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Drug-drug Interactions in Patients with HIV and Cancer in Sub-Saharan Africa

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Abstract

In Sub-Saharan Africa, the cancer burden is predicted to increase by > 85% by 2030, the largest increase worldwide. This region has a large HIV-positive population. Drug-drug interactions (DDIs) from concomitant use of multiple drugs increase the risk of drug toxicities, sub-optimal therapy, and drug resistance. With the increase in polypharmacy, involving antiretroviral (ARV), and anticancer drugs, there is a greater need for an appreciation of clinically relevant DDIs. Anticancer and ARV drugs studied in this review were from The World Health Organization's Model List of Essential Medicines 2017. We reviewed; drug package inserts, www.drugbank.ca and www.UpToDate.com, to evaluate pharmacokinetic interactions with cytochrome P450 (CYP450) and ABCB1. The DDIs between drugs were assessed using the University Of Liverpool, UK HIV Drug Interactions Checker, and the LexiComp Drug Interaction tool of www.UpToDate.com. About 70% of ARVs studied interact with CYP450, all involve CYP3A4, and 55% interact with ABCB1. About 65% of anticancer drugs interact with CYP450, 44% of which do so through CYP3A4. About 75% of anticancer drugs interact with ARV drugs, with nine absolute contraindications to concomitant therapy. There exist a substantial number of DDIs between ARV and anticancer drugs, primarily mediated through CYP450 enzymes. Dolutegravir based regimens offer the safest DDI profile for concurrent use with anticancer drugs. However, there are substantial gaps in our knowledge, and this study serves to highlight the need for additional research to better define these interactions and their effect on drug exposure, as attention to these DDIs is a relatively simple intervention that could lead to optimizing disease treatment. ***(AIDS Rev. 2020;22:13-27)***

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Key words

Human immunodeficiency virus. Cancer. Drug-drug interactions. Cytochrome P450.

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Introduction

Cancer is a major public-health problem in Africa, as in other continents. However, in Sub-Saharan Africa (SSA), the cancer burden is predicted to increase by > 85% by 2030, the largest increase worldwide[1,2]. The high rate of cancer is a trend which is complex in etiology with multiple factors likely contributing, including but not limited to the change in population dynamics; improved life expectancy, changing lifestyles, and diet; continued high prevalence of oncogenic viruses such as Kaposi sarcoma (KS)-associated herpesvirus, human papillomavirus (HPV), and Epstein-Barr virus; and improved health care access[1,3]. Furthermore, there are improving estimates on cancer incidence and mortality in SSA. Apace with the rising cancer burden in SSA is the persistence of infectious diseases, such as HIV, tuberculosis (TB), malaria, hepatitis B, hepatitis C, and helicobacter pylori, which continue to afflict these regions[1,3]. SSA accounts for 71% of the global HIV burden[4]. There are an estimated 26 million people living with HIV in SSA, and this HIV epidemic is a major contributor to the high cancer burden[3,5]. Pathogen associated cancers have high rates of morbidity and mortality and account for one-third of all cancers in most of these regions[3,5].

People living with HIV have an increased risk of developing a range of cancers, which have traditionally been categorized as "AIDS-defining cancers (ADC)," including KS, non-Hodgkin's Lymphoma (NHL), and cervical cancer, as well as other "non-ADC (NADC)"[5-7]. In developed countries, cancer is responsible for approximately one-third of all deaths in people with HIV[7,8]. The advent of combination antiretroviral (ARV) therapy (cART) has significantly reduced the relative incidence of ADCs that occur at low CD4 counts, such as KS and NHL[5,9]. The incidence of NADCs, however, is continuing to increase among HIV positive patients as they receive ART, have fewer infectious complications and have extended lifespans[7,9-12]. This shift in epidemiologic landscape in cancer among the HIV-positive population has been noted in industrialized countries; however, ADCs are still predominate in SSA and other resource-poor regions, in part due to increased prevalence of oncogenic viruses and limited cervical cancer screening infrastructure[1,7,9].

Standard cART for HIV involves a minimum of three drugs; therefore, the trend of multidrug regimens is predicted to become increasingly common among HIV-positive patients with cancer[10,13]. With such increased polypharmacy, involving ARV and anticancer drugs, there is a greater need to promote safe and effective use of these medicines[13]. Concomitant use of multiple drugs may lead to drug-drug interactions (DDIs) resulting in drug toxicities, sub-optimal therapy, treatment failure, and drug resistance, all of which affect the full benefit of treatment, both on individual and population levels[13-16]. The risk of DDIs increases as the number of medications, or polypharmacy increases[17-19].

In SSA, the burden of DDIs in cancer patients is further complicated by concomitant use of traditional medicines[20,21]; inadequate healthcare staff (e.g., medical oncologists, radiation oncologists, pharmacists, and other support staff)[1,3]; inadequate public health infrastructure, and lack of cancer awareness[1]. The growing and aging HIV-positive population adds another layer of complexity to DDIs in the treatment of cancer in SSA[1,22-24].

Avoiding or managing adverse effects from DDIs between ARV and anticancer drugs is an important evolving challenge in the management of people with HIV and cancer. Optimal timing of initiation of ART and treatment of cancer in people who are diagnosed with cancer while not on ART remains an unanswered question. Historically, one approach has been to start chemotherapy first and to add ART only after side effects (e.g., nausea, vomiting, and mucositis) associated with chemotherapy are managed adequately[10,25,26]. However, the increasing efforts to initiate ART at time of HIV diagnosis and the changing WHO recommendations about first-line therapy may affect treatment decisions. Regardless of timing of initiation, it is imperative to recognize that people living with HIV may be on a wide variety of medications for HIV that have variable potential for DDIs with cancer therapy.

