

Potential Interactions Between Antineoplastics and Antiretrovirals

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
|---|---------------------------|---|--|---|
| Altretamine ¹ | Alkylating Agents | Hepatic microsomal oxidation to active and cytotoxic derivatives. Exact isoenzyme unknown. | Potential for ↓ efficacy with P-450 inhibitors. | May need to hold antiretroviral regimens with 3A4 inhibiting drugs, or change to agents that do not inhibit 3A4 when concurrent therapy with altretamine needed. |
| Anastrozole ^{2,3} (Arimidex®) | Endocrine Therapies | Metabolized by N-dealkylation, hydroxylation and glucuronidation. Metabolites inactive. Exact isoenzymes unknown (3A4 possible). | Induction of glucuronidation may ↓ levels of drug and subsequently affect efficacy. CYP450 inhibitors may ↑ levels of anastrozole; inducers may do opposite. | Monitor for ↓ efficacy with ritonavir or nelfinavir (↑ glucuronidation) and nevirapine or efavirenz (induce 3A4) Possible ↑ risk and severity of side effects with PIs/delavirdine (e.g. hot flushes, peripheral edema, constitutional symptoms etc.). |
| Bexarotene ⁴ | Synthetic retinoid analog | Metabolized by CYP3A4 to oxidative metabolites, which are active (degree of activity unknown). Oxidative metabolites may be glucuronidated. Auto-induction occurs with chronic administration, particularly with doses >300 mg/m ² /day. | Inhibition or induction of CYP3A4 may affect levels of bexarotene and subsequently affect efficacy or toxicity. Induction of glucuronidation may promote clearance of active metabolites and possibly impact efficacy. Bexarotene may induce metabolism of CYP3A4 substrates, including PIs and NNRTIs. Virological failure was reported in a 70-year old man on efavirenz , 3TC and abacavir (VL<50 for 12 years) 2 months after starting bexarotene 300 mg QD for a neoplastic disorder. Efavirenz plasma concentration was 595 ng/mL compared to 1478 ng/mL prior to initiation of bexarotene. Bexarotene concentrations were approximately 50% lower vs. steady-state reference pharmacokinetic data. ⁵ | Potential for ↓ bexarotene concentrations with NNRTIs, and ↑ concentrations with PIs; bexarotene may ↓ concentrations of NNRTIs and/or PIs. Consider TDM of both drugs if available, and monitor closely for efficacy/response. May wish to consider using ARV agents that do not impact CYP450 system if possible. |

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| Bleomycin ^{6,7} (Blenoxane®) | Antitumour antibiotics | Hydrolysis by intracellular aminopeptidase. Evidence in rodents suggests possible inhibition of CYP450 system. | Possible ↑ ARV levels, but potential for interactions appears low. | Monitor for PI and NNRTI related side effects. |
| Bortezomib ⁸⁻¹⁰ (Velcade®) | Proteasome inhibitor | Metabolized primarily by CYP3A4, 2C19, 1A2, and 2D6 and 2C9 to a minor extent. In vitro, bortezomib is a weak inhibitor of CYP1A2, 2C9, 2D6, 3A4; it may inhibit 2C19 at clinically relevant dosages. | Potential for ↑ or ↓ bortezomib concentrations with potent CYP inhibitors or inducers of CYP3A4 and 2C19. Coadministration of ketoconazole led to 35% ↑ in bortezomib concentrations, while concomitant omeprazole did not affect bortezomib pharmacokinetics. | Use with caution with concurrent CYP inhibitors or inducers of CYP3A4 and 2C19. Efavirenz and etravirine inhibit 2C19 and induce CYP3A4. Clinical significance unknown; monitor for bortezomib efficacy & toxicity. Rilpivirine induces CYP2C19; monitor for efficacy. |
| Busulfan ¹¹⁻¹⁵ (Myleran®, Busulfex®) | Alkylating Agents | Glutathione-S-transferase (isoform GSTA-1-1). Animal data does not support role for CYP450 system. | Little potential for interaction with ARVs; however, itraconazole ↓ busulfan clearance by average of 20% in one study. Therefore, monitor closely when used concomitantly with HAART. | Concurrent use of 3A4 inhibitors may ↑ risk and severity of myelosuppression. |
| Capecitabine ¹⁶ (Xeloda®) | Antimetabolite | Prodrug of 5-fluorouracil. Inhibits CYP2C9. | Potential for ↑ concentrations of CYP2C9 substrates; significant interactions have been noted with warfarin and phenytoin. ^{16,17} Caution with concomitant etravirine, which is partially metabolized by CYP2C9. Case series of 4 HIV/HCV-coinfected subjects with advanced hepatocarcinoma on HAART (agents not specified) who received oxaliplatin and capecitabine with no apparent interaction or increased toxicity. ¹⁸ | |
| Chlorambucil ^{19,20} (Leukeran®) | Alkylating Agents | CYP450 enzymes not involved in metabolism in one animal study. | Potential for pharmacokinetic interactions with ARVs appears minimal, but very little known about chlorambucil metabolism in humans. | In absence of data, consider possibility for ↑ risk and severity of myelosuppression with CYP450 inhibitors. |
| Cisplatin and | Alkylating | Main route of elimination is | Potential for pharmacokinetic | Monitor serum creatinine and |

