

## Managing drug interactions in HIV-infected adults with comorbid illness

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With the introduction of combination antiretroviral therapy, HIV-1 infection is now considered a treatable chronic infectious disease. Modern combination antiretroviral therapy consists of at least three antiretroviral agents and leads to virologic suppression in most patients who are able to take their medication regularly.<sup>1,2</sup> As a result, HIV-related mortality has been greatly reduced, and the life expectancy of HIV-infected individuals is near normal.<sup>3</sup>

Currently, more than 20 approved antiretroviral drugs are available in Canada, belonging to six medication classes (Box 1). Recent advances in HIV treatment include improved tolerability of newer agents; availability of new medication classes with novel mechanisms of actions, such as the integrase inhibitors; and an increasing number of fixed-dose combination tablets, which greatly reduce the pill burden, in some cases allowing for entire HIV regimens to be provided with a single tablet administered once daily.<sup>2</sup>

As a consequence of decreased mortality and effective treatment, the demographic characteristics of the HIV-infected population have shifted: in the United States, for example, more than half of HIV-infected individuals will be 50 years of age or older by the year 2015.<sup>4</sup> It is also now increasingly recognized that despite effective antiretroviral treatment, the incidence of cardiovascular disease, non-HIV-related cancer, and renal and hepatic impairment is greater among HIV-infected patients 50 years of age and older than among uninfected individuals of the same age.<sup>1,5,6</sup> The premature onset of age-associated medical comorbidities is a phenomenon sometimes called “accelerated aging in HIV-infection” and may be due to effects of chronic viral infection, cumulative toxicity of long-term antiretroviral therapy and/or higher frequency of tobacco and other substance use.<sup>1,5,6</sup>

With a relatively high burden of comorbid conditions and diseases of aging, older HIV-infected patients are at particularly high risk of polypharmacy and drug–drug interactions.<sup>7</sup> Relative to HIV-infected patients under 50 years of age, older HIV patients are substantially more likely to be receiving additional medications, including cardio-

vascular drugs, antacids or acid-suppressing agents, lipid-lowering agents, antiplatelet agents or anticoagulants, oral hypoglycemic agents and erectile dysfunction drugs.<sup>7,8</sup> In addition, in some studies, the use of antidepressants, psychotropics and analgesics was more common among older HIV-infected patients than among HIV-infected patients younger than 50 years.<sup>8,9</sup>

As primary care physicians and other specialists become increasingly involved in the care of HIV-infected individuals, it is essential for them to recognize, prevent and manage clinically important interactions between commonly prescribed drugs and antiretroviral therapy. This review highlights potentially important pharmacokinetic interactions between antiretroviral agents and drugs that are more commonly prescribed for older HIV-infected patients than for younger patients with HIV infection. We defined clinically important pharmacokinetic drug interactions as interactions that might require dosage adjustments or drug combinations that should be avoided. We considered the following drug classes, on the basis of literature suggesting a higher frequency of use by older than by younger HIV-infected adults: acid-suppressing agents, analgesics, antiplatelet agents and anticoagulants, cardiovascular drugs, antipsychotics, statins, antidepressants and antidiabetic agents.<sup>7–9</sup> We also considered phosphodiesterase-5 inhibitors, corticosteroids and anticonvulsants, because they are frequently used in clinical prac-

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### KEY POINTS

- Older HIV-infected patients are at potentially higher risk of drug–drug interactions because of an increased incidence of comorbidities resulting in polypharmacy.
- Many antiretroviral drugs are prone to pharmacokinetic drug–drug interactions because they are substrates as well as inhibitors or inducers of several cytochrome P450 isoenzymes.
- Recommendations for management of antiretroviral drug interactions with medications commonly used in HIV-infected adults with comorbid disease are based primarily on pharmacokinetic studies in healthy volunteers and case reports or small studies in HIV-infected adults.
- Given the potential for serious consequences in older HIV-infected adults, clinicians need to screen for potential drug interactions and be aware of resources to guide management.

tice and carry risks of clinically important interactions with antiretroviral agents; the results of those analyses are presented in Appendix 1 (available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.131626/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.131626/-/DC1)). However, this review is not intended to provide comprehensive information about all potential interactions involving antiretroviral drugs.

