Published in final edited form as:
Curr Opin Oncol. 2009 September ; 21(5): 445–454. doi:10.1097/CCO.0b013e32832f3e04.

Targeted therapies to treat Non-AIDS Defining Cancers in patients with HIV on HAART therapy – treatment considerations and research outlook

John F. Deeken[1], **Liron Pantanowitz**[2], and **Bruce J. Dezube**[3]

[1] Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, D.C.

[2] Department of Pathology, Baystate Medical Center, Tufts University School of Medicine, Springfield, MA.

[3] Department of Medicine [Hematology/Oncology], Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Purpose of review—Highly active antiretroviral therapy (HAART) has led to a dramatic improvement in the prognosis of patients diagnosed with HIV and AIDS. This includes a significant decline in the rates of AIDS-related cancers, including Kaposi Sarcoma and Non-Hodgkin's Lymphoma. Unfortunately, rates of Non-AIDS Defining Cancers (NADCs) are on the rise, and now exceed the rates of AIDS-related cancers in patients with HIV. Treating NADCs in patients who are on HAART therapy is an open and complicated clinical question.

Recent findings—Newer targeted therapies are now available to treat cancers which were historically refractory to traditional cytotoxic chemotherapy. HAART agents are notorious for causing drug-drug interactions. The co-administration of targeted chemotherapies with HAART could well impede the efficacy or increase the toxicity of these targeted therapies. Unfortunately little is known about possible drug-drug interactions because HIV patients are typically excluded from clinical trials.

Summary—We highlight what is known about how and why HAART agents can affect drug metabolism. We then present the clinical and pharmacological data for nine recently approved targeted therapies – imatinib, dasatinib, nilotinib, erlotinib, sunitinib, lapatinib, bortezomib, sorafenib, and temsirolimus. We conclude with considerations on how to use these new agents to treat NADCs, and discuss a future research agenda to better understand and predict potential HAART-targeted therapy interactions.

Keywords

Non-AIDS Defining Cancers; Targeted Chemotherapy; HAART; Drug-Drug Interactions

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) to treat infections caused by the Human Immunodeficiency Virus (HIV) has greatly improved the morbidity and

Correspondence: John Deeken, MD, Podium B, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC, 20007, USA. Fax: +1 [202] 444-9429; deekenj@georgetown.edu; Tel: +1 [202] 444-3958..

mortality of infection patients. With the introduction of HAART, the rates of AIDS-related cancers, including Kaposi's Sarcoma and Non-Hodgkin's Lymphoma, have declined significantly. Unfortunately and for reasons that remain poorly understood, rates of Non-AIDS Defining Cancers (NADCs) are on the rise.[1-4] In fact, cases of NADCs now exceed the rates of AIDS-related cancers in patients with HIV.[5] These NADCs include cancers of the head and neck, lung, kidney, liver, gastrointestinal tract, and anus as well as Hodgkin's Lymphoma. How to treat patients on HAART once a non-AIDS cancer diagnosis is made remains poorly understood, and is complicated by the potential of drug-drug interactions between chemotherapy and HAART agents.

Great strides have been made over the past decade in developing newer agents to treat cancers which have been refractory to traditional cytotoxic chemotherapy in the past. Just over the past several years, more than a dozen new targeted therapies have garnered FDA-approval to treat diseases ranging from chronic myeloid leukemia to renal cell and hepatocellular carcinomas.

According to the National Cancer Institute, ‘targeted’ anticancer therapies are those that use drugs, small molecules, or other substances, such as monoclonal antibodies, to block the growth and spread of cancer by interfering with specific molecules involved in carcinogenesis and tumor growth.[6] While targeted agents represent a new way of treating cancers compared to the use of traditional cytotoxic agents, they nonetheless are pharmaceutical compounds that must be administered, absorbed, metabolized, and excreted *in vivo*. HAART agents, which are notorious for interfering with the enzymes involved in drug metabolism, may in turn interfere with the pharmacology of targeted therapies just as they can with traditional cytotoxic therapies.