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| Carboplatin ²¹⁻²³ (Platinol-AQ®) (Paraplatin®) | Agents | renal. | interactions with ARVs appears minimal. However, cisplatin induced nephrotoxicity may necessitate dosage adjustment for certain ARVs. Potential additive renal toxicity with tenofovir. | creatinine clearance; adjust antiretroviral doses accordingly as needed. |
| Cyclophosphamide ² ₄₋₂₇ (Procytox®, Cytosar®) | Alkylating Agents | CYP2B6 > 2C19 to active metabolite. 3A4 to inactive and possibly toxic metabolites. | Induction of 2B6 may ↑ amount of active metabolite formed. Inhibition of 2B6 may prevent activation of the drug. Induction of 3A4 may ↑ neurotoxicity, whereas inhibition of 3A4 may make more drug available for 4-hydroxylation route (i.e. possibly ↑ efficacy/toxicity). Inhibition of 2C19 may impact activation of the drug, although this may be compensated for by increased shunting through 2B6 pathway. Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began abacavir, lamivudine and raltegravir and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma. ²⁸ | CYP2B6 inducers (e.g., ritonavir, nelfinavir, efavirenz, nevirapine) and CYP3A4 inhibitors (e.g., PIs) may ↑ efficacy and toxicity of cyclophosphamide (i.e. myelosuppression, nausea and vomiting). Efavirenz and etravirine inhibit 2C19; co-administration may impact activation of cyclophosphamide, although this may be compensated for by increased shunting via 2B6 pathway. Clinical significance unknown; monitor for efficacy. Rilpivirine induces CYP2C19; monitor for toxicity. |
| Cytarabine (ara-C) (Cytosar®) | Anti-metabolite | Metabolized in liver by cytidine deaminase | Potential additive toxicity with other agents. | Main toxicities of cytarabine include dose-limiting myelosuppression, nausea, vomiting, urinary retention, renal failure (rare). Caution with AZT; |

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| | | | | tenofovir (??) – renal toxicity |
| Dacarbazine ²⁹ (DTIC®) | Alkylating Agents | CYP1A2 > 2E1 to reactive DNA methylating metabolites. | Inhibition of CYP1A2 and 2E1 may decrease concentrations of pharmacologically active metabolite. | Use of concurrent ritonavir at therapeutic doses may ↑ formation of active metabolites. May ↑ efficacy and risk of nausea, vomiting and myelosuppression. |
| Dactinomycin ³⁰ (Cosmegen®) | Antitumour antibiotics | Minimally metabolized. Unclear which enzyme system involved. | Unlikely to result in significant cytochrome-mediated interactions, given low extent of metabolism (1-4%). | No detrimental pharmacokinetic interactions anticipated with combined HAART. |
| Dasatinib ^{31, 32} (Sprycel®) | Tyrosine kinase inhibitor | Extensively metabolized by CYP3A4 to an active metabolite with activity comparable to parent compound. Other enzymes involved in metabolism include UGT and flavin-containing monooxygenase (FMO3). Dasatinib also acts as a CYP3A4 inhibitor. | Possibility of ↑ levels of dasatinib and ↑ toxicity when concomitant 3A4 inhibitors are administered. A decrease in the dosage or an adjustment of the dosing interval of dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as ritonavir. ³³ In a study of 18 patients with solid tumors, dasatinib 20 mg daily coadministered with ketoconazole 200 mg BID led to four- and five-fold increase of dasatinib Cmax and AUC, respectively. Conversely, possibility of ↓ levels and risk of therapeutic failure with 3A4 inducers. In a healthy subject study, administration of single dose dasatinib in the presence of chronic rifampin 600 mg daily, mean Cmax and AUC of dasatinib were ↓ by 81% and 82%, respectively. | Co-administration of dasatinib and potent CYP3A4 inhibitors including PIs is not recommended; use of an alternate antiretroviral with minimal CYP3A4 inhibition is preferred. If this is not possible, a reduction in dasatinib dose to 20 or 40 mg daily and close monitoring for dasatinib toxicity is recommended. Concomitant use of potent CYP3A4 inducers including NNRTIs with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used. |

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| | | | Also potential for ↑ concentrations of concomitant PIs or NNRTIs. In healthy subjects, coadministration of single dose dasatinib 100 mg and simvastatin resulted in 37% ↑ C _{max} and 20% ↑ AUC of simvastatin. | |
| Daunorubicin ³⁴⁻³⁶ (Cerubidine®) | Antitumour antibiotics | Generally similar to doxorubicin. | Likely similar to doxorubicin. | Likely similar to doxorubicin. |
| Daunorubicin, liposomal ³⁷⁻⁴¹ | Antitumour antibiotics | Appears similar in pattern to free doxorubicin, but smaller ratio of daunorubicinol:daunorubicin with liposomal preparation. | Likely similar to doxorubicin. | Likely similar to doxorubicin. |
| Dexamethasone ⁴²⁻⁵⁰ | Steroids | CYP3A4 Dexamethasone a 3A4 inducer. | ↑ risk of steroid related toxicity with 3A4 inhibitors. Possible ↓ efficacy with 3A4 inducers. Dexamethasone may ↓ levels of NNRTIs and PIs. | Possible ↑ levels and pharmacodynamic effects of steroids when used concurrently with PIs and delavirdine. Opposite effect likely with nevirapine and efavirenz. May need to hold HAART in patients receiving prolonged dexamethasone. Alternatively, consider use of non-3A4 inducing steroid or antiretroviral therapeutic drug monitoring if combination is necessary. |
| Docetaxel ⁵¹⁻⁵³ (Taxotere®) | Taxanes | CYP3A4 | Possibility of ↑ levels of taxane when concomitant 3A4 inhibitor administered. Conversely, possibility of ↓ levels with 3A4 inducers. Effect may be more pronounced with docetaxel, since 3A4 is main enzyme involved in metabolism. Case report of a 40 year-old HIV+ male on LPV/r, TDF, 3TC who experienced febrile neutropenia (NE | ↑ taxane levels may ↑ risk and severity of myelosuppression, constitutional symptoms and peripheral neuropathy. |