The strategy for our literature search is summarized in Box 2. The recommendations presented in this review are based primarily on pharmacokinetic studies involving healthy vol-

unteers and on case reports or case series for HIV-infected patients.

## Why are antiretroviral agents prone to pharmacokinetic drug interactions?

Like the majority of currently prescribed medications, most antiretroviral agents are not water-soluble and therefore must be modified by the cytochrome P450 (CYP450) enzyme system in the liver before they can be excreted from the body via bile or renal filtrate. However, many antiretroviral medications, as an incidental consequence of their particular chemical structure, also exert uniquely powerful effects on the activity of the CYP450 isoenzymes, inhibiting the activity of some isoforms while inducing the activity of others. The uniquely strong effects of antiretrovirals on CYP450 isoenzymes, combined with the fact that these isoenzymes are responsible for the metabolism of many other commonly prescribed agents, leads to a number of clinically important drug interactions. Both the efficacy and the toxicity of non-HIV medications can be drastically affected by the coadministration of antiretrovirals.<sup>2,10</sup>

It is also important for HIV care providers to appreciate the bidirectional nature of HIV drug–drug interactions. Many antiretroviral agents have a narrow therapeutic window. Excessively high plasma concentrations can increase toxic effects and reduce tolerability, whereas low plasma concentrations lead to reduced virologic control and emergence of drug-resistant strains of the virus.<sup>2,10</sup> In either case, the ability to ensure long-term, durable control of HIV infection is compromised. Thus, HIV-infected patients are considered particularly vulnerable to the pharmacokinetic influences of other medications, and any drug that reduces the absorption of an HIV medication or alters its metabolism through the CYP450 system can potentially undermine the efficacy of HIV treatment.

All members of the protease inhibitor class are particularly strong inhibitors of CYP3A4, with ritonavir being the most potent. Indeed, this drug is commonly used at low doses in HIV treatment (100–200 mg/d) not for its antiviral activity but rather to take advantage of its inhibition of CYP3A4, which “boosts” the plasma concentrations of coadministered protease inhibitors and thereby allows for once-daily dosing.<sup>2,10</sup> Ritonavir has a greater potential for drug–drug interactions than other protease inhibitors, because it also inhibits CYP2D6 in the liver and induces CYP2B6, CYP2C19, CYP2C9 and CYP1A2.<sup>10,11</sup>

### Box 1: Antiretroviral agents

#### Nucleoside/nucleotide reverse transcriptase inhibitors

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

#### Non-nucleoside reverse transcriptase inhibitors

- Delavirdine
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

#### Protease inhibitors

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

#### Integrase inhibitors

- Dolutegravir
- Elvitegravir
- Raltegravir

#### CCR5 receptor antagonist

- Maraviroc

#### Fusion inhibitor

- Enfuvirtide

#### Pharmacokinetic enhancers\*

- Ritonavir
- Cobicistat

Note: CCR5 = C-C chemokine receptor type 5.

\*Low-dose ritonavir and cobicistat are not prescribed as active antiretroviral agents but are used to improve the pharmacokinetic profile of other antiretrovirals.

Several of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) have a variety of effects on CYP450 isoenzymes. For example, efavirenz, nevirapine and etravirine are inducers of CYP3A4, whereas efavirenz and etravirine are inhibitors of CYP2C9 and CYP2C19.<sup>10</sup> Rilpivirine does not substantially affect CYP3A4 and is therefore less commonly involved in drug–drug interactions than other members of the NNRTI class.

