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PHARMACOGENETIC BASED DRUG-DRUG INTERACTIONS BETWEEN HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) AND ANTIBLASTIC CHEMOTHERAPY

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ABSTRACT: *The concomitant use of HAART and AC may be associated with an incresead risk of toxicity secondary to pharmacokinetic and pharmacodynamic interactions mediated by drug-metabolizing enzymes or transporters leading to altered drug exposure. For the majority of antiretroviral drugs that are cytochrome P (CYP) 450 substrates, inducers or inhibitors, co-administration with other metabolized drugs could result in drug accumulation and possible toxicity or decreased efficacy of one or both drugs. Same studies have shown that intensive antiblastic chemotherapy (AC) treatment are feasible in HIV-infected patients with cancer and the outcomes is similar to that of HIV-negative patients receiving the same AC regimens. For these reasons it is important that HIV patients affected by cancer underwent to HAART/AC should be individualized according to the regimen treatment selected, liver or renal function, bone marrow suppression, and others co morbidities. The purpose of this review is to summarize existing data on the impact of individual pharmacogenetic profile in order to optimize the clinical management of cancer patients with HIV/AIDS and between antiretrovirals and AC. Based on the individual genetic profiles, the oncologist will have a new features with which to make personalized treatment decision for their patients in order to maximize benefit and minimize toxicity.*

KEY WORDS: *Pharmacogenetics HIV, AIDS, Antiretroviral therapy, Solid cancer, Antiblastic chemotherapy.*

INTRODUCTION

The introduction of Highly Active Antiretroviral Therapy (HAART) into clinical practice has had a dramatic impact on the natural history of HIV-related cancer[1]. The spectrum of cancer disease among people living with HIV/AIDS has Kaposi sarcoma and non-Hodgkin lymphoma, Hodgkin's disease, invasive anal carcinoma, lung carcinoma, skin cancer, colon-rectal cancer and hepatocarcinoma[2-5]. The challenge in the treatment of HIV-related malignancies is represented by the need to maintain an adequate control of HIV infection during the AC[6]. Antiblastic treatments produces a significant decrease in CD4 lymphocytes and significantly increases the risk of opportunistic infections (OIs) in patients with HIV-related malignancies[7]. Patients who receive the combination AC plus HAART may achieve better response rates and higher rates of survival than patients who receive AC therapy alone[8]. However, careful attention must be directed toward the cross toxicity and the possi-

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ble pharmacokinetic and pharmacodynamic interactions between antiretroviral and AC. Drug-drug interactions (DDIs) occur when one drug influences the level or activity of another drug when administered concurrently. Drug-Drug Interactions (DDI) can occur at all levels and failure to recognize them can result in overdosing or sub-treating the patient. Cancer patients receive a large number of drugs during their treatment including those for comorbid conditions and cancer related syndromes such as pain, emesis, depression, and seizures. However in most cases the consequences are adverse and undesirable, compromising the efficacy of the therapeutic agent or enhancing its toxicity. It has been reported that 20-30% of all adverse drug reactions are caused by interactions between drugs[9]. Only limited data are available on DDIs in the treatment of HIV associated malignancies. Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates and potent inhibitors or inducers of the CYP P450 system. Since many antineoplastic drugs are also metabolized by the CYP 450 system, co administration with HAART could result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes of drugs.

In this fields, inter-individual response could be dependent of the genetic variations associated to HAART-AC administrations. A few examples showing the relationship between single nucleotide polymorphisms (SNPs) in the genes coding for antiretroviral metabolizing enzymes (CYP450s and UGTs) and transporters and related toxicities are here described.

Current data show that toxicity, particularly myelosuppression and neurotoxicity, is significantly more frequent in the patients treated with the combined therapy compared with patients treated with antineoplastic drugs alone. On the other hand chemotherapy plus HAART-treated patients have a better survival than chemotherapy alone-treated patients, suggesting that the reduction of OIs morbidity by HAART other than the good performance status of these patients, may improve the overall outcome of the combined treatment patients. This paper reviews the potential interactions and subsequent therapeutic considerations between HAART and the most common AC used in the treatment of HIV-positive cancer patients. Bilirubin is often used as a guide for dose adjustment for AC. Several antiretrovirals as atazanavir or indinavir are associated with unconjugated hyperbilirubinemia secondary to UGT1A1 inhibition similar to that which occurs in Gilbert's syndrome. Unconjugated hyperbilirubinemia in association with these agents and in the absence of other evidence of hepatic dysfunction may be ignored in dosing AC. On the other hand NRTI as didanosine, stavudine and zidovudine may produce steatosis and lactic acidosis. These antiretrovirals should be stopped or replaced before initiating AC with agents that have hepatic metabolism at standard doses but use reduced dosing based on the degree of hepatotoxicity. NRTIs as abacavir, emtricitabine, lamivudine and tenofovir or NNRTI as efavirenz are the less likely to be hepatotoxic and may often be substituted.