Much of the risk of DDIs relates to metabolism by the hepatic cytochrome P450 (CYP450) system. The CYP450 enzymes alone contribute to 75% of total drug metabolism[27]. Any drug may be a substrate of one or more CYP450 isozyme[27]. Drug interactions with CYP450 enzymes occur through various mechanisms. The drugs can be metabolized by a single CYP450 enzyme or multiple enzymes. Significantly, drugs can drive the CYP450 metabolic interactions by serving as an inducers or inhibitors, either alone or in combination with other drugs (Fig. 1). While inducers increase enzyme synthesis, leading to increased clearance of a co-administered drug resulting in low drug plasma levels and thus potentially reduced efficacy, inhibitors block the activity of one or more CYP450 isozymes, leading to higher drug plasma levels and

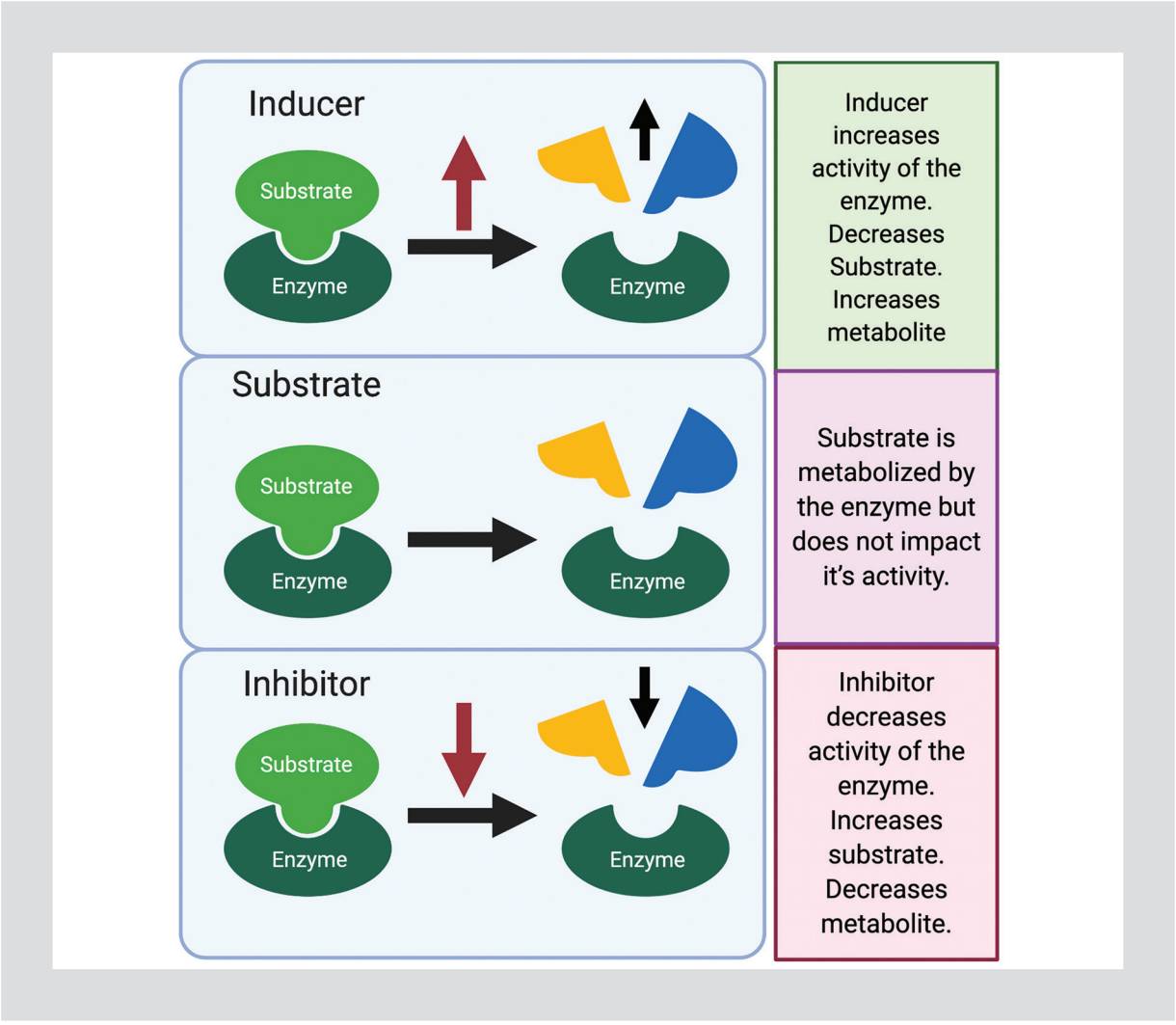

Figure 1. *Mechanisms of interactions. The mechanisms of drugs interaction with enzyme, as substrate, inhibitor, and/or inducer are presented. Figure produced using www.Biorender.com.*

thus potential toxicities[15,27,28]. Some drugs are both inducers and inhibitors and their net effects may be relatively hard to predict. For medications with a narrow therapeutic index, such as many anticancer drugs, DDIs can result in significant clinical effects[29] (Fig. 2). Of the ARV drugs, the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have the greatest propensity to cause drug interactions, as they all can inhibit and/or induce the CYP450 enzymes[27,30].

The purpose of this review is to outline the principal metabolic pathways of ARV and anticancer drugs and to identify the DDIs between ARV and widely used WHO-recommended anticancer drugs, based on the literature review and drug-interaction resources.

Methods

The World Health Organization's (WHO) Model List of Essential Medicines (EML), updated every 2 years, contains medications that are most effective and safe to treat a broad spectrum of diseases and provides the most cost-effective options for key public health problems. For this review, the anticancer drugs studied were selected from "Essential Medicines for Cancer" in the EML drug list of WHO 2017[31]. Drug indications were taken from UptoDate.com Drug Information in October 2019, both package insert and off-label uses were included in the study. Drug indications were included regardless of known use in Africa, and different formulations of the same drugs were not considered. The list