With regard to the integrase inhibitors, raltegravir is metabolized primarily by uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 (also known as UGT1A1) and thus has a lower potential for interactions. Elvitegravir is coformulated with cobicistat, a potent inhibitor of CYP3A4, which is used to boost concentrations of elvitegravir but is also prone to interactions with other coadministered drugs.<sup>12</sup> Cobicistat is also an effective booster of atazanavir and darunavir, and coformulations with these agents are in development.

The nucleoside reverse transcriptase inhibitors are primarily cleared through the renal system, so pharmacokinetic interactions are much less likely to have clinical importance.

## What are examples of clinically important pharmacokinetic interactions with antiretrovirals?

### Absorption: acid-suppressing agents

Reduced gastric absorption of HIV medications can compromise treatment efficacy. Acid-suppressing agents used to treat gastroesophageal reflux disease and dyspepsia, such as H<sub>2</sub>-blockers or proton pump inhibitors, raise gastric pH and thereby reduce the solubility of the NNRTI rilpivirine and the protease inhibitor atazanavir, thus greatly reducing their bioavailability. Rilpivirine and atazanavir are widely used in the treatment of HIV, and this interaction is likely to be commonly encountered.<sup>2</sup>

Conversely, cationic antacids (e.g., calcium carbonate, magnesium hydroxide, aluminum sulphate) form insoluble complexes with some members of the integrase inhibitor class (e.g., elvitegravir, dolutegravir) and can substantially reduce gastric absorption of these HIV drugs.<sup>10</sup>

Several small studies involving both HIV-infected patients and healthy volunteers have evaluated the effect of the H<sub>2</sub>-receptor antagonist famotidine on serum concentrations of atazanavir.<sup>13–15</sup> Higher doses of famotidine and its administration either 2 hours before or within 4 hours after the atazanavir dose appeared to have a greater effect on the area under the concentration–time curve and the minimum concentration of ata-

zanavir.<sup>14</sup> Increasing the dose of atazanavir from 300 to 400 mg daily (in addition to ritonavir 100 mg daily) may compensate for this interaction.<sup>15</sup> Famotidine also significantly reduced rilpivirine concentrations when administered 2 hours before rilpivirine.<sup>16</sup> However, administering famotidine either 4 or 12 hours after rilpivirine did not appear to have much effect.<sup>16</sup>

Pharmacokinetic studies of proton pump inhibitors coadministered with atazanavir in healthy people have shown dramatic decreases in area under the curve and minimum concentration of atazanavir.<sup>17–22</sup> Case series and small studies attempting to evaluate the importance of the interaction between atazanavir and proton pump inhibitors in terms of clinical outcomes (e.g., changes in viral load) have yielded inconsistent results.<sup>23–25</sup> Nonetheless, most HIV care providers would prefer to switch to another protease inhibitor for patients requiring prolonged gastric acid suppression. Proton pump inhibitors should also be avoided in patients receiving rilpivirine, as omeprazole 20 mg daily reduced the area under the curve and minimum concentration of rilpivirine by about 40%.<sup>26</sup>

Although pharmacokinetic data are not available, administration of antacids at the same time as atazanavir or rilpivirine is expected to affect antiretroviral absorption because of altered gastric pH. Separating administration times is therefore recommended.<sup>26,27</sup>

The absorption of integrase inhibitors (dolutegravir, elvitegravir and raltegravir) is substantially reduced, as a result of binding, when these drugs are coadministered with polyvalent cations, including antacids, that contain aluminum, magnesium hydroxide or calcium carbonate.<sup>28–30</sup> Separating administration times by at least

### Box 2: Evidence used in this review

We performed a comprehensive search of the MEDLINE database for English-language articles (January 1998 to February 2014) using the following key search terms: "HIV" and "drug interactions" and either "calcium channel blockers" or "antiplatelet" or "anticoagulants" or "cardiovascular agents" or "phosphodiesterase-5 inhibitors" or "hypoglycemic" or "corticosteroids" or "anticonvulsants" or "herbals" or "proton pump inhibitors" or "antacids" or "statins" or "analgesics" or "antidepressants" or "antipsychotics." We reviewed a total of 303 citations, and included 59 articles in our analysis. We also reviewed conference abstracts and reference lists of pertinent articles, as well as product monographs and prescribing information. The available data were limited primarily to pharmacokinetic studies involving healthy volunteers and case reports.