HAART CLASSIFICATION AND DRUG METABOLISM

US Department of Health and Human Services (DHHS) guideline recommend initiation of HAART for all HIV-1 patients, in particular for people with pretreatment CD4 count ≤ 500 cells/μL, to preserve or improve immune function while decreasing HIV-associated morbidity and mortality. In general, the guidelines recommended in patients naive to HAART regimens include a minimum of three active drugs to prevent resistance: a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with a NNRTIs or a PI boosted with ritonavir or an integrase strand-transfer inhibitor (INSTI). Similar regimens can be used in HIV positive cancer patients according to treatment selected, liver or renal co morbidities, bone marrow suppression[10]. The concomitant use of HAART and AC may be associated with an increseaded risk of toxicity secondary to pharmacokinetic and pharmacodynamic interactions mediated by drug-metabolizing enzymes or transporters leading to altered drug exposure. For the majority of antiretroviral drugs that are CYP 450 substrates, inducers or inhibitors, co administration with other metabolized drugs could result in drug accumulation and possible toxicity or decreased efficacy of one or both drugs[10]. Particularly drugs that inhibit CYP450 enzymes generally lead to decreased metabolism of other drugs metabolized by the same enzyme (Table 1). The decreased metabolism can result in higher drug levels and increased potential of toxicity. Inhibition of CYP450 tends to be rapid, with maximal inhibitory effect occurring when steady-state concentrations of the inhibitor are established. Conversely induction of CYP450 system results in the increased clearance of concomitant medication metabolized by the same enzyme and a decrease of the drug concentration. Enzyme induction occurs more slowly than does inhibition because the full effect of induction is based on the time required for new enzyme synthesis and the half-life of the inducing agent.

TABLE 1. HAART CLASSIFICATION, MECHANISM OF ACTION, DRUG METABOLISM AND DRUG INTERACTION.

HAART drug Class	Metabolism	Hepatic Inducer	Hepatic Inhibitors	Pharmacogenomics evidence
NRTIs	The enzyme has two enzymatic functions. Firstly it acts as a polymerase where it transcribes the single-stranded RNA genome into single-stranded DNA and subsequently builds a complementary strand of DNA. This provides a DNA double helix which can be integrated in the host cell's chromosome. Secondly it has ribonuclease activity as it degrades the RNA strand of RNA-DNA intermediate that forms during viral DNA synthesis			
		No Evidence	No Evidence	Screening for HLA-B*5701 For prevention of the hypersensitivity to Abacavir. Tenofovir Neprho- Toxicity in carriers of ABCC4 3436GG
NNRTIs	The binding occurs allosterically in a hydrophobic pocket located approximately 10 Å from the catalytic site in the palm domain of the p66 subunit site of the enzyme. The NNRTI binding pocket (NNIBP) contains five aromatic, six hydrophobic and five hydrophilic amino acids that belong to the p66 subunit and additional two amino acids (Ile-135 and Glu-138) belonging to the p51 subunit.			
	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor)	Efavirenz: CYP2C9, CYP2C19 . Etravirine: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine 20; 3A4 (potent)	Efavirenz: 3A4 (potent), 2B622, UGT1A123 Etravirine11: 3A4 (weak) Nevirapine12: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).24 A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.	Nevirapine and Efavirenz Neurotoxicity in CYP2B6*6 (516G>T) homozygous individuals. Nevirapine hepatotoxicity in polymorphic ABCB1 3435CC allele (MDR1 C3435T)
PIs	Prevent viral replication by selectively binding to HIV-1 protease and blocking proteolytic cleavage of protein precursors that are necessary for the production of infectious viral particles. The HIV protease contains a binding pocket into which drugs must fit in order to block the activity of the enzyme.			
	Mainly Cyp3A4 and UGT1A1/3	Darunavir, indinavir, nelfinavir, amprenavir >> saquinavir Atazanavir: 3A4, UGT1A1 >>2C8 (weak). Caution when unboosted atazanavir is coadministered with drugs that are CYP2C8 substrates with narrow therapeutic indices (e.g., paclitaxel, repaglinide); clinically significant interactions with 2C8 substrates are not expected when atazanavir is boosted with ritonavir. Nelfinavir: CYP2B6 *in vitro*. Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1. At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition. Ritonavir inhibits CYP2B6 in vitro, but induces 2B6 *in vivo*. Tipranavir: CYP2D6	Nelfinavir: UGT, 2B6, 2C8, 2C9/19. Ritonavir: UGT, CYP1A2, CYP2C9/19, CYP2B6. Tipranavir: mixed induction/inhibition effects; Often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir.	Favorable response (in term of viral suppression) to Nelfinavir in CYP2C19*2 and *3 poor metabolizer patients. Decreased clearance of, indinavir and saquinavir in haplotype CYP3A5*3. Lopinavir plasma levels are higher in SLCO1B1 521CC allele than 521TT . Hig level of bilirubinemia among patients homozyogous for the UGT1A1*28 for indinavir and Atzanavir administration.

TABLE 1 (CONTINUED). HAART CLASSIFICATION, MECHANISM OF ACTION, DRUG METABOLISM AND DRUG INTERACTION.

