



Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

Downloaded from <https://aidsinfo.nih.gov/guidelines> on 2/23/2018

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <https://aidsinfo.nih.gov/e-news>.

What Not to Use (Last updated October 17, 2017; last reviewed October 17, 2017)

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 Drugs Not Recommended

The following ARV drugs are no longer recommended for use because of suboptimal antiviral potency, unacceptable toxicities, high pill burden, or pharmacologic concerns: delavirdine (DLV), didanosine (ddI), indinavir (IDV), nelfinavir (NFV), and stavudine (d4T).

Antiretroviral Regimens Not Recommended

Monotherapy

Nucleoside reverse transcriptase inhibitor (NRTI) monotherapy is inferior to dual-NRTI therapy.¹ Protease inhibitor (PI) monotherapy is inferior to combination antiretroviral therapy (ART).²⁻⁶ Integrase strand transfer inhibitor (INSTI) monotherapy has resulted in virologic rebound and INSTI resistance (AI).^{7,8}

Dual-NRTI Regimens

These regimens are inferior to triple-drug combination regimens (AI).⁹

Triple-NRTI Regimens

Triple-NRTI regimens have suboptimal virologic activity¹⁰⁻¹² or a lack of data (AI).

Antiretroviral Components Not Recommended

Atazanavir plus Indinavir

Both PIs can cause Grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly (AIII).

Cobicistat plus Ritonavir as Pharmacokinetic Enhancers

This combination may be prescribed inadvertently, which may result in additive CYP3A4 enzyme inhibition and may further increase the concentrations of ARV drugs or other concomitant medications (see [Tables 18a](#) and [18d](#)).

Didanosine plus Stavudine

The combination of ddI and d4T can result in peripheral neuropathy, pancreatitis, and lactic acidosis, and it has been implicated in the deaths of several pregnant women (AII).¹³

Didanosine plus Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) increases ddI concentrations,¹⁴ serious ddI-associated toxicities,^{15,16} immunologic nonresponse,¹⁷ early virologic failure,^{18,19} and resistance^{18,20} (AII).

Two Non-Nucleoside Reverse Transcriptase Inhibitor Combinations

Excess clinical adverse events and treatment discontinuation were reported in patients randomized to receive treatment with two non-nucleoside reverse transcriptase inhibitors (NNRTIs).²¹ Efavirenz (EFV) and nevirapine (NVP) are enzyme inducers, and both of these drugs can reduce concentrations of etravirine (ETR) and rilpivirine (RPV) (AI).²²

Emtricitabine plus Lamivudine

Both drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo* (AIII).²³

Etravirine plus Unboosted Protease Inhibitor

ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established (AII).²²

Etravirine plus Fosamprenavir/Ritonavir

ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established (AII).²²

Etravirine plus Tipranavir/Ritonavir

Tipranavir/ritonavir (TPV/r) significantly reduces ETR concentrations (AII).²²

Nevirapine Initiated in ARV-Naive Women with CD4 Counts >250 cells/mm³ or in ARV-Naive Men with CD4 Counts >400 cells/mm³

Initiating NVP below these CD4 count thresholds increases the risk of symptomatic, and sometimes life-threatening, hepatic events.²⁴⁻²⁶ Patients with CD4 counts above these thresholds due to ART can safely switch to NVP (BI).²⁷

Unboosted Darunavir, Saquinavir, or Tipranavir

The virologic benefit of these PIs has been demonstrated only when they were used with concomitant RTV, or in the case of DRV, also with COBI (AII).

Stavudine plus Zidovudine

These NRTIs are antagonistic *in vitro*²⁸ and *in vivo*²⁹ (AII).

Tenofovir Alafenamide plus Tenofovir Disoproxil Fumarate

This combination may be prescribed inadvertently, especially during transition from one formulation to another. There is no data supporting any potential additive efficacy or toxicity if TAF and TDF are used in combination.

References

1. Katlama C, Ingrand D, Loveday C, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naïve patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA*. Jul 10 1996;276(2):118-125. Available at <https://www.ncbi.nlm.nih.gov/pubmed/8656503>.
2. Delfraissy JF, Flandre P, Delaugerre C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naïve HIV-infected patients. *AIDS*. Jan 30 2008;22(3):385-393. Available at <https://www.ncbi.nlm.nih.gov/pubmed/18195565>.
3. Swindells S, DiRienzo AG, Wilkin T, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA*. Aug 16 2006;296(7):806-814. Available at <https://www.ncbi.nlm.nih.gov/pubmed/16905786>.
4. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS*. Jan 16 2010;24(2):223-230. Available at <https://www.ncbi.nlm.nih.gov/pubmed/20010070>.
5. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*. Sep 24

2010;24(15):2365-2374. Available at <https://www.ncbi.nlm.nih.gov/pubmed/20802297>.