2 hours has been shown to compensate for this interaction.<sup>28,29</sup> Table 1 summarizes these interactions and possible management strategies.

**Metabolism: CYP3A4**

**Analgesics**

Interactions between antiretrovirals and methadone have been well described,<sup>31</sup> but data regarding interactions with other opioid agonists commonly used for pain management are limited. Oxycodone and fentanyl are both metabolized by CYP3A4. Pharmacokinetic studies in healthy volunteers have shown a 2.6- to 3-fold increase in oxycodone concentrations when administered with some protease inhibitors.<sup>32</sup> The self-reported effects of oxycodone were also increased in that study.<sup>32</sup> Similarly, ritonavir can increase the area under the curve for fentanyl, and fentanyl toxicity resulting in death has been reported following initiation of

lopinavir–ritonavir as part of HIV postexposure prophylaxis.<sup>33,34</sup> Thus, if cobicistat or a protease inhibitor is initiated in patients who are taking oxycodone or fentanyl, close monitoring and pre-emptive dose reductions may be required to avoid potential opioid-related adverse effects.

**Antiplatelet agents and novel oral anticoagulants**

The novel oral anticoagulants rivaroxaban and apixaban are metabolized by CYP3A4. Concentrations of these agents may be increased by protease inhibitors and cobicistat and may be decreased by NNRTIs, resulting in an increased risk of bleeding events or reduced efficacy, respectively.<sup>35</sup> Dabigatran is cleared primarily through the renal system and thus is less likely to interact with antiretroviral agents, which gives the clinician greater flexibility in choosing an HIV regimen.<sup>35</sup>

**Table 1:** Mechanisms of pharmacokinetic drug interactions between antiretrovirals and medications commonly used in older adults

Mechanism	Relevant antiretrovirals	Coadministered agents	Possible management strategy
<b>Absorption</b>			
Gastric acidity	<ul style="list-style-type: none"> <li>• Atazanavir</li> <li>• Rilpivirine</li> </ul>	Antacids	Separate administration times by at least 2 h <sup>26,27</sup>
		H2-receptor antagonists	<ul style="list-style-type: none"> <li>• Alter timing of administration and limit dose of H2-receptor antagonist</li> <li>• Consider increasing atazanavir dose to 400 mg (along with 100 mg ritonavir)</li> </ul>
		Proton pump inhibitors	Avoid concomitant use
Chelation	<ul style="list-style-type: none"> <li>• Dolutegravir</li> <li>• Elvitegravir</li> <li>• Raltegravir</li> </ul>	Antacids	Separate administration times by at least 2 h <sup>28-30</sup>
<b>Metabolism</b>			
CYP450 3A4	<ul style="list-style-type: none"> <li>• Protease inhibitors, cobicistat</li> <li>• NNRTIs</li> </ul>	<ul style="list-style-type: none"> <li>• Fentanyl, oxycodone</li> <li>• Anticonvulsants (e.g., carbamazepine, phenytoin)</li> <li>• Antiplatelet agents</li> <li>• Anticoagulants</li> <li>• Calcium-channel blockers (e.g., amlodipine, diltiazem, nifedipine, verapamil)</li> <li>• Corticosteroids (e.g., inhaled fluticasone–budesonide, triamcinolone by injection)</li> <li>• Phosphodiesterase inhibitors</li> <li>• Psychotropics (e.g., aripiprazole, quetiapine, ziprasidone)</li> <li>• Statins (e.g., lovastatin, simvastatin)</li> </ul>	<ul style="list-style-type: none"> <li>• Concentrations of coadministered agents may be increased or decreased</li> <li>• Consider agents less likely to interact</li> <li>• Monitor patient’s response and adjust dose of coadministered agent accordingly</li> </ul>
Other CYP450 isoenzymes (e.g., CYP2D6, CYP2B6, CYP2C9, CYP2C19)	<ul style="list-style-type: none"> <li>• Protease inhibitors, cobicistat</li> <li>• NNRTIs</li> </ul>	<ul style="list-style-type: none"> <li>• Antidepressants</li> <li>• Oral hypoglycemic agents (e.g., repaglinide, nateglinide, rosiglitazone)</li> <li>• Warfarin</li> </ul>	<ul style="list-style-type: none"> <li>• Concentrations of coadministered agents may be increased or decreased</li> <li>• Consider agents less likely to interact</li> <li>• Monitor patient’s response and adjust dose of coadministered agent</li> </ul>

