Interactions Between Antiretrovirals and Antiplatelet Agents and Novel Oral Anticoagulants

		Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticagrelor (Brilinta®)	
Dosing		300mg – 600mg loading dose 75 mg daily maintenance dose	60mg loading dose 10mg daily maintenance dose	180mg loading dose 90mg BID maintenance dose	
Metabolism		Prodrug activated by CYP2C19 (major) CYP2C9, CYP2B6 & CYP3A4 metabolism. Inhibitor of CYP2B6.[1] Increased CYP2C19 activity does not lead to greater therapeutic effect.[2]	Prodrug activated by CYP3A4 (major) CYP2B6, CYP2C19 & CYP2C9 metabolism.[3]	Substrate of CYP3A4 and P-gp CYP3A4 produces active metabolite with 30% activity. [4]	
Elimination		Active metabolite metabolized by CYP2C19 and CYP2C9.[2]	Active metabolite 2/3 excreted in urine and 1/3 in feces as inactivated metabolites.[3]	Glucuronidated metabolites 2/3 excreted in urine and 1/3 in bile.[4]	
Protease Inhibitors (PIs)		**Clopidogrel (Plavix®)**	**Prasugrel (Effient®)**	**Ticagrelor (Brilinta®)**	**Clinical management**
Ritonavir	Inhibitor of CYP3A4, P-gp, and CYP2D6 Inducer of CYP2C19, CYP2C9 and CYP1A2[5]	No data with PIs. Ketoconazole 400 mg ↓ clopidogrel active metabolite AUC_{0-24} by 29% in healthy volunteers.[6a] Case report of decreased responsiveness to clopidogrel in a patient receiving isoniazid (CYP2C19, 3A4 inhibitor) and darunavir/ ritonavir once daily suggesting potential contribution of 3A4 inhibition to	Single dose ritonavir 100 mg ↓ AUC of prasugrel active metabolite by 38% in a healthy adult volunteer study. [8] Ketoconazole 400 mg did not significantly impact the AUC of prasugrel active metabolite or inhibition of platelet aggregation.[6] Product monograph states CYP3A inhibitors not anticipated to	No data with PIs. In vivo study with healthy volunteers ketoconazole ↑ AUC of ticagrelor 632% through inhibition of metabolism.[10a] Strong CYP3A inhibitors contraindicated with ticagrelor in product monograph.[11] Possible ↑ risk of bleeding when used with PIs.	Suggest use of prasugrel with concomitant PIs.
Atazanavir	Inhibitor of CYP3A4				
Darunavir	Inhibitor of CYP3A4				
Lopinavir	Inhibitor of CYP3A4				

		decreased effect.[7]	have significant effect on pharmacokinetics of active metabolite.[3] This may be due to ability of multiple additional CYPs to form prasugrel active metabolite.[9]		

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NNRTI		Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticagrelor (Brilinta®)	Clinical management
Efavirenz	Inducer of 3A4 and 2B6 Inhibitor of CYP2C9 and 2C19[12]	In vitro study with efavirenz ↓ AUC of clopidogrel active metabolite by 33% due to inhibition of CYP2C19/2C9 bioactivation.[13] In vivo study in healthy Korean subjects showed clopidogrel pretreatment ↑ AUC of efavirenz and its hydroxyl metabolites.[1] Possible ↓ effect of clopidogrel. Potential for ↑ efavirenz exposure; clinical significance unclear, monitor for toxicity.	No data with efavirenz. In vivo study with healthy male subjects rifampin ↓ AUC of prasugrel active metabolite by 5% through induction of CYP3A4.[14b] Interaction unlikely to be clinically relevant.	No data with efavirenz. In vivo study with healthy male subjects rifampin ↓ AUC of ticagrelor by 10% via induction of CYP3A4.[15b] Interaction unlikely to be clinically relevant.	Suggest use of prasugrel or ticagrelor with efavirenz.
Nevirapine	Inducer of CYP3A4, CYP2B6[12]	No expected effect	Possible ↓ AUC of prasugrel active metabolite due to induction of CYP3A4. Unlikely to be clinically relevant.[14]	Possible ↓ AUC of ticagrelor due to induction of CYP3A4. Unlikely to be clinically relevant.[15]	Suggest use of clopidogrel, prasugrel, or ticagrelor.
Etravirine	Inducer of CYP3A4 Inhibitor CYP2C19 (moderate), CYP2C9 (weak), P-gp (weak)[16]	Possible ↓ bioactivation and ↓ AUC of clopidogrel active metabolite through inhibition of CYP2C19. Possible ↓ clinical effect of clopidogrel.[2]	Possible ↓ AUC of prasugrel active metabolite due to induction of CYP3A4. Unlikely to be clinically relevant.[14]	Possible ↓ AUC of ticagrelor due to induction of CYP3A4. Unlikely to be clinically relevant.[15]	Suggest use of prasugrel or ticagrelor with etravirine.
Ripivirine	Inducer of CYP2C19 (moderate), CYP1A2, 2B6 and	Significant interaction unlikely.[2]	Significant interaction unlikely.[14]	Significant interaction unlikely.[15]	Suggest use of clopidogrel, prasugrel, or ticagrelor.