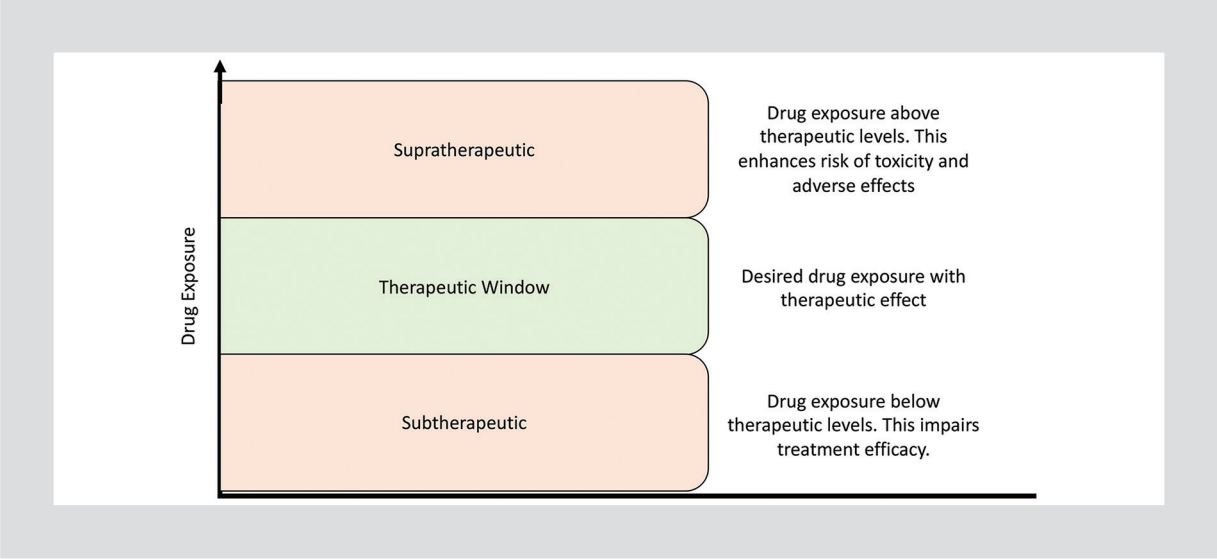

Figure 2. *Therapeutic window. The range of drug exposure that optimizes efficacy and minimizes toxicity.*

of ARV drugs was obtained from the "ARV" section of the aforementioned 2017 EML drug list produced by the WHO and additional commonly used ARVs were selected for study based on Rathbun et al.'s 2018 Medscape article "ARV therapy for HIV infection"[32]. All drugs are Food and Drug Administration approved.

We conducted a review of three resources; drug package inserts, www.drugbank.ca and www.UpToDate.com, to obtain information on potential and known pharmacokinetic interactions of the ARV and anticancer drugs with the CYP450 enzymes and the drug transporter ABCB1. Inducers, inhibitors, and substrate status for each ARV and anticancer drug were assessed.

The DDIs among ARVs, and the DDIs between the ARVs and anticancer drugs, were assessed using the online evidence-based tool constructed by the University Of Liverpool, UK, referred to as the "HIV Drug Interactions Checker"[33] and combinations that could not be independently assessed due to fixed-dose combinations (FDCs) on the University of Liverpool site were assessed using the "LexiComp Drug Interaction"[34] tool of www.UpToDate.com. The DDI information reported in these databases are a consolidation from the published literature on various clinical and experimental pharmacokinetic studies. Drug combinations given "**x**" indicate contraindication, given ◆ indicate moderate to strong interaction; warranting consideration of alternate therapy, dose adjustment, or close monitoring. Combinations given ❍ indicate potential weak interaction; warranting close monitoring, and given ◆ indicate no evidence available for any significant pharmacokinetic interaction.

Results

Anticancer and ARV drugs

The goal of cART is to suppress HIV viral load, restore immune function, prevent HIV transmission, prevent development of resistance, and improve quality of life[35]. There are six classes of drugs that are used in combinations to treat HIV. The entry inhibitors interfere with virus binding and fusion into the host cells and include fusion inhibitors (FIs) and chemokine-receptor antagonists[32]. The NRTIs and the NNRTIs inhibit the reverse transcription of HIV RNA into complementary DNA[32]. Whereas the former inhibits the reverse transcriptase enzymes by serving as nucleoside/nucleotide analogs, the latter are non-competitive inhibitors that bind to the allosteric site of the enzyme[32]. The integrase strand-transfer inhibitors (INSTI) inhibit integrase function, thereby preventing the integration of viral DNA into the DNA of the host cell[32]. The PIs, block HIV protease enzyme that is central for budding of mature virions (Supplementary Table 1A)[30,32]. The standard treatment for people infected with HIV (cART) consists of a combination of at least three active drugs, historically a combination of a double NRTI backbone with a NNRTI and/or a PI boosted with ritonavir and/or an INSTI[10,20,24]. However, WHO updated HIV treatment guidelines, published in December 2018, recommended first-line cART should be dolutegravir based; current recommended first-line therapy is dolutegravir, tenofovir, and emtric-

itabine[36]. However, tenofovir is contraindicated in patients with kidney dysfunction[37], and such contraindication is particularly important in the context of the potential for DDIs[38]. For economic reasons and greater availability, boosted PIs are more commonly used in SSA than in more resource-rich countries. Medication adherence in cART can be challenging because multidrug regimens may result in patients having to take many pills multiple times per day[20]. Hence, many of these drugs are formulated to combine multiple drugs into one single tablet/capsule, known as the FDCs (Supplementary Table 1B).

Chemotherapeutic drugs (CTDs) are a heterogeneous group of drugs with diverse mechanisms of action (MOA)[39,40] (Table 1). These include interference with DNA/RNA biosynthesis, cell division and replication, cell survival, angiogenesis, and/or metastasis[41]. Classification of the widely used CTDs based on the mode of action is presented in Table 1 along with their current on- and off-label indications. CTDs are often combined into multidrug chemotherapeutic regimens composed of multiple agents, generally with unrelated MOA and differing modes of drug resistance, with the intention of enhancing efficacy by blocking the development of multiple intracellular escape pathways essential for tumor survival[41]. Often consideration is given to overlapping toxicities. As with cART, several standardized combinations of CTDs are now in use. Besides the conventional CTDs, several non-cytotoxic therapies, such as targeted therapies, monoclonal antibodies and hormone therapies, are currently in use in resource-rich countries and their role is expanding[42].

While DDIs already pose a significant challenge in cART and combined chemotherapy independently, the scenario becomes more complicated in the treatment of HIV-positive patients with cancer[15,17]. In our endeavor to assess the DDIs of ARV and anticancer drugs, we focused on the WHO's list of essential anticancer drugs, which is based on the national essential medicines lists or national reimbursable medicines lists of 135 countries[31]. This list comprised 41 drugs from 13 different classes of drugs.