HAART drug Class	Metabolism	Hepatic Inducer	Hepatic Inhibitors	Pharmacogenomics evidence
INSTIs	Are a class of antiretroviral drug designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell. Since integration is a vital step in retroviral replication, blocking it can halt further spread of the virus			
	Dolutegravir: UGT1A1, CYP3A4 (10-15%). Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, CYP 2D6 (minor). Raltegravir: UGT1A1	Cobicistat: CYP3A, CYP2D6; also P-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Dolutegravir inhibits the renal organic cation transporter, OCT2.	Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4 *in vitro*. Elvitegravir: CYP2C9 (modest)	
CCR5 receptor antagonists	Are a class of small molecules that antagonize the CCR5 receptor. The C-C motif chemokine receptors CCR5 and CXCR4 are the main chemokine receptors involved in the HIV entry process. These receptors belong to the seven transmembrane G-protein-coupled receptor (GPCR) family and are predominantly expressed on human T-cells, dendritic cells and macrophages, Langerhans cells.			
	Maraviroc: CYP3A family	No Evidence	No Evidence	Evidence of increased risk of susceptibility to hepatitis C virus infection or multiple sclerosis among individuals with CCR5-delta32 mutation.
Fusion Inhibitors	Works by disrupting the HIV-1 molecular machinery at the final stage of fusion with the target cell, preventing uninfected cells from becoming infected. HIV binds to the host CD4+ cell receptor via the viral protein gp120; gp41, a viral transmembrane protein, then undergoes a conformational change that assists in the fusion of the viral membrane to the host cell membrane.			
	Enfuvirtide: is ligand for viral gp41	No Evidence	No Evidence	

Abbreviations: ATP-binding Cassette group C (ABCC); Multidrug Resistance (MDR); Solute Carrier Organic Anion Transporters (SLCO alias OATP); Organic Cation Transporter (OCT); Breast Cancer Resistance protein (BCRP).

ROLE OF PHARMACOGENOMIC ASSOCIATED TO HAART

Even though the benefits of HAART, wide individual variability have been reported both in response to therapy and in the adverse effects of certain antiretroviral drugs. Indeed, response to HAART is highly complex and often limited by the development of short- or long-term toxicities and the emergence of antiretroviral drug resistance (Table 2). This variability can be explained by factors that regulate the availability of drugs (pharmacokinetics), effects on the host (host pharmacodynamics), and the activity of the virus itself (viral pharmacodynamics).

The effectiveness of therapy is affected by viral sensitivity to a drug. Mutagenesis is a constant process in the viral genome; as such, mutations occur at each replication cycle, thereby enabling the virus to easily adapt. Furthermore, initial antiretroviral therapy could be compromised by transmitted HIV drug resistance. A list of the main viral resistance against HAART is available[11].

In addition to viral mutations, other factors may also contribute to treatment failure. Inter individual variability in the pharmacokinetics of antiretroviral drugs can play a role in treatment failure or toxicity, either directly, because sub therapeutic drug levels can increase the risk of a poor virologic response, or indirectly, when high (toxic) drug levels produce significant intolerability, leading to poor adherence. Variability between patients in relation to the bioavailability and distribution of antiretroviral drug regimens is probably driven by genetic and environmental factors such as drug-drug interactions, drug-food interactions, sex, and body weight. In particular, drug-drug interactions and genetic polymorphisms in drug-metabolizing enzymes and drug transporters contribute to wide variability in drug pharmacokinetics, response to therapy, and toxicity. A few examples was reported (Table 1).

The *CYP2B6* gene is highly polymorphic, and more than 28 alleles have been characterized (about 100 SNPs) have. Among different variants, the CYP2B6*6 haplotype (*516 G>T*, and *785 A>G*) leads to reduced catalytic activity and a significant

TABLE 2. KNOWN VIRAL GENOME MUTATIONS INTERFERING WITH HAART.

Mutation	HAART drug Class
NRTIs and Reverse Transcriptase mutations	
M41L	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
A62V	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF
D67N	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
K65R/N	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF
T69D/Ins	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF
K70R/E/G	Stavudine, zidovudine
L74V/I	Abacavir, didanosine
V75I/T/M	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine
F77L	Abacavir, didanosine, stavudine, zidovudine
Y115F	Abacavir, tenofovir/tenofovir DF
F116Y	Abacavir, didanosine, stavudine, zidovudine
Q151M	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF
M184V/I	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
L210W	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
T215F/Y	Stavudine, zidovudine
NNRTIs and mutations against Non-Reverse Transcriptase genome	
L100I K101E/P K103N/S V106A/M V108I V179D/E/F Y181C/I/V Y188L/H/C G190A/S/E P225H F227L/C M230L P236L K238T	Nevirapine, delavirdine, etravirine
PIs and and mutation on genes coding protease	
L23I , D30N	Nelfinavir
L24I V32I L33F M46I/L G48V/M, I50L/V, F53L I54V/T/A/L/M G73S/T, L76V, V82A/T/F/S I84V/A/C L90M	Atazanavir/R, fosamprenavir/R, indinavir/R, lopinavir/R, nelfinavir, saquinavir/R Darunavir
Integrase	
T66I/A/K, E92Q F121Y E138A/KG140S Y143R/C/H S147G Q148H/R/K S153Y N155H/S R263K	Raltegravir/elvitegravir
CCR5 receptor antagonists and mutations in genes coding CCR5, CXCR4	
No significative Evidence to date	Maraviroc
Fusion Inhibitors	No Evidence

Abbreviations: *NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor*; *PI: Phosphatase Inhibitor.*

decrease in protein expression. Several studies reported correletions of Nevirapine and Efavirenz to neurotoxicity in CYP2B6*6 (516G>T) homozygous individuals[12].

Several polymorphisms of the CYP2C19 gene are associated with reduced enzyme activity. In particular, the CYP2C19*2 allele leads to a 681G>A substitution, causing a stop codon splicing. These poor metabolizer patients have a favorable response (in term of viral suppression) to exposure to Nelfinavir[12].

