Examples of significant drug-drug interactions commonly encountered in clinical practice: [8,13]

Drug	**Interaction**
Acid lowering medications	Drugs that increase gastric pH are expected to decrease the concentration of both velpatasvir and ledipasvir. If it is considered medically necessary to co-administer a proton-pump inhibitor (PPI), DAAs should be taken with food, 4 hours before PPI, at a dose that does not exceed that comparable to omeprazole 20mg.
Direct oral anticoagulants (DOACs)	Concentrations of apixaban may increase due to the additive effect of weak inhibition of cytochrome P450 3A4 (CYP3A4) by grazoprevir and inhibition of breast cancer resistance protein (BCRP) by elbasvir/grazoprevir. Any increase in apixaban levels is unlikely to be clinically relevant but patients should be reminded to promptly report any signs of bleeding or bruising.
Certain cytochrome p450/p-glycoprotein (CYP/P) -gp-inducing agents, e.g. carbamazepine, phenytoin and phenobarbital	Contraindicated with all regimens, due to the risk of significantly reduced concentrations of DAAs and therefore high risk of failure of virological response.
Organic anion transporting polypeptide 1B (OATP1B) inhibitors, e.g. ciclosporin, macrolides and statins	Contraindicated with PIs as they can significantly increase their plasma concentrations.

Examples of significant co-morbidities commonly encountered in clinical practice:

- HCV PIs (e.g. Maviret, Zepatier) are not recommended with Child Pugh B/C decompensated cirrhosis. Decompensation events and disease progression are more prevalent in patients with decompensated cirrhosis at baseline receiving a PI when compared to non-PI based first-line treatment or in patients with compensated or no cirrhosis.[14]

- No dose adjustment is required for the current first-line DAA regimens in patients with renal impairment, including those with chronic kidney disease (CKD) stage 4 or 5 and patients with end-stage renal disease on haemodialysis.[8] Glecaprevir, pibrentasvir, velpatasvir and voxilaprevir are not renally excreted. Sofosbuvir is renally excreted and should only be used in patients with severe renal impairment when there is no alternative treatment. Glecaprevir plus pibrentasvir is a preferred regimen for treating HCV in people with severe renal impairment.