generation PIs are. Darunavir also has some decreased side effects for example reduced diarrhoea and lipodystrophy, and it requires only a singular dosage a day when boosted with ritonavir (Mckeage, Perry & Keam, 2009). Normally darunavir has a short half-life of around three hours due to fast metabolism by hepatic catalytic enzyme CYP3A, which is part of the cytochrome P450 superfamily. By boosting with a dose of ritonavir the half-life is increased to approximately 15 hours, hence the need for only one dose.

The next class of ARTs are integrase inhibitors (IIs), which prevent the viral enzyme integrase from transporting the double stranded viral DNA into the nucleus for insertion into the host chromosomal DNA (Cocohoba & Dong, 2008). The first FDA approved drug in this class was raltegravir in 2007, followed by recent approval of elvitegravir in 2012 and dolutegravir in 2013. The integrase enzymes catalytic domain is responsible for the formation of covalent bonds with the phosphodiester backbone in the hosts DNA, allowing integration of the viral DNA. IIs prevent this bond formation hence prevent integration (Hicks & Gulick, 2009).

IIs are not metabolised through the P450 cytochrome hepatic pathway like many other ARTs, but through glucuronidation. This is the addition of glucuronic acid, with assistance from the enzyme UGT1A1, which makes the IIs water soluble and hence allows for their excretion (Brainard *et al.* 2011). This means that IIs can be given to patients with either hepatic or renal problems and drug accumulation will not occur. Another benefit of IIs is that they have a lower incidence of side effects, with only a low percentage of patients experiencing diarrhoea, nausea and headaches (Temesgen & Siraj, 2008). This is a key goal in ART drug development along with decreased drug-drug interactions. Raltegravir has low drug interaction profiles, so can be used on many different patient populations and safe

antiretroviral drugs have turned HIV from a death sentence into a chronic yet manageable disease, much like diabetes. Both require long term management via medication and lifestyle; but if managed well, can offer patients a long life. With new drugs taking around ten years to trial and come into production any HIV mutations could remove a drug's effectiveness even before it has been manufactured. The HAART cocktail of drugs attempts to disrupt different stages in the life cycle of the virus which represents the current best outcome for those infected with HIV. To succeed, management of HIV needs to become a global treatment, including all less developed countries in order to try and eradiate this harmful and persistent pandemic. Inflammation due to enduring immune activation is also a key issue that contributes to complications and increased mortality e.g. cardiovascular disease. HAART reduces viral load but inflammation often remains increased. More long term HIV therapies will therefore need to include inflammation management in order to reduce this major problem. New areas of study are always being explored in order to advance knowledge, in the hope to discover new ways of inhibiting HIV infection. A potentially good area to look into may possibly be in the few individuals that are able to control HIV infection in the absence of therapy. These individuals could have one small mutation that may have a profound effect on inhibiting the final outcome of the HIV infection, and could have the potential to alter the progression of the AIDS pandemic.

(Word count 5000)

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