In this review we will highlight what is known about how HAART agents can affect drug metabolism. Then we will present the clinical and pharmacological data for nine recently approved targeted therapies – imatinib, dasatinib, nilotinib, erlotinib, lapatinib, bortezomib, sorafenib, and temsirolimus. We will conclude with considerations on how to use these new agents in patients with HIV who are on HAART therapy, as well as discuss a future research agenda to better understand, study, and predict potential HAART-targeted therapy interactions in HIV positive patients.

CHEMOTHERAPY / HAART DRUG-DRUG INTERACTIONS

Enzymes and transporters mediate the absorption, distribution, metabolism, and excretion (ADME) of endogenous as well as exogenous metabolic and catabolic end products. Metabolic enzymes are present in the liver as well as in other peripheral tissues. Enzyme-mediated metabolic reactions can either activate prodrugs or inactivate active drugs. Enzymes can catalyze the oxidation, reduction or hydrolysis of compounds in so-called phase I metabolic reactions. The Cytochrome P450 family of enzymes is the largest source of enzymes involved in phase I metabolic reactions, especially CYP3A4. Phase II or conjugation reactions, in which a substrate is added to a drug to render it more readily eliminated in the bile or urine, can alter substrates via acetylation, glucuronidation, sulfation and methylation. Examples of phase II enzymes include UDP-glucuronosyltransferases (UGTs) and glutathione-S-transferases (GSTs).[7]

It is estimated that half of all pharmaceutical agents undergo metabolism either completely or in part by CYP3A4. A key consideration for physicians is whether patients are on drugs that may interfere with this or other enzymes, and in turn affect the pharmacology of other co-administered drugs. Drugs known to induce CYP3A4 function include dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's

Wort. Drugs known to inhibit CYP3A4 include ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, and nefazodone.[8]

HAART therapy typically includes a three to four drug combinations of protease inhibitors (PIs), nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and additional agents.[9] A significant amount of research over the past decade has investigated how these HAART drugs are metabolized, and crucial discoveries have been made in how these agents both induce and inhibit various enzymes involved in drug metabolism.[10] For example, to varying degrees all PIs inhibit CYP3A4, an enzyme that mediates the metabolism of over half of all drugs that undergo hepatic metabolism, including chemotherapy agents. This fact has been used to increase the drug delivery of other HAART agents. For example, saquinavir has been combined with low dose ritonavir (100 mg) because ritonavir's inhibition of CYP3A4 increases the systemic exposure to saquinavir. Delaviridine and efavirenz inhibit CYP3A4, with the latter also inhibiting CYP2B6 and CYP2C9/19. Nelfinavir and ritonavir inhibit CYP2B6 as well as CYP3A4, while amprenavir inhibits CYP2C19.

Other HAART drugs are known to induce increased expression of CYP450 enzymes. Enzyme induction can increase a patient's ability to eliminate other drugs which undergo similar metabolism. For example, nevirapine, efavirenz, ritonavir, and tipranavir induce CYP3A4 expression. Nevirapine also induces expression of CYP2B6. Ritonavir and nelfinavir may also induce expression of glucuronyltransferases.

Table 1 summarizes the effects that each of the commonly used HAART drugs can have on phase I and phase II metabolizing enzymes.[11-57]

TARGETED ANTI-CANCER AGENTS

While only recently approved, the following targeted therapies have undergone extensive pre-clinical and clinical investigations, including pharmacokinetic analyses. This research has led to a reasonable understanding of their anti-cancer mechanisms of action as well as their pharmacology, both in terms of pharmacokinetics and pharmacodynamics. A brief presentation of each targeted therapy follows.

