Hopes for an AIDS cure using triple-combination AIDS therapy have been tempered by problems with partial- or noncompliance with an uncompromisingly rigid drug regimen, the emergence of resistant strains of HIV-1, and pharmacological barriers limiting accessibility of drugs to various critical target tissues and cells. These latter barriers include low bioavailability of the orally administered protease inhibitor (PI) component of the combination therapy, as well as the questionable effectiveness of this treatment strategy for late stage HIV-1 infection with central nervous system (CNS) involvement. Recently, back-to-back reports of hidden reservoirs of fully viable, replication competent, nonmutated HIV-1 viruses in T cells that have survived treatment (1–3) lend credence to the existence of such a barrier. While first pass metabolism by the cytochrome P450 system may partially account for the poor bioavailability of these drugs, an often overlooked major determinant of drug pharmacokinetics and bioavailability, the *MDR*1 multidrug transporter (Pgp), may also be a barrier to the success of PI treatment. Pgp is an energy-dependent transporter of multiple hydrophobic low molecular weight drugs and is expressed at high levels in the gastrointestinal tract, kidney, liver, and capillary endothelial cells of the brain (for review see reference 4). The role of Pgp in absorption and distribution of HIV-1 PIs is addressed in this issue of *The Journal* (5).

Other soon-to-appear reports[1] suggest that most of the FDA-approved HIV-1 PIs are substrates of the multidrug transporter. Here, Kim and colleagues use two approaches to underscore the importance of Pgp in limiting oral absorption and brain entry of these protease inhibitors (5). They examined transport characteristics of the HIV-1 PIs in the gut, using human Caco-2 cells, which when reconstituted as epithelial monolayers on permeable supports exhibit features characteristic of normal human intestine. These cells express *MDR*1 on the apical surface facilitating the study of vectorial transport of potential Pgp substrates. They demonstrated that the basal-to-apical transport of the HIV-1 PIs in these cells is diminished by the addition of Pgp inhibitors, quinidine and PSC833. They further compared drug uptake characteristics of wild-type versus *mdr*1a(−/−) mice (6). Unlike humans with only one multidrug transporting Pgp (*MDR*1), mice have two, encoded by *mdr*1a and *mdr*1b (7, 8). Mouse *mdr*1a is found abundantly in the epithelial cells of the intestines and the endothelial cells of the blood-brain barrier making this knockout mouse an ideal model for uptake studies of potential Pgp substrates in the gut and brain. Kim et al. (5) found that the plasma concentrations of PIs in *mdr*1a(−/−) mice were elevated two- to fivefold upon oral administration, suggesting that the presence of Pgp in the epithelial cells of the gastrointestinal tract poses the first pharmacological barrier for the HIV-1 PIs. This result may explain the relatively poor absorption of these drugs when taken orally. They also found that the concentrations of HIV-1 PIs in the brains of *mdr*1a(−/−) mice were increased 7–36-fold after intravenous administration. Hence, the presence of Pgp at the blood-brain junction could account for the ineffectiveness of this drug regimen for the treatment of HIV-1 infection of the CNS.

What are the implications of these findings? Fig. 1 traces the route a drug takes. The *MDR*1 efflux pump (*dotted red arrows*) can be found at the interface of major organs offering two levels of protection. Its expression in the intestines serves as a first line of defense preventing the absorption of xenobiotics into the body while its expression in the brain provides a second barrier to further protect this sensitive organ. Pgp is also expressed to varying degrees in $CD4^+$ T lymphocytes (9) and monocytes/macrophages (10), major targets of HIV-1 infection. Can variable expression of Pgp in these cells explain the resistance of some patients to PIs?

One strategy to improve both cellular bioavailability and absorption would be to transiently block Pgp function by the addition of a Pgp inhibitor to the current regimen of drugs given to HIV-1 patients. However, the physiological and pharmacological consequences of this strategy would need careful evaluation. Given the wide distribution of Pgp in the adrenal cortex; in transporting epithelia of kidney, liver, pancreas, and placenta; in capillary endothelia of the testis; and in various hematological cells (for review see reference 4), Pgp may also be involved in the transport of steroids and as yet undetermined endogenous metabolites. Will inhibiting the *MDR*1 pump inadvertently affect its other physiological functions and upset the pharmacokinetics of other drugs/xenobiotics that are also given to the patient?

A hopeful observation is that the knockout of both *mdr*1a and *mdr*1b genes in the mouse results in no obvious physiological abnormalities (11). Another encouraging report by the same group demonstrates the feasibility of using a cyclosporin analogue, PSC833, to inhibit intestinal as well as blood-brain barrier Pgp (12). Use of Pgp inhibitors is likely to result in increased toxicity to some drugs of tissues like the brain and reproductive organs. Hints of CNS side effects have been reported already. Schinkel and colleagues demonstrated that some drugs, e.g., the antidiarrheal narcotic analogue loperamide, originally intended to treat peripheral symptoms owing to their inability to enter the brain, regained CNS activity when the Pgp barrier was removed (6, 13).