	3A4 (weak) [12]				
Integrase inhibitors		**Clopidogrel (Plavix®)**	**Prasugrel (Effient®)**	**Ticagrelor (Brilinta®)**	**Clinical management**
Raltegravir	No inhibition or induction of CYP metabolism [17]	No expected effect			There are no expected interactions.
Elvitegravir	Inducer of CYP2C9 (moderate) [18]	No expected effect.	No expected effect	No expected effect	
Cobicistat [c]	Inhibitor of CYP3A4 and P-gp[18]	Ketoconazole 400 mg (CYP3A inhibitor) ↓ clopidogrel active metabolite AUC_{0-24} by 29% in healthy volunteers.[6] Case report of decreased responsiveness to clopidogrel in a patient receiving isoniazid (CYP2C19, 3A4 inhibitor) and darunavir/ritonavir once daily suggesting potential contribution of 3A4 inhibition to decreased effect.[7]	Possible ↓ clinical effect due to ↓ prasugrel bioactivation through CYP3A4. Product monograph states CYP3A inhibitors not anticipated to have significant effect on pharmacokinetics of active metabolite.[3] This may be due to ability of multiple additional CYPs to form prasugrel active metabolite.[9]	Strong CYP3A inhibitors contraindicated with ticagrelor in product monograph.[11] Possible ↑ risk of bleeding when used with cobicistat.	Suggest use of prasugrel with cobicistat.
Dolutegravir	Metabolized by UGT1A1 with some contribution from CYP3A. No inhibition or induction of CYP metabolism. [19]	No expected effect.			There are no expected interactions.
CCR5 inhibitors		**Clopidogrel (Plavix®)**	**Prasugrel (Effient®)**	**Ticagrelor (Brilinta®)**	**Clinical management**
Maraviroc	No inhibition or induction	No expected effect			There are no expected

	of CYP metabolism [20]		interactions.

Interactions Between Antiretrovirals and Antiplatelet Agents and Novel Oral Anticoagulants

		Dabigatran etexilate (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	
Dosing		150mg BID or 110mg BID	20mg daily or 15mg daily with GFR 30-50 ml/min	5mg BID	
Metabolism		No CYP3A4 Dabigatran etexilate, the prodrug, is P-gp substrate	CYP3A4 substrate P-gp substrate	CYP3A4 (primarily), CYP1A2 (minor) P-gp substrate	
Elimination		With GFR > 30ml/min almost entirely renally cleared[21]	1/3 excreted in urine and 2/3 as inactivated metabolites in bile[22]	¼ excreted in urine, ¾ as inactivated metabolites in bile[23]	
Protease Inhibitors (PIs)		**Dabigatran etexilate (Pradaxa®)**	**Rivaroxaban (Xarelto®)**	**Apixaban (Eliquis®)**	**Clinical management**
Ritonavir	Inhibitor of CYP3A4, Pgp and CYP2D6 Inducer of CYP2C19, CYP2C9 and CYP1A2[5]	Significant interaction unlikely based on limited data. Healthy volunteer study found slight (13%) ↓ in AUC of dabigatran etixelate when administered 2 hours separately from 100 mg RTV and no significant effect when given at the same time.[24] Case report showed no interaction when dabigatran administered to a patient on lopinavir/ritonavir.[25]	Ritonavir 600 mg bid ↑ rivaroxaban AUC 2.5-fold due to inhibition of metabolism.[26] Case report of ~ 2-fold ↑ in rivaroxaban concentration in patient on salvage regimen including darunavir/r. Patient experienced bloody diarrhea possibly related to ↑ effects of rivaroxaban.[27] Concomitant use of strong inhibitors of both CYP3A4 and P-gp contraindicated with rivaroxaban in product monograph. [22]	No data with PIs. Ketoconazole ↑ apixaban AUC 2-fold due to inhibition of CYP3A4 and P-gp[23a] Concomitant use of strong inhibitors of both CYP3A4 and P-gp contraindicated in product monograph.[23] Possible ↑ clinical effect with PIs.	Suggest use of dabigatran with concomitant PI.
Atazanavir	CYP3A4 inhibitor				
Darunavir	CYP3A4 inhibitor				
Lopinavir	CYP3A4 inhibitor				