Imatinib (Gleevec, Novartis)

Imatinib is an orally available tyrosine kinase inhibitor approved for the use in treating chronic myeloid leukemia, acute lymphoblastic leukemia, mild dysplastic diseases and gastrointestinal stromal tumors. [58-61] Imatinib inhibits the bcr-abl tyrosine kinase which is constitutively active in chronic myeloid leukemia in patients who contain the Philadelphia chromosome abnormality. The drug is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), stem cell factor (SCF) and c-kit.[61]

The major enzyme involved in the metabolism of imatinib is CYP3A4.[62] Other enzymes involved in the drug metabolism and which play a minor role include CYP1A2, CYP2D6, CYP2C9 and CYP2C19.[61,62] Its main active metabolite is formed by CYP3A4. Imatinib has also been found to be a potent inhibitor of CYP2C9, CYP2D6 and CYP3A4/5.[62]

The FDA-approved Package Insert recommends dose reduction by 50% if patients are on an inhibitor of CYP3A4. It also recommends the consideration of dose adjustment if patients are on a drug known to induce the activity of CYP3A4. Finally, if patients are on drugs known to be metabolized by CYP2C9, CYP2D6 and CYP3A4, caution is recommended given imatinib's inhibition of these crucial enzymes. In healthy subjects receiving imatinib and the CYP3A4 inhibiting drug ketoconazole, blood levels of imatinib (AUC) increased by

40%.[63] Further, serum AUC of the CYP3A4 substrate simvastatin was increased by 3.5 fold when given with imatinib.[64] Of note, in an 11-patient study by van Erp *et al*, researchers did not find a significant increase in imatinib pharmacokinetics in cancer patients treated with the drug after a three day administration of ritonavir.[65] The authors proposed this is due to alternative metabolic pathways which imatinib may undergo in the face of CYP3A4 inhibition. Whether this finding has relevance in patients on chronic HAART therapy including ritonavir is unknown.

Dasatinib (Sprycel, Bristol Myers Squibb)

Dasatinib is an orally available tyrosine kinase inhibitor which has been found to inhibit the bcr-abl, c-kit, PDGFR data and the SRC family of tyrosine kinases.[66,67] It has been approved for use in the treatment of chronic accelerated myeloid or lymphoid blast phase chronic myeloid leukemia in patients who are resistant to prior therapies.[66,68,69] It is undergoing extensive clinical investigation for its possible role in treating many additional solid organ and hematological malignancies.[70] The standard dose is either 70 or 100 mg q.d.

Dasatinib is metabolized primarily by CYP3A4 into its active metabolite.[66,71] This metabolite is equally active compared to the parent compound. Other enzymes found to be involved in the drug metabolism include flavin-containing monooxygenase (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT).[66,71] In addition, dasatinib has been found to inhibit the activity of CYP3A4 but does not inhibit other CYP family enzymes, nor does it induce this class of enzymes.[66,72] In patients who are on drugs known to inhibit CYP3A4, dasatinib drug levels may be increased by as much as 500%, while co-administrations with an inducer of CYP3A4 led to a 82% decrease in dasatinib levels.[66] The Package Insert recommends that use of CYP3A4 inhibitors should be avoided. If this cannot be done a dose decrease to 20 mg per day should be considered -- or reduction of 80% of the standard dose. For patients on a CYP3A4 inducing agent, a dose increase of dasatinib should be considered, but no specific dose is recommended in the Package Insert.

Nilotinib (Tasigna, Novartis)

Nilotinib is an orally available inhibitor of the bcr-abl kinase and is approved for the treatment of imatinib-resistant chronic myelogenous leukemia.[73,74] It is undergoing extensive clinical investigation in a variety of other malignancies.[75] The standard dose is 400mg bid.

Nilotinib is apparently metabolized by CYP3A4.[74] Co-administrated with the inhibitor ketoconazole led to a 3-fold increase in drug levels. If patients must be on a drug known to strongly inhibit CYP3A4, a 50% dose reduction should be done to 400mg once a day (instead of twice a day) based on expected effects to the drug's pharmacokinetics and AUC. This recommendation is not based on clinical data. When co-administered with the inducer rifampicin, an 80% decrease in nilotinib levels were observed.[74] For patients on a strong CYP3A4 inhibitor, the dose of nilotinib may need to be increased but again no recommendation on what that higher dose should be is included in the Package Insert.[74]