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| | | | <p>450 cells/μl) with high CRP (196mg/L) levels 8 days after starting docetaxel (25 mg/m²) for treatment of KS. Microbiological tests were negative and the neutropenia resolved in the following week. Authors hypothesize that RTV inhibited CYP3A4, leading to increased docetaxel levels, and thus may have caused this febrile neutropenia.⁵⁴</p> <p>In a small group of patients with solid tumours who received oral docetaxel 100 mg with ritonavir 100 mg given simultaneously or 1 hour beforehand, the apparent oral bioavailability of docetaxel was 131% and 161%, respectively, compared to IV administration. These findings suggest that ritonavir has a marked inhibitory effect on gut wall and/or hepatic metabolism. The oral combination of docetaxel and ritonavir was well tolerated.⁵⁵</p> <p>In 3 HIV-positive patients on ritonavir-containing regimens (2 on ATV/r, 1 on LPV/r), administration of IV docetaxel resulted in severe hematological and cutaneous toxicity 3-7 days after the first infusion of docetaxel (70-100 mg/m²), despite having normal baseline liver function and blood cell counts. Each patient recovered following the withdrawal of docetaxel. The mechanism is postulated to be CYP3A4 inhibition of docetaxel metabolism by ritonavir.⁵⁶</p> | |

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| Doxorubicin ⁵⁷⁻⁶² | Antitumour antibiotics | <p>Several routes: aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives conjugated to a sulfate or glucuronide metabolite.</p> <p>Enzymes of cytochrome P450 involved in free radical generation in vitro; clinical significance unknown.</p> | <p>Potential for interactions unknown, given uncertainty about role of cytochrome P450 in free radical generation.</p> <p>A pharmacokinetic analysis was conducted in 19 HIV-positive patients with non-Hodgkin's lymphoma treated with CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) with and without concurrent PI-based HAART. Doxorubicin pharmacokinetics were not affected by concomitant PI administration, and PI exposures were not altered by doxorubicin.⁶³</p> <p>Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began abacavir, lamivudine and raltegravir and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma.²⁸</p> | Enzyme inhibitors may ↓ reduction to free radical, which may decrease both antineoplastic and cytotoxic properties. Enzyme inducers may do the opposite. |
| Doxorubicin, liposomal ^{64, 65} | Antitumour antibiotics | Appears similar in pattern to free doxorubicin, but less doxorubicinol detected in plasma. | Similar to doxorubicin. | Similar to doxorubicin. |

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| Droloxifene ⁶⁶⁻⁶⁸ | Endocrine Therapies | Glucuronidation (main) to inactive metabolites. | Induction of glucuronidation may ↓ levels of drug and subsequently affect efficacy. | Nelfinavir and ritonavir may ↓ efficacy through induction of glucuronidation. |
| Epirubicin ⁶⁹⁻⁷³ (Pharmorubicin®) | Antitumour antibiotics | Similar to doxorubicin, except both parent drug and epirubicinol metabolite undergo glucuronidation to inactive metabolites. Glucuronides constitute main metabolites. | Potential for increased conversion to inactive glucuronide derivatives with inducers of glucuronidation. | Ritonavir and nelfinavir may ↓ efficacy of epirubicin by increasing glucuronidation. |

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| Erlotinib ⁷⁴ | Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor | Primarily metabolized by CYP3A4. Metabolized to a lesser extent by CYP1A2 and 1A1. | <p>Potential for ↑ levels with 3A4 inhibitors; coadministration of erlotinib and ketoconazole 200 mg BID for 5 days led to 86% ↑ AUC and 69% ↑ Cmax of erlotinib. When erlotinib was coadministered with ciprofloxacin (an inhibitor of CYP3A4 and 1A2), erlotinib AUC ↑ 39% and Cmax ↑ 17%.</p> <p>Potential for ↓ levels and efficacy with 3A4 inducers. Co-administration with chronic rifampicin resulted in 69% ↓ AUC of erlotinib. In a separate study, subjects pre-treated with rifampin experienced 57.5% ↓ AUC of erlotinib after single dose administration; however, systemic exposure to the active metabolites OSI-413 and OSI-420 was largely unaffected by rifampicin treatment. As a result, the active metabolites consist of 18% of the total erlotinib exposure following the concomitant administration compared to only 5% when erlotinib was given alone.</p> <p>Case report of an HIV-infected woman with bronchioloalveolar carcinoma on HAART (individual agents not specified) who responded to erlotinib therapy.⁷⁵</p> | <p>Caution with concomitant administration of CYP3A4 or 1A2 inhibitors such as PIs. Erlotinib dose should be reduced if toxicity is observed.</p> <p>Potential for reduced efficacy with CYP3A4 inducers such as NNRTIs. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. If this is not possible, the erlotinib dose may be increased from 150 mg up to 450 mg per day.⁷⁶</p> |
| Estramustine ⁷⁷ (EMCYT®) | Alkylating agent | Dephosphorylated during absorption, then undergoes extensive first-pass metabolism to its active components, estromustine, estramustine, estrone and estradiol. | Potential for cytochrome-mediated interactions with ARVs appears minimal. | Unlikely to result in detrimental pharmacokinetic interactions with combined HAART. |

