pregnant or at risk of becoming pregnant, the provider should consult with a clinician who has expertise in both HIV infection and pregnancy. (See [Perinatal Guidelines](#),¹ available at <http://aidsinfo.nih.gov>.)

Emtricitabine (FTC) + lamivudine (3TC). Both of these drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo*, as seen with other dual-cytidine analog combinations.²⁷ These two agents **should not be used** as a dual-NRTI combination (**AIII**).

Etravirine (ETR) + unboosted PI. ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established²⁴ (**AII**).

Etravirine (ETR) + ritonavir (RTV)-boosted atazanavir (ATV) or fosamprenavir (FPV). ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established²⁴ (**AII**).

Etravirine (ETR) + ritonavir (RTV)-boosted tipranavir (TPV). RTV-boosted TPV significantly reduces ETR concentrations. These drugs **should not be coadministered**²⁴ (**AII**).

Nevirapine (NVP) initiated in ARV-naive women with CD4 counts >250 cells/mm³ or in ARV-naive men with CD4 counts >400 cells/mm³. Greater risk of symptomatic hepatic events, including serious and life-threatening events, has been observed in these patient groups. NVP **should not be initiated** in these patients (**BI**) unless the benefit clearly outweighs the risk.²⁸⁻³⁰ Patients who experience CD4 count increases to levels above these thresholds as a result of antiretroviral therapy (ART) can be safely switched to NVP.³¹

Unboosted darunavir (DRV), saquinavir (SQV), or tipranavir (TPV). The virologic benefit of these PIs has been demonstrated only when they were used with concomitant RTV. Therefore, use of these agents as part of a combination regimen **without RTV is not recommended** (**AII**).

Stavudine (d4T) + zidovudine (ZDV). These two NRTIs **should not be used** in combination because of antagonism demonstrated *in vitro*³² and *in vivo*³³ (**AII**).

Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 1 of 2)

	Rationale	Exception
Antiretroviral Regimens <u>Not</u> Recommended		
Monotherapy with NRTI (AII)	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents 	• No exception
Dual-NRTI regimens (AI)	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents 	• No exception
Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)	<ul style="list-style-type: none"> • High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naive patients. • Other triple-NRTI regimens have not been evaluated. 	• ABC/ZDV/3TC (BI) and possibly TDF + ZDV/3TC (BII) in patients in whom other combinations are not desirable
Antiretroviral Components <u>Not</u> Recommended as Part of an Antiretroviral Regimen		
ATV + IDV (AIII)	• Potential additive hyperbilirubinemia	• No exception
ddI + d4T (AII)	<ul style="list-style-type: none"> • High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women 	• No exception
ddI + TDF (AII)	<ul style="list-style-type: none"> • Increased ddI concentrations and serious ddI-associated toxicities • Potential for immunologic nonresponse and/or CD4 cell count decline • High rate of early virologic failure • Rapid selection of resistance mutations at failure 	• Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination.
2-NNRTI combination (AI)	<ul style="list-style-type: none"> • When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR. 	• No exception
EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other ARV options are available and potential benefits outweigh the risks (BIII)
FTC + 3TC (AIII)	<ul style="list-style-type: none"> • Similar resistance profiles • No potential benefit 	• No exception
ETR + unboosted PI (AII)	• ETR may induce metabolism of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted ATV or FPV (AII)	• ETR may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted TPV (AII)	• ETR concentration may be significantly reduced by RTV-boosted TPV	• No exception

Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 2 of 2)

	Rationale	Exception
NVP in ARV-naive women with CD4 count >250 cells/mm³ or men with CD4 count >400 cells/mm³ (BI)	• High incidence of symptomatic hepatotoxicity	• If no other ARV option available; if used, patient should be closely monitored
d4T + ZDV (All)	• Antagonistic effect on HIV-1	• No exception
Unboosted DRV, SQV, or TPV (All)	• Inadequate bioavailability	• No exception

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddl = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emtricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

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