Drug metabolic pathways relevant to DDIs of anticancer and ARV drugs

More than 75% of drugs are metabolized by the CYP450 enzymes[27,43]. These enzymes are bound to the cell (cyto) membrane, contain heme pigments (chrome and P), and absorb light at a wavelength at 450 nm when exposed to carbon-monoxide[27]. The three main CYP450 families are CYP1, CYP2, and CYP3, which are classified further into subfamilies. Although there are more than 50 CYP450 enzymes, six of them, namely, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5, metabolize more than 90% of CYP450-metabolized drugs[27,28]. These enzymes are predominately expressed in the liver, but they can also be found in the small intestine, lungs, placenta, and kidneys[27]. Drug interactions with CYP450 enzymes occur through various mechanisms. The drugs can be metabolized by a single CYP450 enzyme or multiple enzymes. Significantly, drugs can drive the CYP450 metabolic interactions by serving as an inducers or inhibitors, either alone or in combination with other drugs. While inducers increase enzyme synthesis, leading to increased clearance of a coadministered drug resulting in low drug plasma levels and thus potentially reduced efficacy, inhibitors block the activity of one or more CYP450 isozymes, leading to higher drug plasma levels and thus potential toxicities[15,27,28]. Some drugs are both inducers and inhibitors and their net effects may be relatively hard to predict. To minimize the possible adverse DDI involving ARV and anticancer drugs, knowledge of the inducing or inhibiting capabilities of these drugs is important.

In Table 2A, the known interactions of ARV drugs with the CYP450 enzymes and ABCB1 (P-glycoprotein), a well-described efflux pump protein associated with drug metabolism, are listed. About 70% of ARVs interact with the 9 CYP450 isozymes studied and 55% interact with ABCB1. Among the ARV classes, NRTIs are neither inducers nor inhibitors of CYP450 enzymes and only zidovudine is a substrate; therefore, risk of DDIs through CYP450 metabolic pathway is unlikely to be clinically significant[28]. On the other hand, most NNRTIs and PIs are metabolized extensively by CYP450, and thus their use is associated with increased risk of DDIs[28]. All NNRTIs interact with a variety of CYP isozymes, as substrates, inducers, and/or inhibitors, although overall NNRTIs exhibit moderate to weak interactions (Table 2A). Rilpivirine serves as a substrate for CYP3A but does not induce the CYP450 enzyme. Etravirine, a second generation NNRTI, is the only known inhibitor, however with weak activity, of ABCB1 in this class. By contrast to NNRTIs, most PIs are strong inhibitors of CYP isozymes. Among the PIs, darunavir, and atazanavir have the least interactions and ritonavir exhibits the most clinically significant drug interactions[28,30]. Ritonavir is a strong inhibitor of CYP3A4 and ABCB1, and an inducer of CYP1A2, CYP2C9, CYP2C19, and CYP2B6[44,45]. Furthermore, as all PIs are CYP3A4 substrates they are often coadministered with ritonavir to boost drug plasma levels through ritonavir's

Table 1. Anti-cancer drugs

Chemical group	Name of the drugs	Indications	Mechanism of action
Alkylating Agents	Cyclophosphamide	ALL*, Breast Ca.*, CLL*, Ewing sarcoma*, GTN*, HL*, M.Myeloma*, NHL*, Pheochromocytoma*, Ovarian germ cell tumors*, Rhabdomyosarcoma*, SCLC*	Cell-cycle nonspecific. Cytotoxic. Irreversibly binds to DNA forming cross-links disrupting transcription, repair and replication of DNA
	Ifosfamide	Tesicular ca., Bladder ca.*, Cervical ca.*, Ewing sarcoma*, HL*, NHL*, Osteosarcoma*, Ovarian ca., Sarcoma*,Thymomas	
	Procarbazine	HL, NHL*, Primary CNS Lymphoma*, CNS tumors*	
	Bendamustine	CLL, NHL, HL*, M.Myeloma*, Waldenstrom macroglobulinemia*	
	Chlorambucil	CLL*, HL, NHL*,Waldenstrom macroglobulinemia*	
	Dacarbazine	HL, Malignant melanoma, MTC*, PNET*, Pheochromocytoma*, Sarcoma*	
Anthracyclines	Doxorubicin	ALL*, Bladder ca.*, Breast ca., Endometrial ca.*, Ewing sarcoma*, HCC*, HL*, M.Myeloma*, NHL*, Osteosarcoma*, RCC*, SCLC*, Sarcoma*, Salviary gland ca.*, Thymoma, Waldenstrom macroglobulinemia*	DNA intercalation which inhibits DNA and RNA synthesis, blocking the transcription & replication process. Causes direct DNA damage due to reactive oxygen species (ROS) production. Topoisomerase-II inhibition inhibiting DNA repair triggering programmed cell death.
	Daunorubicin	AML*, ALL, APML*	
Platinum Agents	Cisplatin	Anal ca.*, Bladder ca., Breast Ca.*, Cervical ca. *, Endometrial ca.*, Eosphageal ca.*, Gastric ca.*, Head & Neck ca.*, GTN *, HPB ca.*, HL *, Mesothelioma *, M. Myeloma*, NHL *, NSCLC*, Osteosarcoma*, Ovarian ca., Penile ca.*, SCLC*, Testicular ca., Thymomas	Cell-cycle nonspecific. Cytotoxic. Forms intrastrand cross-links; inhibits DNA transcription, replication & repair.
	Carboplatin	Anal ca.*, Bladder ca.*, Breast ca.*, Cervical ca.*, Endometrial ca.*, Esophageal ca.*, Gastric ca.*, Head & Neck ca.*, HL*, Mesothelioma*, Malignant melanoma*, NET*, NHL*, Merkel cell ca.*, NSCLC*, Ovarian ca., Ewing sarcoma*, osteosarcoma*, SCLC*, Testicular ca.*, Thymic ca.*, Anaplastic Thyroid ca.*, Adenocarcinoma of unknown primary*	
	Oxalipaltin	HPB*, CRC, CLL*, Esophageal ca.*, Gastric ca.*, NETs*, Ovarian ca.*, NHL*, Pancreatic ca.*, Testicular ca.*	

(Continues)