Variability in metabolic CYP3A5 function is largely ascribed to the *CYP3A5*3* mutant allele and, to a lesser extent, to the CYP3A5*6 and CYP3A5*7 variants. The variant CYP3A5*3 allele produces an alternate mRNA splicing, resulting in aberrant protein, because the early form of a stop codon. Haplotype CYP3A5*3 has been associated to important decreased clearance of indinavir and saquinavir[13].

Association to polymorphism in ATP binding Cassette (ABCC) and efficacy to therapy was found. Since, drug transporters are viewed as one of the major mechanisms that account for suboptimal tissue concentrations of antiretroviral agents. Major studies reported an association between the ABCB1 polymorphism (*3435 C>T*) and the overall risk of hepatotoxicity after nevirapine treat-

ment. This genotype-phenotype association was confirmed by Ricthie et al[14], which showed that the ABCB1 *3435 TT* allele was less frequent in the patient group displaying hepatic toxicity than polymorphic *3435CC* allele. However, a pharmacogenetics study[15] that included the *C421A* and *G34A* variants, which were associated in vitro with a decrease in ABCG2 activity, found no association of these polymorphisms with intracellular accumulations of zidovudine triphosphate and lamivudine triphosphate, but, to date the literature is low with others Nucleosides analogs.

Recent data suggest an important role in the influx for Solute Carrier Organic Transporters (SLCO alias OATP) family in the pharmacokinetics of antiretroviral agents. In particular, it has been observed that the SLCO1B1 *521T>C* polymorphism was significantly associated with higher plasma concentrations of lopinavir in patients homozygous for the mutant allele (*521CC*), which would suggest that the entry of lopinavir into the liver via the SLCO1A2 influx transporter is an important determinant of lopinavir exposure[16].

Recent study in patients who receive atazanavir and indinavir found that the proportion of grade 3 to 4 hyperbilirubinemia was 80% among patients homozygous for the UGT1A1*28 allele, 29% in heterozygous patients and 18% among patients homozygous for the wild-type allele[17].

Even though, the clinical utility of described polymorphisms involved in HAART based-therapy is in part limited by: 1. The evidence that Pharmacigenomic testing improves clinical outcomes is still an open question; 2. The cost-effectiveness of the testing being unknown; and 3) the need to find clinical expertise to interpret laboratory results[18,19].

ANTICANCER TREATMENT AND OVERVIEW OF HAART/AC COMBINATION AND INTERACTIONS

The therapeutic approach should take into consideration three crucial elements: i) histological nature of the lesion; ii) the assessment of the extension of the tumour development; iii) the evaluation of the general disease state. In the last ten years held considerable importance use of monoclonal antibodies, identification of tumour targets and characterization of mechanism of resistance[20].

The maintenance of dose-schedule and dose-intensity are the primary principals which are thought to contribute to cancer cure. Some studies have shown that intensive AC protocols are feasible in HIV-infected patients and the outcome of HIV-infected patients with Burkitt lymphoma, diffuse large B-cell lymphoma and Hodgkin Lymphoma is similar to that of HIV-negative patients receiving the same AC regimens[21]. The timing of diagnoses of HIV and a malignancy may guide therapy decisions. In some cases cancer treatment should take priority over HAART despite the risk associated with stopping HIV treatment[22]. The concomitant use of antiretrovirals and AC might result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes. Infact, many anticancer agents are metabolized by CYP450 whereby DDIs with HAART is high. Nowadays the availability of >20 approved antiretrovirals permits development regimens that minimize the potential for DDIs and improve compliance with HAART during AC.

Anthracyclines, antimetabolite agents, antitumor antibiotics and platinums undergo non-CYP450 routes of elimination and would be unlikely to be altered by HAART. Camptothecins undergo non enzymatic routes of elimination are substrates but not inhibitors or inducers of CYP450 and UGT isozymes and therefore are likely to be altered by HAART. On the other hand DDIs can be anticipated with alkylating agents, corticosteroids, epipodophyllotoxins, taxanes, tyrosine-kinase inhibitors and vinca alkaloids.

Vinca alkaloids (Vinblastine, Vincristine, Vinorelbina): the vinca alkaloids remain an important class of AC traditionally associated with the treatment of breast, lung, testicular cancer and currently (Vinorelbine, Vinblastine) used for the management of AIDS-related KS. Similarly vinca alkaloids are substrates of CYP3A4 and are vulnerable to PI and NNRTI. Concomitant administration with CYP3A4 inhibitor causes an inhibition of vinca alkaloids metabolism with an increase risk of neurotoxicity and severe myelosuppression. Particularly interaction between ritonavir/lopinavir and vincristine is responsible of paralytic ileus. Infact vincristine is transported by P-gp and is metabolized by CYP3A4. Ritonavir is a potent CYP3A4 isoenzyme and P-gp inhibitor. Lopinavir is also a P-gp inhibitor. These PIs might have delayed vincristine elimination. Conversely CYP3A4 inducers causes an decrease of vinca alkaloids concentrations with decreased efficacy of drugs[10].