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| Etoposide ⁷⁸⁻⁸¹ (Vepesid®) | Epipodophyllot oxins | CYP3A4 (main); CYP2E1, 1A2 (minor) | Possibility of ↑ levels with 3A4 inhibitors, and ↓ levels with 3A4 inducers. | ↑ etoposide levels may ↑ risk and severity of mucositis, myelosuppression and transaminitis. ↑ teniposide levels may ↑ risk and severity of myelosuppression. |
| Exemestane ³ (Aromasin®) | Endocrine Therapies | Metabolized by CYP3A4 and aldoketoreductases. | Potential for ↑ levels with 3A4 inhibitors; possible ↓ levels and efficacy with 3A4 inducers. | Nevirapine and efavirenz may ↓ efficacy of drug; avoid combination if possible. ↑ levels with PIs and delavirdine may ↑ risk and severity of adverse effects (e.g. musculoskeletal pain, constitutional symptoms, peripheral edema, hot flashes etc.) |
| Fludarabine (Fludara®) | Antimetabolite | Rapidly converted into active metabolite (2-FLAA) after administration. ~40% renally excreted. | Potential for cytochrome-mediated interactions with ARVs appears minimal. | Unlikely to result in detrimental pharmacokinetic interactions with combined HAART. |
| 5-Fluorouracil ⁸² | Antimetabolite | Converted to 5-6-dihydrofluorouracil by the enzyme dihydropyrimidine dehydrogenase (DPD). 7-20% renally excreted. | Significant interactions have been noted between capecitabine (5-FU prodrug) and warfarin and phenytoin. ^{16, 17} A similar effect may occur with 5-FU. Case series of 21 HIV-positive subjects on HAART (7 NRTI only, 6 on PI, 6 on NNRTI and 2 on PI/NNRTI containing regimens) with anal carcinoma who received radiotherapy plus mitomycin C and 5-fluorouracil without need for dose reductions. The complete response rate was 81%, and 62% remained free of any tumor relapse during additional follow-up (median, 53 months), and there was no increased risk of HIV progression. ⁸³ | |

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| | | | Case series of 5 HIV-positive patients on HAART (4 PI, 1 NRTI) with advanced colorectal cancer who were treated with oxaliplatin, leucovorin and fluorouracil (FOLFOX-4 regimen) without apparent increase in antineoplastic-associated toxicity. ⁸⁴ | |
| Formestane ⁸⁵ | Endocrine Therapies | Two pathways: reductive metabolism by hepatic hydroxysteroid dehydrogenase and glucuronidation. | Induction of glucuronidation may ↓ levels of drug and subsequently affect efficacy. | Nelfinavir and ritonavir may ↓ efficacy through induction of glucuronidation. |
| Gefitinib ⁸⁶ (Iressa®) | Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor | Primarily metabolized by CYP3A4. Major metabolite O-desmethyl gefitinib is produced via CYP2D6 | Potential for ↑ levels with 3A4 inhibitors; in healthy volunteers, coadministration of gefitinib and itraconazole led to 80% ↑ AUC of gefitinib. Potential for ↓ levels and efficacy with 3A4 inducers. In healthy volunteers, co-administration with rifampicin resulted in 83% ↓ AUC of gefitinib. | Caution with concomitant administration of CYP3A4 or 2D6 inhibitors such as PIs, as adverse effects of gefitinib are related to dose and exposure. Potential for reduced efficacy with CYP3A4 inducers such as NNRTIs. |
| Gemcitabine (Gemzar®) | antimetabolite | extensively metabolized to 2',2'-difluorodeoxyuridine (dFdU) after continuous oral dosing. The main metabolite dFdU has a long terminal half-life after oral administration. After 1 week, 92-98% dose is recovered in the urine. | Potential for cytochrome-mediated interactions with ARVs appears minimal. | Unlikely to result in detrimental pharmacokinetic interactions with combined HAART. |
| Idarubicin ^{69, 87, 88} (Idamycin PFS®) | Antitumour antibiotics | Converted mainly to idarubicinol by aldo-ketoreductase (as active as parent drug). Less superoxide generation in vitro relative to daunorubicin and | Potential for cytochrome-mediated interactions with ARVs appears minimal. | Unlikely to result in detrimental pharmacokinetic interactions with combined HAART. |

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| | | doxorubicin. | | |
| Ifosfamide ^{89, 90} (Ifex®) | Alkylating Agents | CYP3A4 to active metabolite. 3A4 and 2B6 involved in detoxification. 3A4 metabolism of (S)-ifosfamide may generate neurotoxic metabolite. | Induction of 3A4 may ↑ activation of the drug, but may also produce more potentially neurotoxic metabolite. Inhibition of 3A4 is not recommended, since it would theoretically inhibit drug activation. | May need to hold antiretrovirals or change to regimen without potential for 3A4 inhibition if concomitant therapy with ifosfamide needed. Induction of 3A4 may ↑ efficacy and toxicity of ifosfamide (i.e. myelosuppression, arrhythmia, hemorrhagic cystitis). |
| Imatinib ⁹¹ (Gleevec®) | Tyrosine kinase inhibitor | Extensively metabolized by CYP3A4; other P450 enzymes play minor role. An N-demethylated piperazine derivative is the main circulating metabolite, which has in vitro activity similar to the parent compound. In vitro, imatinib was metabolized to the active metabolite CGP74588 by CYP3A4 and CYP3A5 and, to a lesser extent, by CYP2D6. Imatinib significantly inhibits CYP3A4 activity in vitro. | Caution is recommended when administering imatinib with CYP3A4 inhibitors; potential for ↑ plasma levels of imatinib. Imatinib may also theoretically ↑ levels of PIs/NNRTIs. 11 cancer patients receiving imatinib for at least 2 months were administered ritonavir 600 mg daily for 3 days. Imatinib AUC was unchanged from days 1 to 4, and ritonavir day 4 AUC and Cmax were comparable to historical data. In vitro, ritonavir (1 micromol/L) completely inhibited CYP3A4-mediated metabolism of imatinib to CGP74588 but inhibited metabolism in microsomes by only 50%. At steady state, it appears that imatinib is insensitive to potent CYP3A4 inhibition and relies on alternate elimination pathways. However, these findings may not be representative of chronic co-administration of both drugs ⁹² . | Monitor patients for signs of imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia). |
| Irinotecan ⁹³ (Camptosar®) | Camptothecins | hCE2 to SN-38 metabolite (active); CYP3A4 and glucuronidation to inactive metabolites. | Inhibition of 3A4 may ↑ formation of SN-38. Induction of 3A4 or glucuronidation may ↑ conversion of SN-38 to inactive metabolites. | Inhibition of 3A4 may ↑ risk and severity of myelosuppression. Induction of 3A4 or glucuronidation may ↓ efficacy of |