Table 1. Anti-cancer drugs *(Continued)*

Chemical group	Name of the drugs	Indications	Mechanism of action
Antimetabolites	5-Fluorouracil	CRC, Breast ca., Gastric ca., Pancreatic ca., Anal ca.*, Bladder ca.*, Cervical ca.*, Esophageal ca.*, Head&Neck ca.*, HPB*, NET*, Penile ca.*, Vulvar ca.*, SCC of unknown primary*	Cell cycle specific. Cytotoxic. Inhibits DNA and RNA synthesis; acts as false metabolite and is incorporated into DNA and RNA, eventually inhibiting their synthesis.
	Gemcitabine	Bladder ca.*, Breast ca., Cervical ca.*, Head&Neck ca.*, HPB*, HL*, Mesothelioma*, NHL*, NSCLC, SCLC*, Testicular Germ cell ca.*, Sarcoma*, Pancreatic ca., Ovarian ca., Uterine ca.*, Adenocarcinoma of unknown primary*	
	6-Mercaptopurine	ALL, APML*, NHL*	
	Fludarabine	CLL, AML*, NHL*, Waldenstroms macroglobinemia	
	Capecitabine	CRC, Breast ca., Gastric ca.*, Pancreatic ca.*, Anal ca.*, Bladder ca.*, Cervical ca.*, Esophageal ca.*, Head&Neck ca.*, HPB*, NET*, Ovarian ca.*	
	Cytarabine	AML, APML*, ALL*, CLL*, CNS lymphoma*, HL*, NHL*, CNS prophylaxis	
	Asparaginase	ALL	
	Tioguanine	ALL*, AML	
	Hydroxyurea	CML, Head&Neck ca., AML*, HES, Meningioma*	
	Methotrexate	ALL, APML*, Bladder ca.*, Breast ca., GTN, NHL, Head&Neck ca., CNS lymphoma*, onleukemic meningeal cancer*, Mycosis Fungoides, Osteosarcoma, sarcoma*	
Taxanes	Docetaxel	Breast ca., Gastric ca., Head&Neck ca., NSCLC, Prostate Ca., Bladder ca.*, Esophageal ca.*, Ewing sarcoma*, Ovarian ca.*, SCLC*, Sarcoma*, Adenocarcinoma of unknown primary*	Inhibits the depolymerization of tubulin - destabilizes microtubules. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.
	Paclitaxel	Breast ca., NSCLC, Kaposi sarcoma, Ovarian ca., Bladder ca.*,Cervical ca.*, Esophageal ca.*, Gastric ca.*, Head&Neck ca.*, Penile ca.*, SCLC*, Sarcoma*, Testicular germ cell tumor*, Thymoma*, Adenocarcinoma of unknown primary*	
Vinca Alkaloids	Vinblastine	Bladder ca.*, HL*, Kaposi sarcoma*, Metastatic Melanoma*, NSCLC*, Sarcoma*, Testicular ca.*	Cell-cycle specific. Binds to tubulin and inhibits microtubule formation, therefore, arresting the cell at metaphase by disrupting the formation of the mitotic spindle.
	Vinorelbine	NSCLC, Breast ca.*, Cervical ca.*, HL*, Mesothelioma*, Ovarian ca.*, SCLC*, Sarcoma*, Salivary gland ca.*	
	Vincristine	ALL, CNS Tumors*, CLL*, Ewing sarcoma*, GTN*, HL, M.Myeloma*, Merkel cell ca.*, NHL, Ovarian ca.*, Pheochromocytoma*, CNS lymphoma*, Rhabdomyosarcoma, SCLC*, Thymoma*	

(Continues)

Table 1. Anti-cancer drugs *(Continued)*

Chemical group	Name of the drugs	Indications	Mechanism of action
Topoisomerase Inhibitors	Irinotecan	CRC, Cevical ca.*, CNS tumor*, Ewing sarcoma*, Esophageal ca.*, Gastric ca.*, NSCLC*, Ovarian ca.*, Pancreatic ca.*, SCLC*, Adenocarcinoma of unknown primary*	Cell-cycle specific. Inhibits topoisomerase I/II; causing DNA strand breaks preventing DNA replication and transcription
	Etoposide	GTN*, HL*, NSCLC, Ovarian ca.*, SCLC, Testicular ca.*, thymoma*, Adenocarcinoma of unknown primary*	
Hormonal Therapy	Bicalutamide	Prostate ca.	Multiple modes of action aimed at inhibiting the hormone-driven stimulation of cell growth in hormone sensitive cancers
	Tamoxifen	Breast ca. , Endometrial ca.*, Ovarian ca.*	
	Leuprolide	Prostate ca., Breast ca. ovarian suppression*	
	Anastrazole	Breast ca., Endometrial ca.*, Uterine ca.*, Ovarian ca.*	
Anti-Tumor Antibiotics	Dactinomycin	Wilms tumor, Rhabdomyosarcoma, Ewing's sarcoma, GTN, Ovarian germ cell tumors*	Binds DNA causing intercalations between base pairs inhibiting DNA & RNA synthesis, blocking the transcription & replication process
	Bleomycin	HL*, Testicular ca.*, Ovarian germ cell tumor*	
Tyrosine kinase Inhibitors	Nilotinib	CML (Ph+), ALL (Ph+)*, GIST*	Inhibits tyrosine kinases; blocking activation of proteins in signal transduction cascades
	Dasatinib	CML (Ph+), ALL (Ph+), GIST*	
	Imatinib	CML (Ph+), ALL (Ph+), MDS/MPD, ASM, HES/CEL, DFSP, GIST, C-KIT mutated malignant melanoma*, Chordoma*, Desmoid tumors *	
Monoclonal antibody	Rituximab	NHL, CLL, Burkitt lymphoma*, CNS lymphoma*, HL*, PTLD*, Gastriuc lymphoid tissue lymphoma, Waldenstrom macroglobulinemia*, Splenic marginal zone lymphoma	Monoclonal antibody directed against the CD20 antigen. Activates complement-dependent B-cell cytotoxicity; and mediates cell killing through an antibody-dependent cellular toxicity.
	Trastuzumab	HER2+ - Breast ca, Gastric ca., Endometrial ca.*	Monoclonal antibody targeting HER-2, mediates antibody-dependent cellular cytotoxicity
Other	All-Trans Retinoid Acid	APML	Tretinoin appears to bind one or more nuclear receptors and decreases proliferation and induces differentiation of APL cells
	Zoledronic Acid	M.Myeloma, Bone metastases from solid tumors, Hypercalcemia of maligancy	Bisphosphate - it inhibits osteoclastic activity and skeletal calcium release induced by tumors

M: myeloma; CLL: chronic lymphocytic leukemia; HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma; Ph+: Philadelphia chromosome-positive; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS/MPD: myelodysplastic/myeloproliferative diseases; ASM: aggressive systemic mastocytosis; HES/CEL: hypererosinophilic syndrome and/or chronic eosinophilic leukemia; DFSP: dermatofibrosarcoma protuberans; APML: acute promyeolocytic leukemia; SCC: squamous cell carcinoma; GIST: gastrointestinal stromal tumours; GTN: gestational trophoblastic neoplasia; HPB: hepatobiliary cancers; MTC: medullary thyroid carcinoma; PNET: pancreatic neuroendocrine tumours.