Nilotinib inhibits *in vitro* CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1.[74,76] Administration of nilotinib with the CYP3A4 substrate midazolam in healthy volunteers led to a 30% increase in midazolam levels.[74] Warfarin, as a substrate of both CYP2C9 and CYP3A4, should be avoided. Nilotinib also induces CYP2B6, CYP2C8, and CYP2C9, and may decrease drug concentration of substrates for these enzymes.[74]

Erlotinib (Tarceva, OSI Pharmaceuticals)

Erlotinib is an orally available tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR) used in the treatment of non-small-cell lung cancer as well as pancreatic cancer.[77-79] The drug inhibits the EGFR tyrosine kinase on the intracellular component down regulating this critical pathway.

In vitro assays have shown that erlotinib is primarily metabolized by CYP3A4.[79-81] CYP1A2 plays a lesser role including the extrahepatic isoform of CYP1 as well as the extrahepatic form of CYP1A1.[80,82] The administration of the CYP3A4-inhibitor ketoconazole led to a 67% increase in blood levels of erlotinib.[79] The Package Insert recommends that in patients who are on a drug known to inhibit CYP3A4 a dose reduction of erlotinib should be considered, though there is no recommendation of what this lower dose should be. In addition, in patients who are on agents known to induce CYP3A4, significantly lower drug levels of erlotinib may be expected. In fact, the area under the concentration curve (AUC) of erlotinib may be reduced by 67% to 80% when patients are on drugs such as rifampicin and other known CYP3A4 inducers.[79] The Package Insert recommends that patients seek alternative treatment to the drug known to induce CYP3A4 activity if they are going to be placed on erlotinib. If that is not clinically possible, the dose of erlotinib may be increased from 150 mg q.d. to up to 450 mg q.d. Finally, the co-administration of drugs known to be metabolized by CYP3A4 when given in conjunction with erlotinib may be effected by erlotinib-mediated inhibition of CYP3A4.[81] The administration of erlotinib with midazolam led to a 24% increase in midazolam blood levels.[79]

Sunitinib (Sutent, Pfizer)

Sunitinib is an orally available multi-targeted tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma and imatinib-refractory gastrointestinal stromal tumor.[83-85] The drug inhibits PDGFR, VEGFR1 and 3, KIT, FLT3, the receptor stem cell factor (SCF), and RET.[83,86-88] In pre-clinical studies, sunitinib and its equally active metabolite SU012662 inhibit Flk1/KDR activity and PDGFR activity.

Sunitinib is metabolized by CYP3A4 to produce the active metabolite SU012662.[85] No other major metabolites have been identified. Sunitinib did inhibit the metabolic activity, or to induce expression, of CYP3A4 or any other member of the CYP family of enzmes *in vitro*. Concomitant administration of sunitinib with ketoconazole resulted in a 74% increase in blood levels of sunitinib and a 12% decrease in SU12662, with a net increase of 51% of total drug. When given with the CYP3A4 inducing drug rifampin, a 46% decrease in total drug blood levels was observed. The Package Insert recommends the consideration of dose reduction if patients are on a drug known to strongly inhibit CYP3A4, and to increase the dose if they are on a drug that strongly induces CYP3A4, but no specific dose recommendations are included.[85]

Lapatinib (Tykerb, GlaxoSmithKline)

Lapatinib is an orally available multi-tyrosine kinase inhibitor approved for the treatment of patients with advanced or metastatic breast cancers that overexpress HER2 when given with capecitabine (Xeloda).[89,90] When given with capaecitabine (Xeloda) for the treatement of breast cancer, the recommended dose of lapatinib is 1,250mg q.d. with no days off of treatment.