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| | | | <p>The effect of lopinavir/ritonavir on the pharmacokinetics of irinotecan (CPT11) was investigated in 7 patients with Kaposi's sarcoma. Coadministration of LPV/RTV resulted in 47% ↓ clearance of CPT11 (P=0.0008), and was associated with an 81% ↓ in AUC (P=0.02) of the oxidized inactive metabolite APC (7-ethyl-10-[4-N- (5-aminopentanoic-acid)-1-piperidino]-carbonyloxycamptothecin). LPV/RTV also inhibited the formation of SN38 glucuronide (SN38G), with a 36% ↓ in the SN38G/SN38 AUCs ratio (P=0.002) consistent with UGT1A1 inhibition by LPV/RTV. This dual effect resulted in increased availability of CPT11 for SN38 conversion and reduced inactivation on SN38, leading to a 204% increase (P=0.0001) in SN38 AUC in the presence of LPV/RTV. One patient had to stop irinotecan therapy despite 50% dose ↓ due to persistent grade 2 neutropenia. The clinical significance of this interaction requires further investigation.⁹⁴</p> <p>Potential for ↑ irinotecan-related toxicities with atazanavir, which also inhibits UGT1A1.</p> | drug. |

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| Lapatinib ⁹⁵ (Tykerb®) | Dual tyrosine kinase inhibitor | Extensively metabolized by CYP3A4. Lapatinib inhibits CYP3A4 and 2C8. Lapatinib is also a substrate for P-gp and BCRP, and inhibits P-gp, BCRP and OATP1A1 in vitro. | <p>Potential for ↑ lapatinib concentrations with CYP3A4 inhibitors including PIs. In healthy subjects, coadministration of ketoconazole 200 mg BID for 7 days plus lapatinib resulted in 3.6-fold ↑ lapatinib AUC.</p> <p>Potential for ↓ lapatinib concentrations with CYP3A4 inducers including NNRTIs. In healthy subjects, administration of lapatinib in the presence of chronic carbamazepine resulted in 72% ↓ lapatinib AUC.</p> | <p>Avoid concomitant use of strong CYP3A4 inhibitors or inducers if possible, or consider dose adjustment of lapatinib. With strong CYP3A4 inhibitors, dose reduction from 1250 mg to 500 mg daily is anticipated to provide lapatinib AUC in the target range. If the strong CYP3A4 inhibitor is discontinued, a one week washout period is recommended before the lapatinib dose is readjusted upwards.</p> <p>Coadministration with moderate CYP3A4 inhibitors should be done with caution, and patients should be carefully monitored for adverse reactions.</p> <p>If patients require therapy with a strong CYP3A4 inducer, the lapatinib dose may be titrated gradually from 1250 mg up to 4500 mg daily based on tolerability. If the strong inducer is discontinued, lapatinib dose should be reduced over approximately 2 weeks to the indicated dose.</p> |
| Lenalidomide ⁹⁶ (Revlimid®) | Immunomodulatory agent | In vitro lenalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. | Cytochrome-mediated interactions are unlikely. | No detrimental pharmacokinetic interactions anticipated with combined HAART. |
| Letrozole ^{3, 97} (Femara®) | Endocrine Therapies | Metabolized to carbinol metabolite (inactive) by CYP2A6 and 3A4. Inhibits CYP2A6 and 2C19. | Potential for ↑ levels with 3A4 inhibitors; possible ↓ levels and efficacy with 3A4 inducers. | Similar interaction potential as with exemestane. |

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| Lomustine ^{98, 99} (Ceenu®) | Alkylating Agents | Extensive first pass metabolism to metabolites with ↑ activity and ↓ toxicity relative to parent. Exact isoenzymes involved unknown. | Potential for interaction with CYP450 inhibitors (i.e. ↑ availability of parent drug, therefore ↓ efficacy and ↑ toxicity). | May need to hold antiretrovirals or consider use of non-CYP inhibiting regimen during concomitant lomustine therapy. |
| Mechlorethamine ¹⁰⁰ (Mustargen®) | Alkylating Agents | Rapid chemical transformation. | Cytochrome-mediated interactions are unlikely. | No detrimental pharmacokinetic interactions anticipated with combined HAART. |
| Melphalan ¹⁰¹ (Alkeran®) | Alkylating Agents | Spontaneous chemical degradation in plasma to inactive metabolites. | Cytochrome-mediated interactions are unlikely. | No detrimental pharmacokinetic interactions anticipated with combined HAART. |
| Mercaptopurine ¹⁰² (Purinethol®) | Antimetabolite | Converted into active thioguanine nucleotides by the enzyme xanthine oxidase. Also undergoes methylation by enzyme thiopurine methyltransferase to form S-methylated nucleotides, which are also cytotoxic. | Cytochrome-mediated interactions are unlikely. | No detrimental pharmacokinetic interactions anticipated with combined HAART. |
| Methylprednisolone ⁴²⁻⁵⁰ | Steroids | CYP3A4 | ↑ risk of steroid related toxicity with 3A4 inhibitors. Possible ↓ efficacy with 3A4 inducers. | Possible ↑ levels and pharmacodynamic effects of steroids when used concurrently with PIs and delavirdine. Opposite effect likely with nevirapine and efavirenz. May need to hold HAART in patients receiving prolonged steroid therapy. Alternatively, consider use of non-3A4 inducing steroid or antiretroviral therapeutic drug monitoring if combination is necessary. |
| Methotrexate (Metoject®) | Antimetabolite | Metabolized in the liver; almost all drug is excreted unchanged in urine. | Avoid concomitant therapy with cotrimoxazole, pyrimethamine, NSAIDs (with high-dose methotrexate) due to increased risk of methotrexate toxicity. Increased monitoring of renal function with | Methotrexate toxicity includes leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations. |