Table 2A. Antiretroviral drug metabolic pathways

Drug Class	Drugs	CYP450									Transport Proteins
		CYP1			CYP2			CYP3			ABCB1
		A2	B6	C8	C9	C19	D6	A	A4	A5	(P-gp)
NNRTIs	Efavirenz	↓	↑,⊙		↓	↓,↑		↑	↑,⊙		
	Nevirapine	↓	↑,⊙				↓,⊙	↑	↑,⊙	⊙	
	Delavirdine				↓	↓	↓,⊙	↓	↓,⊙		⊙
	Etravirine				↓,↑,⊙	↓,⊙		↑,⊙	↑,⊙		↓,↑
	Rilpivirine	↓						⊙	⊙		
NRTIs	Tenofovir										⊙
	Zidovudine			⊙	⊙	⊙			⊙		
	Stavudine*										
	Didanosine*										
	Lamivudine*										
	Abacavir*										
	Emtricitabine*										
PIs	Darunavir ¡				↑		↓,⊙	⊙	↓,⊙		↓,⊙
	Indinavir						↓,⊙		↓,⊙	↓,⊙	↓,⊙
	Ritonavir	↑,⊙	↑,⊙		↑	↓,↑	↓,⊙	↓,↑,⊙	↓,⊙	↓,⊙	↓,⊙
	Lopinavir ¡							↓,⊙	↓,⊙		↓,⊙
	Nelfinavir	↑	↑		⊙	⊙	⊙		↓,⊙	↓,⊙	↓,⊙
	Tipranavir ¡	↑				↑	↓	⊙	↑,⊙		⊙
	Saquinavir			⊙			⊙	↓,⊙	↓,⊙	⊙	↓,⊙
	Atazanavir ¡								↓⊙		↓,⊙
	Fosamprenavir ¡				⊙		⊙	⊙	↓,⊙ ↑		↓,↑⊙
INSTIs	Raltegravir*										
	Elvitegravir ¡							⊙	↓⊙		
	Dolutegravir							⊙	⊙		⊙
FIs	Enfuvirtide					⊙					
CRAs	Maraviroc				↓	↓		⊙	↓⊙		↓⊙
PKE	Cobicistat ⁝						↓,⊙	⊙	↓,⊙	↓,⊙	↓

*No known CYP450 or ABCB1 interactions based on available data.
¡Marketed with a booster.
⁝No direct antiretroviral activity.
⊙Substrate
↑Inducer
↓Inhibitor
NNRTIs: non-nucleoside reverse-transcriptase inhibitors; INSTIs: integrase strand transfer inhibitors; PIs: protease Inhibitors; FIs: fusion Inhibitors; CRAs: chemokine receptor antagonists; NRTIs: nucleoside/nucleotide reverse transcriptase inhibitors; PKE: pharmacokinetic enhancer.

inhibition of CYP3A4. Cobicistat is an alternative drug with a similar role in HIV treatment; while it has no direct ARV activity its pharmacokinetic properties of CYP3A4 inhibition are used to boost the plasma concentration of ARVs[32]. Among INSTIs there are minimal CYP450 interactions, with the exception of elvitegravir which is a moderate to strong CYP3A inhibitor. Dolutegravir displays minimal interactions, only a weak CYP3A4 and ABCB1 substrate, a pertinent fact given the 2018 WHO guidelines recommending dolutegravir-based regimens as first-line cART[36]. However, alternative hepatic metabolism may play a role in INSTIs DDIs, for example, raltegravir is metabolized extensively by glucuronidation through the UGT1A1 enzyme[45].

Anticancer drugs can also induce or inhibit CYP450 enzymes and/or the ABCB1 transporter (Supplementary Table 2), and they are often substrates of these enzymes. About 65% of the WHO EML 2017 anticancer drugs interact with the CYP450 enzymes studied. About 44% of these drugs (18/41) are either substrates or inhibitors of CYP3A4, a trend that has been observed with other non-cancer drugs[27]. Cyclophosphamide, ifosfamide, daunorubicin, paclitaxel, tamoxifen, and etoposide were predicted CYP3A4 inducers, and given 70% of ARVs are metabolized by CYP3A4, have the potential to increase clearance of the coadministered ARV, increasing risk of ineffective therapy and drug resistance. Most of the anticancer drugs that interacted with CYP450 enzymes also interact with the ABCB1 (17/26). The antimetabolites, platinum agents, monoclonal antibodies, and antitumor antibiotics exhibited the least CYP450 and ABCB1 interactions (Table 2B).

ARV and anticancer drug interactions

As shown in Table 3, there are a large number of DDIs among ARVs. NNRTIs and PIs are extensively metabolized by the CYP450 enzymes in the liver, whereas NRTIs are largely not eliminated by CYP450, nor do they induce or inhibit CYP450 enzymes[20,28]. However, emtricitabine, a first-line ARV, displayed one ARV DDI with a contraindication to use with lamivudine; this is not secondary to pharmacokinetics but rather coadministration of cytidine analogues[33]. In addition, emtricitabine had significant interactions with hydroxyurea and cisplatin, a highly relevant DDI given the prevalence of sickle cell disease and hematological malignancies in SSA[1,20]. FIs, such as enfuvirtide, do not undergo hepatic metabolism and are not likely to result in significant drug interac-