Taxanes: several trials have established the efficacy of paclitaxel for the treatment of AIDS-related KS. Concomitant administration of paclitaxel with CYP3A4 inhibitor causes an increase of taxane concentrations with an increase risk of severe myelosuppression and peripheral neuropathy. The CYP3A4 inducers efavirenz and dexamethasone do not have a significant effect on docetaxel expo-

sure. In an in vivo experiment, docetaxel 20 mg/kg IV was administered in the presence and absence of dexamethasone or efavirenz for 4 days, or single dose ketoconazole or ritonavir[23]. The CYP3A4 inducers efavirenz and dexamethasone did not have a significant effect on docetaxel AUC. However, the CYP3A4 inhibitors ritonavir and ketoconazole resulted in a 6.9- and 3.1-fold increase in AUC, respectively[24]. Additional risk benefeti to CYP2C8*3 in breast cancer were reported[24].

Epipodophyllotoxins (Etoposide and Tenoposide): these class of AC is used primarily for the management of haematological malignancies. The metabolism is mediated primarily by CYP3A4 pathway therefore inhibition of CYP3A4 pathway may increase concentrations of epipodophyllotoxins with an increase risk of mucositis, transaminitis and myelosuppression[10].

Alkylating agents (cyclophosphamide and ifofosfamide): Despite their structural similarity and similar mechanisms of action, important differences exist in the metabolism of cyclophosphamide and its isomer ifofosfamide. Cyclophosphamide is alkylating agents used in the management of HD and NHL for patients with HIV and is metabolised by two separate pathways (CYP3A4 and CYP2B6). Induction of CYP2B6 may increase amount of active metabolite formed; conversely PI may decrease efficacy of cyclophosphamide through CYP2B6 inhibition[24].

A pharmacokinetic analysis conducted in 29 HIV-positive patients with non-Hodgkin's lymphoma treated with CHOP with and without concurrent indinavir based HAART showed a decrease of cyclophosphamide clearance from 70 to 41-46 mL/min/m^2. However, this didn't translate into excessive toxicity[24]. Induction of CYP3A4 may make more drug available for 4-hydroxylation route and may increase efficacy and toxicity of cyclophosphamide. In contrast ifosfamide is administred as a racemic mixture of its two enantiomeric forms: R and S-ifosfamide through the CYP3A4 pathway. Induction of CYP3A4 may increase activation of the drug and may also produce more potentially neurotoxic metabolite[25].

Anthracyclines (Doxorubicin and Daunorubicin): they are commonly used agents in the treatment of both AIDS-related NHL and KS. Fortunately the potential for adverse drug interactions between CYP-pathways and anthracyclines appears to be minimal. Interactions with PIs or NNRTIs and CYP-pathways may decrease reduction to free radicals, which may decrease both antineoplastic and cytotoxic properties. Enzyme inducers may do the opposite. Two pharmacokinetic analyses were conducted in HIV-positive patients with non-Hodgkin's lymphoma treated with CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) with and without concurrent PI-based HAART. The first study in 19 patients showed that doxorubicin pharmacokinetics were not affected by concomitant PIs administration, and PIs exposures were not altered by doxorubicin[26]. The other study in 29 HIV-positive patients also showed similar clearance rates of doxorubicin when administered with an indinavir-based cART[24].

Antimetabolites (5-Fluorouraxil, Mtotrexate, Gemcitabine, etc.): includes several nucleoside analogs drugs used in combination with others antineoplastics in carcinomas and NHLs. Fortunately the potential for adverse drug interactions with HAART appears to be minimal, but the clinical trials in this fields is low. Potential toxicity are considered for high exposures to etravirine due to CYP2C9 inhibition, however, close monitoring may be considered.

Case series of 21 HIV-positive subjects on cART (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[27]. Case series of 5 HIV-positive patients on cART (4 PI, 1 NRTI) with advanced colorectal cancer who received oxaliplatin, leucovorin and fluourouracil (FOLFOX-4 regimen) without apparent increase in antineoplastic associated toxicity[28].

MISCELLANEOUS

***Irinotecan*:** (CPT-11), is a DNA topoisomerase I inhibitor with a broad spectrum of activity against solid tumours. The model of angiogenesis bFGF-induced in mouse cornea suggested that Irinotecan is active also in KS HIV-releted. Recent data show that lopinavir/ritonavir has a strong effect on the pharmacokinetic profile of CPT-11 when used as monotherapy in HIV patients with advanced KS. Lopinavir/ritonavir reduces the clearance of CPT-11 by 47%; the area under the curve (AUC) of the oxidized metabolite APC by 81%; and inhibithed the formation of SN38 glucuronide. This effect resulted in increased availability of CPT-11 and severe toxicity. Conversely induction of CYP3A4 or glucuronidation may decrease efficacy of drug[6]. Pharmacogenomics profile UGT1A1 *28 haplotype with homozygous 7 TA repeat are high risk for irenotecan-related toxicities with atazanavir, which also inhibits UGT1A1.

TABLE 3. DRUG-DRUG INTERACTIONS IN HAART/ANTIBLASTIC COMBINED THERAPY.