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| | | | concomitant tenofovir may be warranted. | |
| Mitomycin ^{59, 103-106} | Antitumour antibiotics | Exact pathway unclear. CYP450 may be involved in reductive bioactivation, but multiple other enzymes also participate in this process. | <p>Potential for interactions with ARVs unclear. Since multiple pathways for bioactivation, modulation of CYP450 may not be significant.</p> <p>Case series of 21 HIV-positive subjects on HAART (7 NRTI only, 6 on PI, 6 on NNRTI and 2 on PI/NNRTI containing regimens) with anal carcinoma who received radiotherapy plus mitomycin C and 5-fluourouracil without need for dose reductions. The complete response rate was 81%, and 62% remained free of any tumor relapse during additional follow-up (median, 53 months), and there was no increased risk of HIV progression.⁸³</p> | Further study needed. |
| Mitoxantrone ¹⁰⁷⁻¹¹¹ | Antitumour antibiotics | Metabolized to inactive carboxylic acid derivatives (exact pathway unclear). In vitro evidence that CYP450 involved in oxidation to reactive intermediate. | Potential for interactions unknown. In vitro inhibition of CYP450 ameliorates mitoxantrone cytotoxicity; impact on antiproliferative effect unknown. | Possible ↓ efficacy and toxicity with inhibitors of CYP450. Further study needed. |
| Nilotinib ¹¹² (Tasigna®) | Protein tyrosine kinase inhibitor | <p>Primarily metabolized by CYP3A4; also a substrate for P-gp.</p> <p>Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 <i>in vitro</i>. It also inhibits P-gp at an intracellular level.</p> | <p>Possibility of ↑ levels of nilotinib and ↑ toxicity with CYP3A4 inhibitors, including PIs. A decrease in the dosage or an adjustment of the dosing interval of nilotinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as ritonavir.³³</p> <p>In healthy volunteers, the bioavailability of nilotinib was increased 3-fold when coadministered with ketoconazole.</p> | <p>The administration of nilotinib with strong CYP3A4 inhibitors should be avoided. If this is not possible, it is recommended to interrupt nilotinib therapy, otherwise close monitoring for QT interval prolongation is indicated.</p> <p>Based on pharmacokinetic data, nilotinib dose may be reduced from 400 mg twice daily to once daily in the presence of strong</p> |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| | | | <p>Potential for ↓ nilotinib concentrations with CYP3A4 inducers including NNRTIs. An 80% ↓ nilotinib concentrations was observed in the presence of chronic rifampin.⁷⁶</p> <p>Potential for ↑ concentrations of PIs or NNRTIs.</p> | <p>CYP3A4 inhibitors.⁷⁶</p> <p>In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered.</p> <p>May also wish to consider antiretroviral TDM.</p> |
| Oxaliplatin ¹¹³ (Eloxatin®) | Alkylating Agent | Undergoes extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism in vitro. | <p>Potential for interactions with ARVs appears minimal.</p> <p>Case series of 5 HIV-positive patients on HAART (4 PI, 1 NRTI) with advanced colorectal cancer who were treated with oxaliplatin, leucovorin and fluorouracil (FOLFOX-4 regimen) without apparent increase in antineoplastic-associated toxicity.⁸⁴</p> <p>Case series of 4 HIV/HCV-coinfected subjects with advanced hepatocarcinoma on HAART (agents not specified) who received oxaliplatin and capecitabine with no apparent interaction or increased toxicity.¹⁸</p> | No detrimental interactions anticipated with combined HAART. |
| Paclitaxel ¹¹⁴⁻¹¹⁷ (Taxol®) | Taxanes | CYP2C8 > CYP3A4 | <p>Case reports of ↑ paclitaxel levels and toxicity when concomitant 3A4 inhibitors were administered. Conversely, possibility of ↓ levels with 3A4 inducers. Effect may be more pronounced with docetaxel, since 3A4 is main enzyme involved in metabolism.</p> <p>Life-threatening paclitaxel toxicity</p> | ↑ taxane levels may ↑ risk and severity of myelosuppression, liver function test elevations, constitutional symptoms and peripheral neuropathy. |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
|------|-------|------------|--|----------|
| | | | <p>was observed in two HIV-positive patients treated with paclitaxel 100 mg/m² IV for refractory KS. The first patient was on didanosine, delavirdine and lopinavir/ritonavir. Two days after receiving paclitaxel, he developed myalgias and arthralgias, and by day 8 he was acutely ill, neutropenic and died of sepsis. The second patient was on indinavir 800/ritonavir 200 mg BID and developed febrile neutropenia on day 7 after starting paclitaxel. A second course of paclitaxel resulted in profound cytopenia and total body alopecia. Subsequently, his paclitaxel dose was reduced to 60 mg/m² and was tolerated for 6 cycles.¹¹⁸</p> <p>In 34 HIV-positive patients with KS who received paclitaxel 100 mg/m², paclitaxel exposure was higher in patients taking protease inhibitors (either indinavir, nelfinavir, or both) compared to those who not taking protease inhibitors. The increased exposure did not correlate with efficacy or toxicity. Of the 20 patients assessable for response, 6 (30%) had an objective response and median progression-free survival was 7.8 months (95% confidence interval, 5.6, 21.0 months).¹¹⁹</p> <p>In a case report of an HIV-positive patient with Kaposi's sarcoma who received paclitaxel 100 mg/m² with concomitant nevirapine-based</p> | |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| | | | therapy, nevirapine concentrations were not altered in the presence of paclitaxel, and paclitaxel concentrations were comparable to historical controls. ¹²⁰ | |