Lapatinib is metabolized extensively by CYP3A4 and CYP3A5, with CYP2C19 and CYP2C8 playing a minor role in parent drug metabolism.[90] Lapatinib also inhibits CYP3A4 and CYP2C8 *in vitro* at clinically relevant dose levels, and thus, lapatinib may

increase concentration of drugs metabolized by these enzymes. Drug inhibitors and inducers of CYP3A4 should be avoided while taking lapatinib. Ketoconazole caused a 3.6-fold increase in lapatinib blood levels in healthy subjects, whereas the CYP3A4-inducing drug carbamazepine caused a 72% increase in blood levels.[91] According to the Package Insert, a dose reduction in lapatinib should be considered in patients on a known CYP3A4-inhibitor to 500mg per day (or a dose reduction of 60%). If on a CYP3A4 inducing agent, the Package Insert recommends a gradual dose increase up to 4,500mg/day – or an increase of 360% -- as tolerated by the patient. These recommendations are based on pharmacological modeling and not on clinical data.

Bortezomib (Velcade, Millennium Pharmaceuticals)

Bortezomib is a proteosome inhibitor that is approved for the treatment of multiple myeloma and mantle cell lymphoma.[92-94] The drug is administered intravenously with the recommended dose being 1.3mg/m2 given twice weekly for two weeks, on a three week cycle.

Bortezomib is metabolized by CYP3A4, CYP2C19, and CYP1A2, with minor contributions made by CYP2D6 and CYP2C9, into inactive metabolites.[95] Administration of ketoconazole with bortezomib led to a 35% increase in bortezomib levels, whereas co-administration with the CYP2C19 inhibitor omeprazole had no effect on the pharmacokinetics of bortezomib.[94,96] There is no reported data on the effects of CYP3A4 inducing agents on bortezomib's pharmacokinetics. The Package Insert does not make any recommendations to alter dosing if patients are on concomitant drugs that affect CYP3A4 function. Finally, bortezomib is a poor inhibitor of CYP enzymes 1A2, 2C9, 2D6 and 3A4; however, it may inhibit CYP2C19 at clinically relevant dosages, and in turn effect levels of drugs that are substrates for this liver enzyme.[97]

Sorafenib (Nexavar, Bayer)

Sorafenib is an orally available multi-kinase inhibitor approved for the use in treating unresectable hepatocellular carcinoma and renal cell carcinoma and is being extensively studied in a wide range of malignancies.[98-101] The drug inhibits intracellular CRAF, BRAF, and mutant BRAF, as well as membrane kinases including KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-beta.[100,102] The standard dosing is 400mg twice daily.

Sorafenib is metabolized by CYP3A4 and UGT1A9.[100] Interestingly, when given to healthy volunteers along with the CYP3A4 inhibitor ketoconazole, no change was seen in plasma sorafenib levels, likely due to alternative metabolic pathways available to disposition including via UGT1A9.[103] Therefore, dose adjustment is unlikely to be needed in patients on a CYP3A4 inhibiting drug. In hepatocyte preclinical studies, sorafenib was not found to induce CYP3A4 or CYP1A2.[100] When co-administered with the CYP3A4 inducing agent rifampicin, a 37% decrease in sorafenib drug levels was observed.[100] Thus, increasing the standard dose should be considered if patients are on a known CYP3A4 inducing agent, though no clinical data exists on what dose should be used.

Sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 enzymes, and caution is recommended if patients need to be on agents metabolized by these critical phase II enzymes. [100] In a clinical study using sorafenib and irinotecan -- which is metabolized by UGT1A1 -- an increase of 67 to 120% was seen in the active metabolite of irinotecan, SN-38.[100,104,105] Sorafenib also inhibits CYP2B6 and CYP2C8, which in turn could lead to higher serum levels of drugs metabolized by these two enzymes.[100] While *in vitro* human hepatocyte experiments found that sorafenib inhibited CYP2C19, CYP2D6, and

CYP3A4, clinical studies found no effect on the pharmacokinetics of substrates of these enzymes (omeprazole, dextromethorphan, and midazolam, respectively).[100] Additional clinical studies found increases in drug levels of docetaxel, doxorubicin, and fluoruracil when given with sorafenib.[100,106] The pharmacokinetics of gemcitabine, oxaliplatin, gefitinib, and erlotinib where not affected by concomitant use of sorafenib.[107-110]