Antiblastic Drug	Metabolism	Reported Interactions HAART	#Pharmacogenomics annotations	Comments
Vinca alkaloids				
Vincristine, vinblastine and vinorelbine	CYP3A4	Ritonavir and others PIs	Not well documented	High vinca levels may have high risk and severity of peripheral neuropathy, and myelosuppression. If possible, consider modifying cART to a non-PI based regimen
Taxanes				
Paclitaxel Docetaxel	CYP2C8>CYP3A4	Caution when unboosted atazanavir is coadministered with drugs that are CYP2C8 substrates with narrow therapeutic indices clinically significant interactions with CYP2C8 substrates are not expected when atazanavir is boosted with ritonavir	Breast Cancer Patients carrying CYP2C8*3 haplotype are associated to increased risk of neurotoxicity[35]. Polymorphism T274M in Beta Tubulin VI (BTT VI) gene is associated to severe myelosuppression in patient treated to Taxanes[36]	High taxane levels with CYP3A4 inhibitors may have high risk and severity of myelosuppression, and peripheral neuropathy
Epipodophyllotoxins				
Etoposide Teniposide	CYP3A4 (main); CYP2E1, 1A2 (minor)	Risk of toxicity with all CYP3A4 inhibitors	ND	High etoposide/teniposide levels may have high risk and severity of mucositis, myelosuppression and transaminates.
Alkylating agents				
Ciclophosphamide	CYP2B6 > 2C19 to active metabolite. 3A4 to inactive and possibly toxic metabolites [2]	CYP2B6 inducers (e.g., ritonavir, nelfinavir, efavirenz, nevirapine) and CYP3A4 inhibitors (e.g., PIs, elvitegravir/ cobicistat). Etravirine inhibits 2C19 Rilpivirine induces CYP2C19; monitor for toxicity	ND	Induction of 2B6 have high amount of active metabolite formed. Inhibition of CYP2B6 may prevent activation of the drug. Induction of 3A4 may have neurotoxicity, whereas inhibition of 3A4 may make more drug available for 4-hydroxylation route. Inhibition of 2C19 may impact activation of the drug, although this may be compensated for by increased shunting through 2B6 pathway.
Ifosfamide	CYP3A4 to active metabolite. 3A4 and 2B6 involved in detoxification	May need to hold anti-retrovirals or change to regimen without CYP3A4 inhibitors		CYP3A4 metabolism of (S)-ifosfamide may generate neurotoxic[25]. Induction of 3A4 may produce myelosuppression, arrhythmia, hemorrhagic cystitis
Platin-derivates	Primarly renal elimination post Glutathione additions (GSTP1, GSTM1 and others)	Potential for pharmaco-kinetic interactions with ARVs appears minimal. However, cisplatin induced nephrotoxicity may necessitate dosage adjust ment for certain ARVs. Potential additive renal toxicity with tenofovir.	Polymorphism *GSTP1* rs1695 Ile105Val (313A>G in exon 5, sometimes labelled GSTP1*B) has been associated with reduced enzyme activity and toxicity[37]	Monitor serum creatinine and creatinine clearance; adjust antiretroviral doses accordingly as needed.

TABLE 3 (CONTINUED). DRUG-DRUG INTERACTIONS IN HAART/ANTIBLASTIC COMBINED THERAPY.

Antiblastic Drug	Metabolism	Reported Interactions HAART	#Pharmacogenomics annotations	Comments
Anthraczyclines				
Daunorubicin Dactinomycin Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives conjugated to a sulfate or glucuronide metabolite. Involved in free radical generation. Substrate of P-gp which may influence intracellular concentrations	Monitor for efficacy and toxicity with concomitant P-gp inhibitors or inducers	Resistance prevention by Detection of MDR1 (ABCB19) 3435C>T rs1045642	Potential for interactions un known, given uncertainty about role of CYP450 in free radical generation. P-gp inhibitors may increase intracellular accumulation of doxorubicin, which may enhance cytotoxic effects and/or systemic toxicity.
Corticosteroids				
Dexamethasone Prednisone	CYP3A4 Dexamethasone is a 3A4 inducer	Dexamethasone may reduce levels of NNRTIs, PIs and elvitegravir/cobicistat[2].	Resistance prevention by Detection 3435C>T rs1045642. In addition check Vitamin D receptor (VDR) Taq, Apa, BsmI, FokI.	Consider use of non-CYP3A4 inducing steroid, or modifying to a non-CYP based cART regimen (e.g., dolutegravir, raltegravir).
Antimetabolites				
Cytarabine	Metabolized in liver by Cytidine Deaminase (CDA)	Caution with AZT; tenofovir due to renal toxicity	CDA haplotype: -451C>T, -92A>G, Lys27Gln results in toxicity[38].	Main toxicities of cytarabine include dose-limiting myelosuppression, nausea, vomiting, urinary retention, renal failure (rare).
Fluoropyrimidines	Metabolism by the dihydropyrimidine dehydrogenase (DPD). 7-20% renally excreted. Strong inhibitor of CYP2C9	Possibile interaction with either CYP2C9 inhibitors (eg Efavirenz and Etravirine) or 2C9 Inducer (Elvitegravir)	DPYD*2A haplotype results in severe toxicity[39].	Severe mucosites and gatrintestinal for DPYD deficient
Gemcitabine	Extensively metabolized to 2',2'-difluorodeoxyuridine (dFdU) by CDA enzyme The main metabolite dFdU has a long terminal half-life after oral administration	Potential for cytochrome-mediated interactions with ARVs appears minimal.	Need to asses CDA haplotype: -451C>T, -92A>G, Lys27Gln. In additions check polymorphisma on Nucleotide Trasporters (hENT1) [40].	Unlikely to result in detrimental pharmacokinetic interactions with cART
Tyrosine Kinase Inhibitors				
Erlotinib	Primarily metabolized by CYP3A4. Metabolized to a lesser extent by CYP1A2 and 1A1.	Dosing reduction of erlotinib 50 mg daily when coadministering with ritonavir 100 mg daily	Erlotinib binding affinity for EGFR exon 19 deletion or exon 21 L858R mutations is higher than its affinity for the wild type receptor.	Alternative treatments lacking potent CYP3A4 inducingactivity should be considered when possible.
Imatinib	Extensively metabolized by CYP3A4. And N-demethylated piperazine derivative is the main circulating metabolite.	Interferences PIs, NNRTIs, and elvitegravir/cobicistat	Consider specific resistance to imatinib due to acquired mutations of ABL gene (i.e T315I)	Monitor patients for signs of imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia)