Another consideration is that Pgp inhibitors may change the bioavailability and biodistribution of coadministered anti-HIV drugs. Hence, further studies are needed to identify appropriate inhibitors that will improve the delivery of these drugs without too many side effects. Ideally, the Pgp inhibitor to be used for AIDS treatment should not potentiate HIV-1 replication nor have other side effects on the already immunocompromised patient nor interact negatively with other antiviral or therapeutic drugs. Finally, while Kim et al. (5) highlight HIV-1 PIs as substrates of Pgp, it is prudent to also consider

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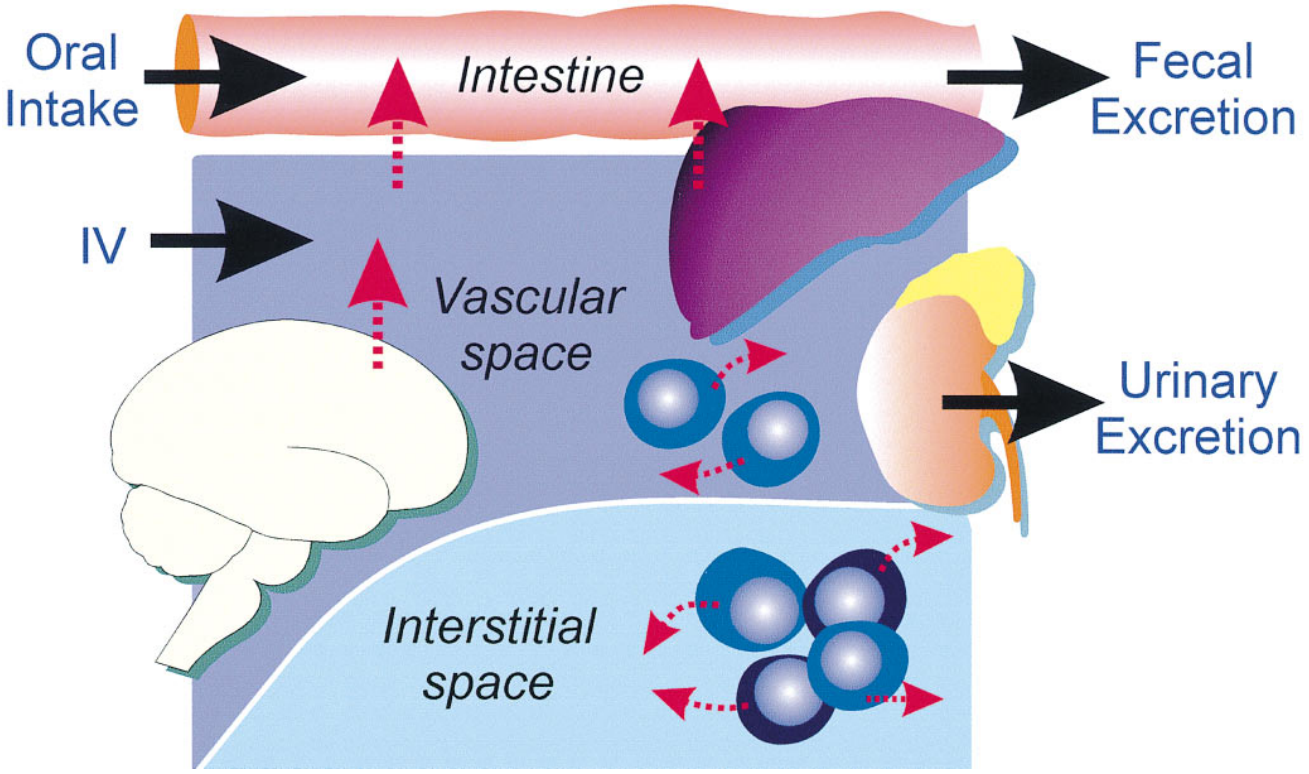


*Figure 1.* Schematic illustrating the effect of the *MDR*1 multidrug transporter (Pgp) on the bioavailability of drugs. Solid arrows represent the drugs' route while dotted red arrows and the solid arrow to "Urinary Excretion" represent Pgp. Illustration by Naba Bora, Medical College of Georgia.

the role of Pgp in the interaction of various other drugs in the patient's regimen. In addition to drugs to inhibit HIV-1 replication, an AIDS patient may also take supplementary drugs to alleviate other symptoms. Furthermore, it has been proposed that an additional protease inhibitor be added to the triple-drug combination to further reduce viral loads. One has to be aware that while a drug when taken alone may not have adverse effects due to the protective barrier imposed by Pgp, the addition of another drug, which is also a Pgp substrate, could compete for the *MDR*1 transporter and affect the pharmacodynamics of the first drug. Depending on its effects, this may have a useful outcome or it may complicate the intervention scheme. Whatever strategy is ultimately pursued, knowledge of the physiological role of the multidrug transporter will allow more rational approaches to the treatment of AIDS.

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