Temsirolimus (Torisel, Wyeth)

Temsirolimus is an mTOR inhibitor and approved for the treatment of refractory renal cell carcinoma.[111,112] mTOR (Mammalian Target of Rapamycin) is a critical protein in the PI3 kinase/AKT pathway, and blockage of mTOR activity results in reduced levels of HIF-1 and HIF-2 alpha as well as vascular endothelial growth factor. The mTOR target may have wide ranging clinical benefit in solid and hematologic malignancies.[113] Temsirolimus is being testing in a variety of malignancies.[114] The drug is administered as an intravenous infusion, with a set dose of 25mg per week given to patients - a dose which is not based on body surface area.[111]

Temsirolimus is metabolized by CYP3A4 into five metabolites, the predominant one being the active metabolite sirolimus.[115] Co-administration of ketoconazole did not effect blood levels of temsirolimus but increased sirolimus levels by 3.1 fold.[116] The Package Insert recommends a dose reduction of 50% to 12.5 mg/week in patients on a CYP3A4 inhibitor, though no clinical data supports this recommendation. Co-administration with the CYP3A4 inducer rifampin did not effect temsirolimus blood levels but reduced sirolimus levels by 43% to 56%.[117] If patients are on a CYP3A4-inducer, the Package Insert recommends a dose increase by 100% to 50mg/week should be considered – though again this is based on pharmacokinetic modeling and not on clinical research. A phase I clinical study combining sunitinib and temsirolimus resulting in dose limiting toxicities in two of the 3 patients treated at the lowest dose levels (sunitinib 25mg and temsirolimus 15mg), and the trial was closed.[118] *In vitro* studies indicated that temsirolimus inhibited CYP3A4 and CYP2D6, but clinical studies showed no effect on the pharmacokinetics of the CYP2D6 substrate desipramine.[111]

TREATING HIV-POSITIVE PATIENTS WITH TARGETED AGENTS

The development of these and other new targeted therapies has significantly improved our ability to treat many hematologic and solid tumor malignancies. These cancers are now occurring at high rates in men and women with HIV, and targeted therapies can and should be employed to treat Non-AIDS Defining Cancers in HIV-positive patients. However, significant interactions between HAART agents and these targeted therapies is possible and even likely. Since past clinical studies testing these newer agents typically excluded patients with HIV, there are no guidelines and little clinical experience in how to use these agents in the setting of HIV and HAART. How to treat patients with HIV on HAART with newly-diagnosed NADCs using targeted therapies is an open clinical question.

Nevertheless, based on what is known about the pharmacology of HAART agents and targeted anti-cancer drugs, it is possible to posit treatment considerations for medical oncologists facing this clinical dillema. Table 2 is a heat map-like grid that cross references HAART agents and targeted compounds in terms of potential interactions that may alter the targeted drugs' pharmacokinetics, and in turn either increase drug toxicity or reduce drug efficicay. Blocks in red indicate a HAART-targeted therapy combination that poses a high risk for interaction, and dose reduction of the targeted therapy from the start of therapy should be considered. Lighter red, lined blocks are those were an interaction may occur, and careful clinical observation and possible dose reductions after therapy is started should be considered. Blocks in green are for a HAART-targeted therapy combination in which

HAART-caused enzyme induction may lead to reduced levels of the targeted therapy and a dose adjustment upwards should be considered.

Table 3 summarizes the effects on the pharmacokinetics of targeted therapies casued by either the inhibition of, or the induction of, the crucial metabolizing enzyme CYP3A4. As can be seen, though many of these targeted therapies are substrates for this enzyme, there is a great variability in terms of how much blood levels in patients may be affected by inhibition or induction of this enzyme. For those targeted therapies in which a significant effect is seen in its pharmacokinietics (i.e. an increase of more than 100% or a decrease by more than 50%), then great caution should be observed in dosing these drugs if patients are on HAART agents known to inhibit or induce CYP3A4. For these agents, following the recommendations contained in the FDA Package Insert is critical, including dose alterations from the very beginning of treatment, and titrating therapy based on patient tolerance and response.