6. Stohr W, Dunn DT, Arenas-Pinto A, et al. Factors associated with virological rebound in HIV-infected patients receiving protease inhibitor monotherapy. *AIDS*. Nov 13 2016;30(17):2617-2624. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27456983>.
7. Oldenbuettel C, Wolf E, Ritter A, et al. Dolutegravir monotherapy as treatment de-escalation in HIV-infected adults with virological control: DoluMono cohort results. *Antivir Ther*. 2017;22(2):169-172. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27588613>.
8. Brenner BG, Thomas R, Blanco JL, et al. Development of a G118R mutation in HIV-1 integrase following a switch to dolutegravir monotherapy leading to cross-resistance to integrase inhibitors. *J Antimicrob Chemother*. Jul 2016;71(7):1948-1953. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27029845>.
9. Hirsch M, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis*. Sep 1999;180(3):659-665. Available at <https://www.ncbi.nlm.nih.gov/pubmed/10438352>.
10. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis*. Dec 1 2005;192(11):1921-1930. Available at <https://www.ncbi.nlm.nih.gov/pubmed/16267763>.
11. Bartlett JA, Johnson J, Herrera G, et al. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. *J Acquir Immune Defic Syndr*. Nov 1 2006;43(3):284-292. Available at <https://www.ncbi.nlm.nih.gov/pubmed/16967040>.
12. Barnas D, Koontz D, Bazmi H, Bixby C, Jemsek J, Mellors JW. Clonal resistance analyses of HIV type-1 after failure of therapy with didanosine, lamivudine and tenofovir. *Antivir Ther*. 2010;15(3):437-441. Available at <https://www.ncbi.nlm.nih.gov/pubmed/20516563>.
13. Food and Drug Administration. Caution issued for HIV combination therapy with Zerit and Videx in pregnant women. *HIV Clin*. 2001;13(2):6. Available at <https://www.ncbi.nlm.nih.gov/pubmed/11810823>.
14. Kearney BP, Sayre JR, Flaherty JF, Chen SS, Kaul S, Cheng AK. Drug-drug and drug-food interactions between tenofovir disoproxil fumarate and didanosine. *J Clin Pharmacol*. Dec 2005;45(12):1360-1367. Available at <https://www.ncbi.nlm.nih.gov/pubmed/16291710>.
15. Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis*. Apr 15 2003;36(8):1082-1085. Available at <https://www.ncbi.nlm.nih.gov/pubmed/12684925>.
16. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet*. Jul 3-9 2004;364(9428):65-67. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15234858>.
17. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS*. Mar 24 2005;19(6):569-575. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15802975>.
18. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS*. Jan 28 2005;19(2):213-215. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15668550>.
19. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS*. Jul 22 2005;19(11):1183-1188. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15990571>.
20. Podzamczar D, Ferrer E, Gatell JM, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther*. 2005;10(1):171-177. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15751775>.
21. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. Apr 17 2004;363(9417):1253-1263. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15094269>.

22. Tibotec Inc. Intelence package insert. 2009. Available at <http://www.intelence.com/shared/product/intelence/prescribing-information.pdf>.
23. Bethell R, Adams J, DeMuys J, et al. Pharmacological evaluation of a dual deoxycytidine analogue combination: 3TC and SPD754. Presented at Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, California.
24. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):538-539. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15021321>.
25. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis*. Mar 15 2005;191(6):825-829. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15717255>.
26. Boehringer Ingelheim. Dear Health Care Professional Letter: Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE® (nevirapine). 2004.
27. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS*. Aug 24 2009;23(13):1689-1699. Available at <https://www.ncbi.nlm.nih.gov/pubmed/19487907>.
28. Hoggard PG, Kewn S, Barry MG, Khoo SH, Back DJ. Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation in vitro. *Antimicrob Agents Chemother*. Jun 1997;41(6):1231-1236. Available at <https://www.ncbi.nlm.nih.gov/pubmed/9174176>.
29. Havlir DV, Tierney C, Friedland GH, et al. In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis*. Jul 2000;182(1):321-325. Available at <https://www.ncbi.nlm.nih.gov/pubmed/10882616>.