Table 2B. Anti-cancer drugs metabolic pathways

Drug class	Anti-Cancer Agents	CYP450									Transport Proteins
		CYP1	CYP2					CYP3			ABCB1
		A2	B6	C8	C9	C19	D6	A	A4	A5	(P-gp)
Alkylating Agents	Cyclophosphamide		↑,⊙	↑,⊙	↑,⊙	⊙	⊙		↓,↑,⊙		↓
	Ifosfamide		⊙	↑,⊙	↑,⊙	⊙			↓,↑,⊙	⊙	
	Bendamustine	⊙									⊙
	Procarbazine*										
	Chlorambucil*										
	Dacarbazine	⊙									
Anthracyclines	Doxorubicin		↓				↓,⊙		↓,⊙		↓,↑,⊙
	Daunorubicin	↓							↑,↓		↓,↑,⊙
Platinums	Cisplatin		↓		↓						⊙
	Carboplatin*										
	Oxaliplatin	⊙									
Antimetabolites	5-Fluorouracil*										
	Gemcitabine										⊙
	6-Mercaptopurine*										
	Fludarabine Phosphate*										
	Hydroxyurea*										
	Asparaginase*										
	Tioguanine	↓				↓					
	Methotrexate*										
	Capecitabine				↓						
	Cytarabine								⊙		
Taxanes	Docetaxel								↓,⊙	⊙	⊙
	Paclitaxel			⊙	⊙				↓,↑,⊙	⊙	↓,⊙
Vinca Alkaloids	Vinblastine						↓,⊙		↓,⊙		↓,↑,⊙
	Vinorelabine						↓,⊙	↓,⊙			↓
	Vincristine								↓,⊙	⊙	↓,↑,⊙
Topoisomerase Inhibitors	Irinotecan		⊙						↓,⊙	⊙	
	Etoposide	⊙		↓					↓,↑,⊙	↑,⊙	↓,⊙
Hormonal Therapies	Bicalutamide					↓			↓		
	Anastrozole	↓			↓				↓		
	Tamoxifen	⊙	↓,⊙	↓	↓,⊙	⊙	↓,⊙		↓,↑,⊙	⊙	↓,↑,⊙
	Leuprolide Acetate*										
Tyrosine kinase Inhibitors	Nilotinib	↓				↓			↓,⊙		↓
	Dasatinib	⊙							⊙	⊙	↓,⊙
	Imatinib mesylate	⊙			↓,⊙	⊙	↓,⊙		↓,⊙	↓,⊙	↓,⊙
Monoclonal Antibodies	Trastuzumab*										
	Rituximab*										
Anti-tumor Antibiotics	Bleomycin*										
	Dactinomycin								⊙		⊙
Other	All-Trans Retinoid Acid*										
	Zolendronic Acid*										

*No known CYP450 or ABCB1 interactions based on available data.
ǂMarketed with a booster.
⊡No direct antiretroviral activity.
⊙Substrate
↑Inducer
↓Inhibitor
NNRTIs: non-nucleoside reverse-transcriptase inhibitors; INSTIs: integrase strand transfer inhibitors; PIs: protease Inhibitors; FIs: fusion Inhibitors; CRAs: chemokine receptor antagonists; NRTIs: nucleoside/nucleotide reverse transcriptase inhibitors; PKE: pharmacokinetic enhancer.

tions. INSTIs have minimal activity with CYP450 metabolism; dolutegravir is a weak CYP3A4 substrate while elvitegravir is a strong inhibitor of CYP3A4, demonstrating that ARVs must be assessed independently as there is significant variation in metabolic interactions within the same class. Dolutegravir has no contraindications to concomitant treatment with any of the ARV or anticancer drugs studied. It shows four interactions with other ARVs; namely, NNRTIs efavirenz, etravirine and nevirapine, and PI fosamprenavir, and three interactions with anticancer drugs; namely, paclitaxel, vinblastine, and oxaliplatin. NNRTIs, PIs, and maraviroc have a predicted higher propensity for DDIs than FIs and NRTIs (Table 3). This susceptibility of NNRTIs and PIs for DDIs warrants careful supervision with dose adjustments and careful monitoring if coadministered in cART therapy, and/or when used in combination with anticancer drugs as outlined in Table 4. The drugs tipranavir and cobicistat have substantial interactions with several of the other ARV drugs (Table 3) and warrant close monitoring when prescribed in combination with some commonly used anticancer drugs, such as paclitaxel, vincristine, and cisplatin (Table 4). The extensive DDIs of NNRTIs/PIs, the intrinsic resistance of HIV-2 to most NNRTIs, and the low genetic barrier to resistance, significantly limits administering more than one NNRTI drug, as shown in table 3[32]. It is important to note that coadministration of multiple CYP450 active drugs may augment or reduce each respective drugs interactions, this renders combined drug regimens (FDC), which are in widespread use, *in vivo* pharmacokinetics difficult to predict on a patient level.

Most traditional anticancer drugs have narrow therapeutic indices and minor changes in their doses

Table 3. Antiretroviral drugs potential interactions with concomitant antiretroviral drugs

Drug Class	Anti-Retroviral Drugs	Abacavir	Didanosine	Emtricitabine	Lamivudine	Stavudine	Tenofovir DF	Zidovudine	Efavirenz	Etravirine	Nevirapine	Rilpivirine	Delavirdine	Atazanavir	Fosamprenavir	Indinavir	Lopinavir	Ritonavir	Saquinavir	Darunavir	Nelfinavir	Tipranavir	Raltegravir	Dolutegravir	Elvitegravir	Enfuvirtide	Cobicistat	Maraviroc
NRTIs	Abacavir																											
	Didanosine	◆																										
	Emtricitabine	◆	◆																									
	Lamivudine	◆	◆	X																								
	Stavudine	◆	X	◆	◆																							
	Tenofovir DF	◆	X	◆	◆	◆																						
	Zidovudine	◆	◆	◆	◆	X	◆																					
NNRTIs	Efavirenz	◆	◆	◆	◆	◆	◆	◆																				
	Etravirine	◆	◆	◆	◆	◆	◆	◆	X																			
	Nevirapine	◆	◆	◆	◆	◆	◆	◆	X	X																		
	Rilpivirine	◆	◆	◆	◆	◆	◆	◆	X	X	X																	
	Delavirdine	◆	◆	◆	◆	◆	◆	◆	X	X	◆	X																
PIs	Atazanavir	◆	◆	◆	◆	◆	X	◆	X	X	X	◆	◆															
	Fosamprenavir	◆	◆	◆	◆	◆	◆	◆	◆	X	◆	◆	X	◆														
	Indinavir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	X	◆													
	Lopinavir	❍	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆												
	Ritonavir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆											
	Saquinavir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	X	◆	◆	X	◆										
	Darunavir	❍	◆	◆	◆	◆	❍	❍	◆	◆	◆	❍	◆	◆	◆	◆	X	◆	X									
	Nelfinavir	❍	◆	◆	◆	◆	◆	❍	❍	❍	❍	❍	◆	◆	◆	◆	◆	◆	◆	◆								
	Tipranavir	X	◆	◆	◆	◆	◆	X	◆	X	◆	X	◆	X	X	X	X	◆	X	X	X								
INSTIs	Raltegravir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	❍	◆	◆	◆	◆	◆	◆	◆	◆						
	Dolutegravir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆						
	Elvitegravir	◆	◆	◆	◆	◆	◆	◆	X	❍	X	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆				
FIs	Enfuvirtide	◆	◆	◆	◆	◆	❍	◆	◆	◆	◆	◆	◆	❍	❍	❍	❍	❍	❍	❍	❍	❍	◆	◆	◆			
PKE	Cobicistat	◆	◆	◆	◆	◆	◆	◆	❍	❍	◆	❍	◆	◆	X	◆	◆	X	X	◆	◆	X	◆	◆	◆	◆		
CRAs	Maraviroc	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	❍	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	