TABLE 3 (CONTINUED). DRUG-DRUG INTERACTIONS IN HAART/ANTIBLASTIC COMBINED THERAPY.

Antiblastic Drug	Metabolism	Reported Interactions HAART	#Pharmacogenomics annotations	Comments
Sunitinib	Metabolized primarily by CYP3A4 to active metabolite SU012662 which is also metabolized by CYP3A4	Avoid concomitant administration of CYP3A4 inhibitors such as PIs and elvitegravir/cobicistat, or inducers such as NNRTIs if possible. Sunitinib dose may be reduced	Patients with metastatic Renal Carcinoma carrying an ABCG2 421 AA genotype developed significantly more grade 3 or grade 4 thrombo-cytopenia, neutropenia	Potential for high concentrations with CYP3A4 inhibitors. In healthy volunteers, coadministration of single dose sunitinib and ketoconazole led to 49% high Cmax and 51% high AUC of sunitinib[41]
Miscellaneous				
Irinotecan	hCE2 to SN-38 metabolite (active); CYP3A4 and Glucuronidation by UGT1A1.	Potential for augment irenotecan-related toxicities with atazanavir, which also inhibits UGT1A1.	Need to detect UGT1A1 *28. Haplotype carrying TA repeat 7/7 is high risk toxicity due poor metabolizer.	Inhibition of 3A4 may have high risk and severity of myelosuppression. Induction of 3A4 or glucuronidation may augment efficacy of drug[6].
Bortezomib	Metabolized primarily by CYP3A4, 2C19, 1A2, and CYP2D6 and CYP2C9 to a minor extent. It may inhibit CYP2C19 at clinically relevant dosages.	Efavirenz and etravirine inhibit CyP2C19 and induce CYP3A4. Clinical significane unknown; monitor for bortezomib efficacy & toxicity. Rilpivirine induces CYP2C19 [42].		Potential variation for bortezomib concentrations with potent CYP inhibitors or inducers of CYP3A4 and CyP2C19. monitor for efficacy[32]
Tamoxifene	Multiple isoenzymes involved: CYP3A4>CYP1A2 to N-desmethyl-tamoxifen. In addition CYP2D6, CYP2C9/ 19,CYP3A4 and CYP2B6 to trans-4-hydroxytamoxifen may inducer to CYP3A4.	Potential for reduction levels of PIs, NNRTIs or elvitegravir/ cobicistat [29]	Genotyping FDA and EMA recomandation guidelines for CYP2D6 *4 Pro34Ser 42	Inhibition of 3A4 may augment risk and severity of tamoxifen related side effects (e.g. hot flushes, nausea and vomiting). Avoid concomitant use of CYP2D6 inhibitors
Exemestrane Letrozole	Metabolized by CYP3A4 and Aldoketoreductases Letrozole is a substrate to CYP2A6 too.	Nevirapine and efavirenz may reduce efficacy. High levels with PIs and delavirdine may augment risk and severity of adverse effects (e.g. musculo-skeletal pain, peripheral edema, hot flashes, etc.	Genome wide study in breast cancer treated with aromatase inhibitors shown significant polymorphism in TUBB1 rs10485828[36]	Avoid combination to efavirenz and PIs if possible.

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Aromatase Inhibitors (Tamoxifen, Letrozoley, exemestrane): the concomitant use of endocrine-based therapies that lack the potential for CYP3A4 induction should be considered. Tamoxifen a commonly used estrogen antagonist undergoes extensive hepatic metabolism involving several isoforms of the CYP system. Induction of CYP3A4 by tamoxifen may decrease NNRTIs or PIs concentrations. Conversely inhibition of CYP3A4 isoforms with PIs or NNRTIs may be increase efficacy and risk and severity of tamoxifen-related adverse effects. Several studies have shown that nelfinavir induces cell cycle arrest, endoplasmic reticulum stress, autophagy and apoptosis in

cancer cells and may be an effective drug against breast cancer when combined with tamoxifen in patients with no hormone-responsive tumours[29]. Interactions between HAART and aromatase inhibitors are also theoretically feasible. Letrozoley and exemestrane are both metabolized to some CYP3A4 to inactive metabolites. NNRTis may decrease efficacy of drugs conversely PIs may increase concentration and severity adverse effects of letrozoley and exemestrane[30].