Interactions Between Antiretrovirals and Antiplatelet Agents and Novel Oral Anticoagulants

NNRTI		Dabigatran etexilate (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Clinical management
Efavirenz	Inhibitor of CYP2C9 and 2C19 (both moderate) Inducer of 3A4, 2B6	No expected drug interaction.[28]	Possible ↓ rivaroxaban AUC and clinical effect due to induction of CYP3A4 metabolism. Case report describing ↓ clinical effect of rivaroxaban with concurrent use of nevirapine.[29] Expect similar interaction with efavirenz and etravirine.	Possible ↓ apixaban AUC and clinical effect due to induction of CYP3A4 metabolism. In vitro studies showed rifampin ↓ apixaban AUC by 33% due to induction of metabolism.[b] Most likely to occur with efavirenz, nevirapine and etravirine.[30,31]	Suggest use of dabigatran with concurrent NNRTIs. Rilpivirine less likely to interact with rivaroxaban and apixaban as compared to other NNRTIs.
Nevirapine	Inducer of CYP3A4 and CYP2B6				
Etravirine	Inducer of CYP3A4 Inhibitor CYP2C9 (weak), CYP2C19 (moderate), P-gp (weak)				
Ripilvirine	Inducer of CYP2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak)				
Integrase inhibitors		**Dabigatran etexilate (Pradaxa®)**	**Rivaroxaban (Xarelto®)**	**Apixaban (Eliquis®)**	**Clinical management**
Raltegravir	No inhibition or induction of CYP metabolism	No expected effect[17]			
Elvitegravir	Induction of CYP2C9 (moderate)				
Cobicistat [c]	Inhibitor of CYP3A4 and P-pg.[18]	Possible ↑ dabigatran bioavailability due to inhibition of P-gp in gut. Unlikely to be clinically relevant if administration times are separated by 2 hours. [21]	Possible ↑ rivaroxaban AUC and clinical effect. Concomitant use of strong inhibitors of both CYP3A4 and P-gp contraindicated with rivaroxaban in product monograph.[22]	Possible ↑ apixaban AUC and clinical effect due to inhibition of CYP3A4 and P-gp.[30,31] Concomitant use of strong inhibitors of both CYP3A4 and P-gp contraindicated in product monograph.[23]	Suggest use of dabigatran with concomitant cobicistat.
Dolutegravir	Metabolized by	No expected effect.			There are no

	UGT1A1 with some contribution from CYP3A. No inhibition or induction of CYP metabolism.[19]				expected interactions.
CCR5 inhibitors		**Dabigatran etexilate (Pradaxa®)**	**Rivaroxaban (Xarelto®)**	**Apixaban (Eliquis®)**	**Clinical management**
Maraviroc	No inhibition or induction of CYP metabolism	No expected effect.[21-23]			No expected interactions.

a - ketoconazole is a strong inhibitor of CYP3A4 which is comparable to PIs and a weak inhibitor of CYP2C9 and 2C19[32]
b – rifampin is a strong inducer of CYP3A4 with even greater induction compared to NNRTIs. Rifampin is also a moderate inducer of CYP 2C8, 2C9, 2C19[32]
c - cobicistat is not an integrase inhibitor but is currently only available in combination with elvitegravir

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