Finally, just as HAART agents may interfere with the metabolism of targeted therapies, so too can targeted drugs interfere with the metabolism of HAART drugs. Table 4 highlights potential combinations that can lead to altered blood levels of HAART agents. Red blocks indicate combinations of that may lead to higher blood levels of the HAART drug in question due to inhibition of its metabolism by a targeted drug. In these cases, higher toxicities associated with the HAART drug may be observed. Green blocks indicate a combination that can lead to reduced levels of the HAART drug due to enzyme induction by the targeted therapy. In this later case, immune parameters would need to be carefully monitored, and a slow titration up of the HAART drug may be considered.

CONCLUSION

New advances in the treatment of cancers through the use of targeted therapies has improved the clinical outcomes of HIV-negative patients, an improvement that can and should be extended to HIV-positive patients diagnosed with NADCs. However, a better knowledge of specific drug-drug interactions between HAART and targeted agents, both at the molecular level and clinically, would aid in establishing clear guidelines for how specific NADCs should be treated in patients with HIV. A new research focus on the part of the National Cancer Institute as well as the AIDS Malignancy Consortium may help elucidate these potential interactions and hopefully lead to the development of treatment guidelines. The first of a number of planned clinical trials will investigate drug-drug interactions between sunitinib and differing HAART combinations. Given the growing incidence of NADCs in HIV-positive patients, and the need for such patients to remain on HAART, this pharmacologic and clinical research is timely and needed. If successful, this research should aid medical oncologists in choosing the right targeted therapy, at the right dose, to treat their patient. Only though this and other clinical and translational research will we have the same success in addressing the NADC epidemic in HIV-positive patients has we have had over the past decade in treating AIDS-defining cancers, as well as HIV infection itself.

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Table 1

Enzymes and HAART Agents.

Drugs	Class	Substrate	Inhibit	Induce	References
Abacavir (Ziagen)	NRTI	ALDH			11,12
Amprenavir (Agenerase)	PI	CYP3A4	CYP3A4		13-15
Atazanavir (Reyataz)	PI	CYP3A4	CYP3A4, UGT1A1, CYP2C8		16-19
Delavirdine (Rescriptor)	NNRTI	CYP3A4 CYP2D6	CYP3A4 CYP2C9 CYP2C19 CYP2D6		20
Didanosine (Videx)	NRTI				21,22
Efavirenz (Sustiva)	NNRTI	CYP2B6	CYP2B6	CYP3A4	23-26
Indinavir (Crixivan)	PI	CYP3A4	CYP3A4 UGT1A1		15,17, 27-29
Lamivudine (Epivir)	NRTI				30,31
Lopinavir	PI	CYP3A4			32-34
Maraviroc (Selzentry)	C5I	CYP3A4	CYP2D6		35,36
Nelfinavir (Viracept)	PI	CYP3A4, CYP2C19	CYP3A4 CYP2B6		15,37,38
Nevirapine (Viramune)	NNRTI	CYP3A4 CYP2B6		CYP3A4 CYP2B6	39,40
Raltegravir (Isentress)	IGI	UGT1A1			41-43
Ritonavir (Norvir)	PI	CYP3A4 CYP2D6	CYP3A4 CYP2D6 CYP2B6	CYP2C9	28,44,45
Saquinavir (Invirase)	PI	CYP3A4	CYP3A4		15, 46-48
Stavudine (Zerit)	NRTI				49
Tenofovir (Viread)	NtRTI	CYP3A4			50,51
Tipranavir (Aptivus)	PI	CYP3A4	CYP1A2 CYP2C9, CYP2C19, CYP2D6		52,53
Zalcitabine (ddC)	NRTI				54
Zidovudine (AZT)	NRTI	UGTB7			55-57

Enzymes that are known to metabolize commonly used HAART agents are listed, as well as enzymes that are inhibited or induced by each agent. If a HAART drug inhibits a metabolizing enzyme, then blood levels of other drugs that are substrates for that same enzyme may be increased. Likewise, if a HAART agent inducing the expression or function of an enzyme, than drugs that are substrates for that same enzyme will be more rapidly metabolized and eliminated.