| Prednisone ¹²¹⁻¹²⁴ | Steroids | Converted to active metabolite prednisolone by 11 β -hydroxy-dehydrogenase (non-CYP mediated). Prednisone and prednisolone also substrates of cytochrome P450 system; 3A4 likely involved, but other isoenzymes also probable. | <p>↑ risk of steroid related toxicity with 3A4 inhibitors (possible lower propensity for adverse interaction relative to dexamethasone or methylprednisolone). Possible ↓ efficacy with 3A4 inducers.</p> <p>Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began abacavir, lamivudine and raltegravir and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma.²⁸</p> | Monitor for ↑ pharmacodynamic effects with PIs and delavirdine. Monitor for loss of efficacy with nevirapine and efavirenz. |
| Procarbazine ^{125, 126} | Alkylating Agent | CYP2B > 1A to active metabolites. | Inhibition of CYP1A or 2B isoenzymes may ↓ efficacy of drug. Induction of CYP1A or 2B may potentially ↑ activity and/or toxicity. | Potential for ↑ efficacy/toxicity of drug with CYP2B6 or 1A inducers (e.g., ritonavir, nelfinavir, efavirenz, nevirapine, tipranavir). |
| Sorafenib ¹²⁷ (Nexavar®) | Multikinase inhibitor | Metabolized by CYP3A4 and glucuronidated by UGT1A9. Sorafenib inhibits UGT1A1 and UGT1A9. Sorafenib also inhibits CYP2B6 and 2C8 in vitro. Sorafenib does not inhibit or induce CYP3A4, 2D6, or 2C19. | Coadministration of sorafenib and ketoconazole once daily for 7 days in healthy male volunteers did not alter the mean AUC of 50 mg single dose sorafenib, likely due to sorafenib metabolism via alternate pathways including UGT1A9. Therefore, interactions between sorafenib and | Caution is recommended when administering sorafenib together with compounds that are metabolized/eliminated predominantly by the UGT1A1 and UGT1A9 pathways (eg, irinotecan). |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| | | metabolites and DNA adducts. May induce 3A4. | Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen citrate metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen), has been reported in the literature. | and vomiting). Avoid concomitant use of CYP2D6 inhibitors (risk of ↓ concentrations of active metabolite). |
| Temozolomide ¹⁴⁶ (Temodal®) | Alkylating agent | Undergoes non-enzymatic hydrolysis to MTIC, followed by renal excretion. Cytochrome P450-mediated metabolism does not contribute significantly to the plasma clearance of temozolomide. | Potential for pharmacokinetic interactions with ARVs appears minimal. In a small case series, continuous low-dose temozolomide treatment was well tolerated in two HIV-positive patients on HAART (agents not specified) with glioblastoma multiforme. ¹⁴⁷ | No detrimental pharmacokinetic interactions anticipated with combined HAART. Monitor for additive lymphopenia with zidovudine. |
| Temsirolimus ¹⁴⁸ (Torisel®) | mTOR inhibitor | CYP3A4 to five metabolites, including active metabolite sirolimus. Temsirolimus inhibits CYP3A4 and 2D6 in vitro. It is also a substrate and potential inhibitor of P-glycoprotein. | Potential for ↑ temsirolimus concentrations with CYP3A4 inhibitors including PIs. In healthy subjects, coadministration of temsirolimus and ketoconazole 400 mg did not significantly affect temsirolimus pharmacokinetics, but sirolimus AUC ↑ 3.1-fold, and AUCsum ↑ 2.3-fold compared to temsirolimus alone. A 51% ↑ in sirolimus half-life and 69% ↓ in clearance were also observed. ¹⁴⁹ Potential for ↓ temsirolimus concentrations with CYP3A4 inducers, including NNRTIs. When co-administered with rifampin 600 mg, temsirolimus pharmacokinetics were not significantly affected, but sirolimus Cmax ↓ 65% and AUC ↓ 56%, while AUCsum ↓ 41% | Concomitant use of strong CYP3A4 inhibitors or inducers should be avoided. In patients who are on CYP3A4 inhibitors, temsirolimus dose reduction to 12.5 mg per week may be considered, although this is not supported by clinical data. ⁷⁶ In patients on a CYP3A4 inducer, temsirolimus dose increase to 50 mg per week may be considered, based on pharmacokinetic modeling. ⁷⁶ Caution should be taken when temsirolimus is co-administered with agents that are metabolized by CYP2D6. |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| | | | <p>compared to temsirolimus alone.¹⁵⁰</p> <p>In healthy subjects, co-administration of single dose administration of desipramine (a CYP2D6 substrate) 50 mg and 25 mg IV temsirolimus did not alter exposure of desipramine and the combination was well tolerated.¹⁵¹</p> | |
| Teniposide ⁷⁸⁻⁸¹ (Vumon®) | Epipodophyllo- toxins | CYP3A4 (main); CYP2E1, 1A2 (minor) | Possibility of ↑ levels with 3A4 inhibitors, and ↓ levels with 3A4 inducers. | ↑ etoposide levels may ↑ risk and severity of mucositis, myelosuppression and transaminitis. ↑ teniposide levels may ↑ risk and severity of myelosuppression. |
| Thalidomide ¹⁵² (Thalomid®, Celgene®) | Immunomodula ting agent | Undergoes non-enzymatic hydrolysis in plasma. | Cytochrome-mediated interactions are unlikely. | Use with caution with agents that may cause peripheral neuropathy, including didanosine and stavudine. |
| Thioguanine ¹⁵³ (Lanvis®) | Antimetabolite | Undergoes methylation to 2- amino-6-methyl-thiopurine and deamination to 2- hydroxyl-6-mercaptopurine. | Cytochrome-mediated interactions are unlikely. | No detrimental pharmacokinetic interactions anticipated with combined HAART. |