Note: CYP450 = cytochrome P450, NNRTI = non-nucleoside reverse transcriptase inhibitor.

The antiplatelet agent ticagrelor is also a CYP3A4 substrate, whereas prasugrel is bioactivated by CYP3A4 to its active metabolite. In a study involving healthy volunteers, inhibition of CYP3A4 by ritonavir reduced the area under the curve for the active metabolite of prasugrel by 40%.<sup>36</sup> For patients receiving protease inhibitors or cobicistat, use of clopidogrel may be preferable, as a clinically important interaction with the latter would not be expected. However, for HIV-infected patients receiving the NNRTI efavirenz or etravirine, prasugrel or ticagrelor may be a safer option because of a lower risk of interactions. Clopidogrel is bioactivated primarily by CYP2C19; efavirenz and etravirine can inhibit this isoenzyme, which could reduce the efficacy of clopidogrel. On the basis of the CYP2C19 inhibitory effects of efavirenz observed in an *in vitro* study, efavirenz was predicted to reduce the area under the curve for the active metabolite of clopidogrel *in vivo* by up to 29%.<sup>37</sup>

#### Calcium-channel blockers

Most currently used calcium-channel blockers (e.g., amlodipine, diltiazem, felodipine, nifedipine and verapamil) are metabolized by CYP3A4. Data are limited, but pharmacokinetic studies in healthy volunteers have shown that ritonavir-boosted indinavir significantly increased exposure to amlodipine (90% increase in area under the curve) and diltiazem (27% increase in area under the curve).<sup>38</sup> Similarly, atazanavir increased diltiazem concentrations and area under the curve about two-fold in studies involving healthy volunteers.<sup>27</sup> Serious adverse effects (e.g., hypotension, edema, bradycardia) have been described in case reports of patients stabilized on calcium-channel blocker therapy who were initiated on protease inhibitors.<sup>39,40</sup> Conversely, pharmacokinetic studies have shown that efavirenz decreased diltiazem concentrations (69% decrease in area under the curve).<sup>41</sup> Thus, adjustment of the calcium-channel blocker dose may be necessary when protease inhibitor, cobicistat or NNRTI therapy is initiated.

#### Psychotropic agents

No pharmacokinetic data are available, but antipsychotics such as aripiprazole, quetiapine and ziprasidone are CYP3A4 substrates, and dose adjustments may therefore be required when these drugs are given with protease inhibitors, cobicistat or NNRTIs.<sup>42</sup> Reports of increased adverse effects due to quetiapine<sup>43,44</sup> and aripiprazole<sup>45</sup> in patients receiving protease inhibitors have been published.

