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Management of drug-drug interactions between antiretrovirals and moderate intensity statins

Moderate intensity statin therapy (i.e., atorvastatin 20 mg once daily, pitavastatin 4 mg once daily, rosuvastatin 10 mg once daily) may be used in people with a low to moderate risk for cardiovascular disease.

Of the recommended statins, atorvastatin has the highest potential for drug-drug interactions (DDIs) as it undergoes metabolism by CYP3A4, whereas rosuvastatin and pitavastatin are minimally metabolized by CYP enzymes. All three statins are substrates of the hepatic uptake transporter OATP1B1. In addition, atorvastatin and rosuvastatin (but not pitavastatin) are substrates of the efflux transporters BCRP and MRP2.

Boosted antiretrovirals increase the exposure of statins to various extents depending on the contribution of CYP3A4 to the statin metabolism and also on the strength of OATP1B1 inhibition (highest → lowest: atazanavir > darunavir > ritonavir, cobicistat). NNRTIs (i.e., efavirenz, etravirine, nevirapine) can decrease the exposure of certain statins.

Guidance for the management of DDIs is given in the following tables. The dosing guidance is based on available DDI studies which are listed under each table with the statin dose used in the DDI study mentioned in brackets.

Atorvastatin

Recommended dose in the absence of a DDI: 20 mg once daily

Antiretrovirals		Recommendation for management of DDIs
NRTIs	ABC, FTC, 3TC, TAF, TDF, ZDV	No interaction expected. No dose adjustment required.
NNRTIs	DOR, RPV	No interaction expected. No dose adjustment required.
	EFV, ETV, NVP	Decrease in atorvastatin exposure. [1] Monitor lipid values and adjust dose as needed.
PIs and Boosted ARVs	ATV, ATV/r, ATV/c	Substantial increase in atorvastatin exposure. [2] Do not coadminister; if PI is needed, use darunavir.
	DRV/r, DRV/c	Increase in atorvastatin exposure. [3] Reduce atorvastatin dose to 10 mg once daily. Monitor for adverse effects. Do not exceed 20 mg/day.
	EVG/c	Increase in atorvastatin exposure. [4] Reduce atorvastatin dose to 10 mg once daily. Monitor for adverse effects. Do not exceed 20 mg/day.
Integrase Inhibitors	BIC, CAB, DTG, RAL	No interaction expected. No dose adjustment required.
Other	FTR	Potential increase in atorvastatin exposure. [5] Reduce atorvastatin dose to 10 mg once daily. Monitor for adverse effects.
	LEN, MVC	No interaction expected. No dose adjustment required.

Notes

1. Efavirenz decreased atorvastatin (10 mg) AUC by 43%. Etravirine decreased atorvastatin (10 mg) AUC by 37%.
2. Atazanavir/cobicistat increased atorvastatin (10 mg) AUC by 822% (inhibition of CYP3A4 and OATP1B1, BCRP). A similar magnitude of interaction is expected for atazanavir and atazanavir/ritonavir. Coadministration is not recommended as it can increase the risk of adverse effects while reducing the pharmacodynamic effect.
3. Darunavir/ritonavir resulted in atorvastatin exposure (10 mg) similar to that obtained with atorvastatin (40 mg) alone. Darunavir/cobicistat increased atorvastatin (10 mg) AUC by 290%.
4. Elvitegravir/cobicistat increased atorvastatin (10 mg) AUC by 160%.
5. Fostemsavir inhibits OATP and BCRP and has the potential to increase atorvastatin exposure although to a lower extent than PIs as fostemsavir does not inhibit CYP3A4.
6. Caution is recommended in older persons as they may be more susceptible to developing statin related adverse effects

Full details of DDI studies available at www.hiv-druginteractions.org

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Abbreviations ABC abacavir ATV atazanavir FTC emtricitabine DRV darunavir 3TC lamivudine EVG elvitegravir TAF tenofovir alafenamide /c cobicistat /r ritonavir TDF tenofovir-DF BIC bictegravir ZDV zidovudine CAB cabotegravir DOR doravirine DTG dolutegravir EFV efavirenz RAL raltegravir ETV etravirine FTR fostemsavir NVP nevirapine LEN lenacapavir RPV rilpivirine MVC maraviroc

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Drug-Drug Interactions with Moderate Intensity Statins