| Thiotepa ¹⁵⁴⁻¹⁵⁷ | Alkylating Agents | CYP3A4 > 2B6 to active metabolite (TEPA). | Induction of 3A4 may ↑ TEPA production, whereas inhibition may ↓ formation of pharmacologically active metabolite. | May need to hold antiretroviral regimens with 3A4 inhibiting drugs, or change to agents that do not inhibit 3A4 when concurrent therapy with thiotepa needed. |
| Topotecan ¹⁵⁸⁻¹⁶⁰ (Hycamtin®) | Camptothecins | Non-enzymatic hydrolysis to inactive species (main). CYP450 system (minor; isoenzyme unknown), glucuronidation (minor). | CYP450 induction may ↑ conversion to active metabolite; may ↓ drug efficacy if ↓ in lactone exposure > metabolite production. Inhibition of CYP450 may not be clinically relevant, since minor route of metabolism. | Induction of CYP450 and/or glucuronidation may ↓ efficacy of topotecan. |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| Toremifene ¹⁶¹ | Endocrine Therapies | CYP3A4 to active metabolites. | Induction of CYP3A4 may ↓ levels of both parent and active metabolite (N-demethyltoremifene). Inhibition of 3A4 may ↑ levels of parent drug and/or compromise efficacy. | Nevirapine and efavirenz may compromise toremifene efficacy by ↓ levels of drug. Inhibition of 3A4 may ↑ risk and severity of side effects. |
| Vincristine (Oncovin®), vinblastine (Velbe®) and vinorelbine ¹⁶²⁻¹⁶⁷ (Navelbine®) | Vinca Alkaloids | CYP3A4 Vinblastine may induce CYP3A4. ¹⁶⁸ | Possibility of ↑ levels with 3A4 inhibitors, and ↓ levels with 3A4 inducers. Case report of a potentially life-threatening interaction between vinblastine and antiretroviral therapy in an HIV-positive patient receiving abacavir, lamivudine, zidovudine, nevirapine and lopinavir/ritonavir along with vinblastine for multicentric Castleman's disease. The first course of vinblastine was well tolerated at the usual dose of 6 mg/m ² , in the absence of HAART. HAART was subsequently resumed for two following courses of vinblastine therapy, resulting in unexpected severe digestive and haematological toxicities, and moderate renal failure. HAART was discontinued and vinblastine was again tolerated without toxicity. When HAART was reinitiated, a decreased vinblastine dose of 2 mg/m ² was well tolerated. ¹⁶⁹ Case report of an HIV-infected patient on abacavir, 3TC and lopinavir/ritonavir who was diagnosed with Burkitt lymphoma and received cyclophosphamide, doxorubicin, methotrexate and vincristine. At day 12 the patient | ↑ vinca levels may ↑ risk and severity of autonomic and peripheral neuropathy, and myelosuppression. |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| | | | <p>developed paralytic ileus lasting 10 days. For the subsequent cycle of chemotherapy, vincristine was replaced with etoposide and was well tolerated. The authors speculated that an interaction between lopinavir/ritonavir and vincristine was responsible for the adverse event.¹⁷⁰</p> <p>In a retrospective comparison of HIV-positive patients treated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for non-Hodgkin lymphoma with and without concurrent PI-based HAART, the patients on HAART had a significantly higher incidence of autonomic neuropathy (17% vs 0%, respectively, p = 0.002). This was presumed to be due to the interaction between vincristine and PIs. Severe anemia and CSF use was higher in the HAART group (58% were on zidovudine/lamivudine), other toxicity was similar in the two groups. Compared to the non-HAART group, the HAART group had a significantly lower incidence of opportunistic infections (18% vs. 52%, p = 0.05) and mortality (38% vs. 85%, p = 0.001).¹⁷¹</p> <p>In a retrospective review of 16 HIV-positive patients on cART (n=5 on boosted PI, 2 on unboosted PI, 8 on NNRTI, 1 on raltegravir) who received vinblastine-based regimens for Hodgkin's lymphoma, PI use was independently associated with</p> | |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| | | | <p>WHO grade III–IV neutropenia (OR 34.3, 95%CI 1.9–602.4; P=0.02). An inverse correlation between ritonavir dose and mean nadir neutrophil count was found.¹⁷²</p> <p>Report of 3 patients who experienced severe vinblastine-associated neurotoxicity during treatment with ABVD for Hodgkin’s lymphoma while on lopinavir/ritonavir-based cART. Two cases were characterized by early-onset autonomic neuropathy with severe medical ileus requiring hospitalization, and the last patient developed late-onset but severe and painful peripheral neuropathy.¹⁷³</p> <p>Case report of a 55 year old male with newly diagnosed advanced HIV and large B-cell lymphoma who simultaneously began abacavir, lamivudine and raltegravir and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with intrathecal methotrexate. The patient achieved and maintained an undetectable viral load throughout 6 CHOP cycles. Two months after the patient completed chemotherapy, a positron emission tomography scan indicated no active lymphoma.²⁸</p> | |

| Drug | Class | Metabolism | Actual/Theoretical Interaction | Comments |
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| Vorinostat ¹⁷⁴ (Zolinza®) | Histone deacetylase inhibitor | Major pathways of metabolism include glucuronidation and hydrolysis followed by β -oxidation; negligible involvement of CYP enzymes. | Cytochrome-mediated interactions are unlikely. | No detrimental pharmacokinetic interactions anticipated with combined HAART. |

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