#### Statins

Lipid disorders are frequently observed in older HIV-infected individuals, in part because of the dyslipidemic effects of some antiretroviral agents. Most statins are extensively metabolized by the CYP450 enzyme system in the liver, although the degree to which this occurs is variable. For example, lovastatin and simvastatin are lipophilic molecules that depend to a greater extent on CYP3A4 metabolism for clearance than do less lipophilic drugs. As a result, greater increases in serum concentrations of these statins occur when they are coadministered with potent CYP3A4 inhibitors such as protease inhibitors or cobicistat.<sup>46,47</sup> As an example, a 31-fold increase in the area under the curve for simvastatin was seen when this statin was coadministered with ritonavir-boosted saquinavir in healthy volunteers.<sup>48</sup> Although drug interaction data are not available for newer protease inhibitors or cobicistat, both lovastatin and simvastatin are contraindicated for patients receiving these agents.<sup>2,49</sup> This contraindication is further supported by small studies and case reports suggesting a greater risk of liver and muscle toxicity when lovastatin and simvastatin were coadministered with protease inhibitors.<sup>50</sup> Conversely, atorvastatin and rosuvastatin are less lipophilic and less dependent on CYP3A4, and smaller increases in the area under the curve have been seen when these statins are combined with protease inhibitors.<sup>47,51</sup> Atorvastatin and rosuvastatin can be safely used in HIV-infected patients who are taking protease inhibitors or cobicistat but should be administered at the lowest possible doses.<sup>2,49,51–56</sup>

Efavirenz has been shown to reduce the area under the curve for atorvastatin, simvastatin and pravastatin by about 40%–60% in healthy adult volunteers.<sup>57</sup> Etravirine reduced the area under the curve for atorvastatin by 37% in pharmacokinetic studies,<sup>58</sup> whereas rilpivirine did not appear to significantly affect this variable.<sup>26</sup> When a statin is used with NNRTIs, the statin dose may require adjustment according to lipid response; however, the dose should not exceed the maximum daily recommended dose.<sup>2</sup>

#### Metabolism: other CYP450 isoenzymes

The majority of antiretroviral drug interactions involve CYP3A4, but agents metabolized through other CYP450 isoenzymes, including CYP2B6, CYP2D6, CYP2C8, CYP2C19 and CYP2C9, may also interact with antiretrovirals. Such medications include antidepressants, oral hypoglycemic agents and warfarin.

### Antidepressants

Most antidepressants, including tricyclic antidepressants, selective serotonin reuptake inhibitors, bupropion and trazodone, are substrates of CYP2D6, CYP2B6, CYP2C19 or, to a lesser extent, CYP3A4. It is therefore possible that the use of protease inhibitors or NNRTIs may increase or decrease concentrations of antidepressants, which makes close monitoring essential, with dose adjustments based on the patient's response or the occurrence of adverse effects. Pharmacokinetic data are limited with respect to interactions with antiretrovirals; however, ritonavir and other boosted protease inhibitors have been shown to reduce the area under the curve for bupropion and sertraline by up to 50%–60% through induction of CYP2B6.<sup>59–61</sup> The boosted protease inhibitors fosamprenavir and darunavir have also been shown, in studies of healthy volunteers, to reduce the area under the curve for paroxetine by about 40%–60%; however, the mechanism for this interaction is unclear, as paroxetine is primarily a substrate of CYP2D6.<sup>61,62</sup> Serotonin syndrome was reported in a case series of patients receiving fluoxetine (a CYP2D6 substrate) in conjunction with high-dose (200–600 mg twice daily) ritonavir-based combination antiretroviral therapy.<sup>63</sup> High-dose ritonavir has also been shown to increase the area under the curve for desipramine by 145% and to increase the maximum concentration of trazodone by 33%.<sup>64,65</sup> The significance of interactions with lower (boosting) doses of ritonavir is unclear, but patients starting antidepressant therapy should be carefully monitored for adverse effects, and the dose should be adjusted according to patients' response (without exceeding the maximum recommended dose).