Corticosteroids: corticosteroids are part of combination AC regimens and may be subjects to changes in their pharmacokinetic and pharmacodynamic effects as a result of antiretroviral-mediated modulation of their biotransformation. In particular dexamethasone and methylprednisolone are vulnerable to interactions with HAART since the CYP3A4 isoform is the main enzyme mediating the metabolism of these drugs. Dexamethasone may decrease concentrations of NNRTIs and PIs. PIs may increase pharmacodynamic effects of corticosteroids when used concurrently. CYP3A4 inducers conversely may decrease efficacy of these drugs. Therefore it is necessary to hold HAART in patients receiving prolonged dexamethasone or alternatively consider use of non-CYP3A4 inducing corticosteroid or antiretroviral drugs monitoring if combination is necessary[2].

Erlotinib, a tyrosine kinase inhibitors, approved for the treatment of non-small cell lung and pancreatic cancer, is metabolized by CYP3A4. Inducers or inhibitors of CYP3A4 enzymes such as PIs (e.g. ritonavir) or NNRTIs (e.g efavirenz) can modify the metabolism and efficacy of the drug. Recent data suggest that to achieve desired drug exposure, the clinically used dose (150 mg daily) of Erlotinib may have to be significantly reduced (25 mg every other day) or increase (300 mg daily) respectively when ritonavir or efavirenz is coadministered[31].

Imatinib a specific inhibitor of tyrosine kinase receptor in particular of the proto-oncogene c-kit, used in the treatment of chronic myelogenous leukaemia is also metabolized by the CYP450 system[6].

Sunitinib, an oral multi-targeted tyrosine kinase inhibitor used for the treatment of advanced renal cancer and gastrointestinal stromal tumors (GISTs) is bio-transformed by CYP3A4 in a major pharmacologically active N-desethyl metabolite[6]. The inhibition of proteasomal activity by specific proteasome inhibitors or cross-reactivity of certain PIs with proteasomal enzymes recently became of interest because of the anti-tumoral properties of these agents.

Recent data show that ***bortezomib*** and nelfinavir induced cell cycle arrest in cervical cancer cells as reflected by marked changes in the expression of cell cycle-regulatory cyclins and ensuing mitochondrial independent apoptosis[32]. Therefore, the combination of ritonavir and bortezomib induced apoptosis and inhibits renal cancer growth synergistically at clinically feasible concentrations[33]. The effectiveness of the combination is caused by protein ubiquitination and histone acetylation.

Lenalidomide, analogue of thalidomide do not show pharmacokinetic interaction with HAART because it is not metabolized by the liver but are eliminated by renal route.

CONCLUSIONS

The concomitant use of HAART and AC might result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes. Infact, many AC are metabolized by CYP450 whereby DDIs with HAART is high. All PIs are potent inhibitors of CYP3A which is important in the metabolism of approximately 50% of all drugs. Conversely NNRTIs may induce metabolism and potentially reduce the efficacy of AC. Although, raltegravir has a low potential for DDIs, the presence of viral mutations limit its use as single active agent in a regimen (Table 2). Interactions can also be a result of modification in the activities of glucuronosyltrasferases and of transport proteins[6].

Ritonavir is an inhibitor of P-glycoprotein which leads to increased expositions towards many antineoplastic drug. Generally to prevent DDIs and avoid severe toxicity, treatment options include substituting an antiretroviral alternative, or temporarily discontinuing HAART or selecting an alternative chemotherapy regimen[10]. Zidovudine is associated with severe neutropenia whereby it should not be combined with cytotoxic regimens containing neutropenic agents. Didanosine and stavudine, NRTIs once used, are associated with irreversible peripheral neuropathy, which is also a common side effect of platinating agents, taxanes, vinca alkaloids and bortezomib. Antiblastic chemotherapy induced neuropathy is generally cumulative or dose related with management consisting of dose-reduction or lower dose intensity. PIs and newer molecularly targeted AC including the tyrosine kinase inhibitors may cause QT prolongation, arrhythmias and sudden death. In addition to PIs appears to significantly potentiate the myelotoxicity of AC. Bilirubin is often used as a guide for dose adjustment for AC agents such as docetaxel, doxorubicin, etoposide, irinotecan, paclitaxel, sorafenib, vincristine. Several antiretrovirals as atazanavir and indinavir are associated with unconjugated hyperbilirubinemia secondary to UGT1A1 inhibition similar to that

which occurs in Gilbert's syndrome. If no other signs of liver dysfunction exist suggested dose modifications of AC based on liver function test may be ignored. For these reasons it is important that patients with cancer should be screening for HIV infection and the treatment of HIV infection should be started immediately[34]. HAART should be individualized according to the cancer treatment plan (AC or radiotherapy or surgery), liver or renal diseases, bone marrow suppression, mitochondrial dysfunction and for individual genetic profile. Finally, Anticancer drug metabolism were described and treatment regimens should be plan calibrating dosage on individual genomic profile. In the table 3 were reported the most important warning of: i.e Taxan[35,36], Platin-derivates[37], Cytarabine[38], Pirymidines[39], Gemcitabine[40], Aromatase inhibitors[41],

We accounting that HIV treatment has entered a new era in which multidrug treatments and genetic variations (host and virus) must be taken in consideration when formulating chemotherapeutic/HAART regimens, in order to maximize benefits and minimize toxicity[42].

Finally, not to be underestimated the importance of cooperation between oncologists and laboratory specialist in the management of these information related individual genetic profile to aimed patients at a personalized treatment strategy.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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