Abbreviations : NNRTI - non-nucleoside reverse transcriptase inhibitor; NRTI - nucloeside reverse transcriptase inhibitor; PI - protease inhibitor; IGI - integrase inhibitor; C5I - CCR5 nhibitor; ALDH - Alcohol dehydrogenase.

Table 2

Potential Effects on Targeted Anticancer Drugs by HAART Agents in Heat Map Format.

Targeted Drug	Protease Inhibitors								NRTIs							NNRTIs			Other	
	Ritonavir	Amprenavir	Atazanavir	Indinavir	Lopinavir	Nelfinavir	Saquinavir	Tipranavir	Abacavir	Didanosine	Lamivudine	Stavudine	Zalcitabine	Zidovudine	Tenofovir	Delavirdine	Efavirenz	Nevirapine	Maraviroc	Raltegravir
Imatinib																				
Dasatinib																				
Nilotinib																				
Erlotinib																				
Sunitinib																				
Lapatinib																				
Bortezomib																				
Sorafenib																				
Temsirolimus																				

Potential drug-drug interactions are highlighted by color code. A red block indicates a potential HAART-targeted therapy combination that poses a high risk for interaction leading to high pharmacokinetic levels of the targeted agent. Lighter red, lined blocks indicate an interaction that may occur. Blocks in green indicate a HAART-targeted therapy combination in which HAART-caused enzyme induction may lead to reduced levels of the targeted therapy.

Table 3

Effect on targeted drug pharmacokinetics by CYP3A4 Inhibition and Induction

Drug	Pharmacokinetic Change in Drug Levels (AUC) (%)	
	Inhibitor	Inducer
Imatinib	40	-380 (RMP)
Dasatinib	500	- 82 (RMP)
Nilotinib	300	- 80 (RPC)
Erlotinib	67	- 67 to - 80 (RPC)
Sunitinib	51	- 46 (RMP)
Lapatinib	360	- 72 (CBZ)
Bortezomib	35	n/a
Sorafenib	0	-37 (RPC)
Temsirolimus	310 *	-56 * (RMP)

Percent change in pharmacokinetics of targeted agents as measured by Area Under Concentration (AUC) curve by the co-administration of drugs known to inhibit or induce the CYP3A4 metabolizing enzyme. A CYP3A4 inhibitor prevents metabolism of the drug and leads to *higher* serum drug levels as reflected in drug AUC, whereas an enzyme inducer would lead to *decreased* blood levels. Ketoconazole was used as the inhibiting agent, whereas rifampin (RMP), rifampicin (RPC), or carbamazepine (CBZ) were used as inducing agents. References and discussion are included in the text.

* For temsirolimus, the parent drug was unaffected but the active metabolite sirolimus was affected by the inhibiting and inducing agents.

Table 4

tial Effects on HAART drugs by Targeted Anticancer Drugs in Heat Map Format.

ted Agents	Protease Inhibitors								NRTIs							NNRTIs			Other	
	Ritonavir	Amprenavir	Atazanavir	Indinavir	Lopinavir	Nelfinavir	Saquinavir	Tipranavir	Abacavir	Didanosine	Lamivudine	Stavudine	Zalcitabine	Zidovudine	Tenofovir	Delavirdine	Efavirenz	Nevirapine	Maraviroc	Raltegravir
nib																				
nib																				
nib																				
nib																				
nib																				
nib																				
zomib																				
enib																				
rolimus																				

d therapies can also affect drug metabolizing enzymes by inhibiting and inducing their function. Blocks marked with red indicate a targeted therapy/HAART drug combination which may lead to higher HAART agent levels due to enzyme inhibition by the targeted
locks in green indicate a potential interaction in which patients may experience lower levels of the HAART drug due to enzyme induction by the targeted anticancer drug.