### Oral hypoglycemic agents

Diabetes mellitus is increasingly seen in HIV-infected individuals, especially as this population ages.<sup>6</sup> Furthermore, some antiretroviral agents may impair glucose tolerance or even lead to hyperglycemia.<sup>2</sup>

Certain classes of oral hypoglycemic agents are metabolized via the CYP450 system and may be susceptible to interactions with antiretrovirals, although data are very limited.<sup>66</sup> Sulfonylureas are CYP2C9 substrates, and their concentrations may be affected by the NNRTIs etravirine and efavirenz (CYP2C9 inhibitors), the protease inhibitor ritonavir (a CYP2C9 inducer) and the integrase inhibitor elvitegravir (a CYP2C9 inducer). Repaglinide and nateglinide are substrates of CYP3A4, CYP2C8 and CYP2C9, and coadministration of protease inhibitors, elvitegravir–cobicistat and NNRTIs may increase or decrease exposure to these agents.<sup>66</sup> Rosiglitazone, a thiazolidinedione,

is a CYP2C8 substrate, whereas pioglitazone is metabolized by both CYP2C8 and CYP3A4. In an open-label, crossover study in healthy people, coadministration of atazanavir 400 mg daily with rosiglitazone 4 mg daily resulted in a 35% increase in area under the curve for rosiglitazone, whereas coadministration of atazanavir 300 mg/ritonavir 100 mg daily with rosiglitazone resulted in a 17% decrease in rosiglitazone exposure.<sup>67</sup> The effect of NNRTI coadministration on thiazolidinedione pharmacokinetics has not been studied. Nevertheless, these classes should be coadministered with caution, as NNRTIs have inducing and/or inhibiting properties and may also affect thiazolidinedione exposure.

### Warfarin

Warfarin is a racemic mixture: the CYP2C9 isoenzyme is primarily responsible for metabolism of the more potent *S*-warfarin, whereas *R*-warfarin is metabolized by CYP1A2 and CYP3A4. A pharmacokinetic study in healthy volunteers showed a 21% decrease in the area under the curve for *S*-warfarin when combined with darunavir–ritonavir.<sup>68</sup> Numerous case reports have shown the need to monitor international normalized ratio closely when initiating protease inhibitor therapy, with substantial increases in the warfarin dose often being needed.<sup>69–73</sup> The effects of NNRTIs, including efavirenz, are less clear. One case described the need for an increase in warfarin dose with efavirenz,<sup>69</sup> but another reported a decrease in warfarin dose after initiation of the same NNRTI.<sup>72</sup>

## How can drug interactions be identified?

There are a number of ways to improve the identification of drug interactions, including accurate recording of patients' medication therapy, computerized systems for electronic records, support from pharmacists and use of available antiretroviral drug interaction websites and other general drug interaction tools. In a retrospective study of outpatient visits to an HIV clinic, clinically important interactions were noted for 27% of 159 patients,<sup>74</sup> but only 36% of these interactions were identified by the physician. Box 3 lists drug interaction websites for antiretrovirals that have been ranked highly for content and usefulness (reliability, accessibility, navigation).<sup>75</sup>

## Conclusion

Combination antiretroviral therapy has reduced mortality from AIDS-related diseases; however,

**Box 3: Useful websites for information about interactions involving antiretroviral drugs<sup>75</sup>**

**Immunodeficiency Clinic (Toronto)**

www.hivclinic.ca

Antiretroviral drug interaction tables

**University of Liverpool**

www.hiv-druginteractions.org

Searchable drug interaction website;

downloadable app available

**HIV InSite, University of California, San Francisco**

http://hivinsite.ucsf.edu/insite?page=ar-00-02

Searchable drug interaction website

the management of the aging HIV-infected population presents new challenges. Antiretroviral agents, especially protease inhibitors, NNRTIs and cobicistat-boosted elvitegravir, are prone to bidirectional drug–drug interactions due to their metabolism through CYP3A4 and their potent influence on the activity of a wide range of CYP450 isoenzymes. Clinicians should routinely screen for important drug–drug interactions using available online resources before initiating new medications. Routine communication among health care professionals caring for HIV-infected patients is imperative to avoid unnecessary toxic effects and/or therapeutic failure.

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