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Pitavastatin

Recommended dose in the absence of a DDI: 4 mg once daily

Antiretrovirals		Recommendation for management of DDIs
NRTIs	ABC, FTC, 3TC, TAF, TDF, ZDV	No interaction expected. No dose adjustment required.
NNRTIs	DOR, EFV, ETR, NVP, RPV	No interaction expected. No dose adjustment required.
PIs and Boosted ARVs	ATV, ATV/r, ATV/c	Modest increase in pitavastatin exposure. [1] No a priori dose adjustment but monitor for adverse effects.
	DRV/r	No interaction expected. No dose adjustment required.
	DRV/c EVG/c	Potential modest increase in pitavastatin exposure. [2] No a priori dose adjustment but monitor for adverse effects.
Integrase Inhibitors	BIC, CAB, DTG, RAL	No interaction expected. No dose adjustment required.
Other	FTR	Potential modest increase in pitavastatin exposure. [3] No a priori dose adjustment but monitor for adverse effects.
	LEN, MVC	No interaction expected. No dose adjustment required.

Notes

1. Atazanavir increased pitavastatin (4 mg) AUC by 31%. This modest increase does not necessarily warrant a dose reduction.
2. Potential modest increase in pitavastatin exposure (inhibition of OATP1B1); a dose reduction is not necessarily warranted.
3. Fostemsavir has a lower inhibitory effect on OATP1B1 compared to atazanavir (fostemsavir increased rosuvastatin (10 mg) AUC by 69% versus 213% for atazanavir/ritonavir). Atazanavir increased pitavastatin (4 mg) AUC by 31%; consequently, fostemsavir is expected to minimally increase pitavastatin exposure.

Full details of DDI studies available at www.hiv-druginteractions.org

Rosuvastatin

Recommended dose in the absence of a DDI: 10 mg once daily

Antiretrovirals		Recommendation for management of DDIs
NRTIs	ABC, FTC, 3TC, TAF, TDF, ZDV	No interaction expected. No dose adjustment required.
NNRTIs	DOR, EFV, ETR, NVP, RPV	No interaction expected. No dose adjustment required.
PIs and Boosted ARVs	ATV, ATV/r, ATV/c	Increase in rosuvastatin exposure. [1] Reduce rosuvastatin dose to 5 mg once daily. Monitor for adverse effects. Do not exceed 10 mg/day.
	DRV/r	Modest increase in rosuvastatin exposure. [2] No a priori dose adjustment but monitor for adverse effects.
	DRV/c	Rosuvastatin exposure increased by 2-fold. [3] Consider reducing rosuvastatin dose to 5 mg once daily. Monitor for adverse effects. Do not exceed 20 mg/day.
	EVG/c	No relevant increase in rosuvastatin exposure. [4] No dose adjustment required.
Integrase Inhibitors	BIC, CAB, DTG, RAL	No interaction expected. No dose adjustment required.
Other	FTR	Modest increase in rosuvastatin exposure. [5] No a priori dose adjustment but monitor for adverse effects.
	LEN, MVC	No interaction expected. No dose adjustment required.

Notes

1. Atazanavir/ritonavir and atazanavir/cobicistat increased rosuvastatin (10 mg) AUC by 213% and 242% (inhibition of OATP1B1 and BCRP). A similar effect is expected for atazanavir alone.
2. Darunavir/ritonavir increased rosuvastatin (10 mg) AUC by 48%.
3. Darunavir/cobicistat increased rosuvastatin (10 mg) AUC by 93%.
4. Elvitegravir/cobicistat increased rosuvastatin (10 mg) AUC by 38%, an increase which is not considered clinically relevant.
5. Fostemsavir increased rosuvastatin (10 mg) AUC by 69%.

Full details of DDI studies available at www.hiv-druginteractions.org

Abbreviations ABC abacavir ATV atazanavir FTC emtricitabine DRV darunavir 3TC lamivudine EVG elvitegravir TAF tenofovir alafenamide /c cobicistat /r ritonavir TDF tenofovir-DF BIC bictegravir ZDV zidovudine CAB cabotegravir DOR doravirine DTG dolutegravir EFV efavirenz RAL raltegravir ETV etravirine FTR fostemsavir NVP nevirapine LEN lenacapavir RPV rilpivirine MVC maraviroc

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