◆ Light diamond: no known potential interactions.
◆ Dark diamond: potential interactions; monitor closely, dose adjust and/or consider alternate therapy.
❍ Circle: potential weak interactions; monitor therapy.
X Cross: contraindications to concomitant therapy.

can either result in sub-therapeutic effect or overdosing leading to adverse events[10,39,46]. Supplementary Table 3 lists interactions between CTDs and ARVs. Many CTDs are metabolized by the CYP450 pathway in the liver[16,47]. At the same time, antimetabolite agents (5-FU, 6-MP, and cytarabine), and platinum agents (carboplatin, and oxaliplatin) undergo non-CYP450 routes of elimination and are unlikely to be altered by coadministration with ART (Table 4)[10,48]. The antitumor antibiotics (bleomycin, and dactinomycin), monoclonal antibodies, and the anti-androgens (bicalutamide, and leuprolide acetate) did not show any interactions with ARV drugs (Table 4).

The prevalence of ADCs in SSA is significantly higher than those seen in developed countries[1]. GLOBOCAN data estimated cancer incidence in SSA as 3.6, 4.6, and 31.7/100,00 population/year for KS, NHL, and cervical cancer, respectively[49]. Anticancer drugs used in the treatment of ADC varies in SSA due to resource constraints[1]. NCCN Framework for Resource Stratification of NCCN Guidelines tailors' guidelines to the available resources, stratifying recommendations by basic, core, and enhanced resources[50]. For AIDS related NHL in basic resource settings the first-line treatment is cyclophosphamide, doxorubicin, vincristine, and prednisone with anti-CD20 monoclonal antibody if available. As shown in table 4, dolutegravir combined with NNRTIs, such as abacavir and lamivudine, does not show any significant DDIs with the NCCN recommended therapy for NHL[50].

A similar interaction profile with ARVs was observed for taxanes and topoisomerase inhibitor drug classes. Paclitaxel is a commonly used drug for KS and other cancers in SSA, though primarily metabolized by CYP2C8, it has interactions with CYP3A4[51,52]. Therefore,

Table 4. Anti-cancer and antiretroviral drug-drug interactions

Drug class	Anti-Cancer Agents	Abacavir	Didanosine	Emtricitabine	Lamivudine	Stavudine	Tenofovir DF	Zidovudine	Efavirenz	Etravirine	Nevirapine	Delavirdine	Rilpivirine	Atazanavir	Fosamprenavir	Indinavir	Lopinavir	Ritonavir	Saquinavir	Darunavir	Nelfinavir	Tipranavir	Raltegravir	Elvitegravir	Dolutegravir	Enfuvirtide	Cobistat	Maraviroc
Alkylating Agents	Cyclophosphamide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	○	◆	◆	◆	◆	◆	◆	◆
	Ifosfamide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	○	◆	◆	◆	◆	◆	○	◆
	Chlorambucil	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Dacarbazine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Bendamustine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Procarbazine	◆	◆	◆	◆	◆	◆	◆	○	◆	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Anthracyclines	Doxorubicin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Daunorubicin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	◆	◆	◆	◆	X	◆	◆	◆	◆	◆	◆	◆	◆	◆
Platinum	Cisplatin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Carboplatin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Oxaliplatin	◆	◆	◆	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Antimetabolites	5-Fluorouracil	○	○	○	○	○	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Gemcitabine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	6-Mercaptopurine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Fludarabine Phosphate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Cytarabine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Hydroxyurea	◆	X	◆	◆	X	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Methotrexate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Capecitabine	○	○	○	○	○	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Asparaginase	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Tioguanine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Taxanes	Docetaxel	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Paclitaxel	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Vinca Alkaloids	Vinblastine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Vinorelabine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○	○	○	○	○	◆	◆	◆	◆	◆	○	◆
	Vincristine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Topoisomerase Inhibitors	Irinotecan	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	X	◆	◆	◆	◆	◆	X	X	◆	◆	◆	◆	◆	X	◆
	Etoposide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Hormonal Therapies	Tamoxifen	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Bicalutamide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Leuprolide acetate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Anastrozole	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	○	○	○	○	◆	◆	○	◆	◆	◆	◆	◆	◆
Anti-Tumor Antibiotic	Dactinomycin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Bleomycin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Tyrosine kinase inhibitors	Nilotinib	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	◆	◆	◆	◆	X	◆	◆	◆	◆	◆	◆	◆	◆	○
	Dasatinib	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	◆	◆	◆	◆	X	◆	◆	◆	◆	◆	◆	◆	◆	○
	Imatinib mesylate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	○	◆	◆	◆	◆	◆	○	◆
Other	All-Trans Retinoid Acid	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	◆	◆	◆
	Zolendronic Acid	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Monoclonal Antibodies	Trastuzumab	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Rituximab	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

◆ Light diamond: no known potential interactions.
◆ Dark diamond: potential interactions; monitor closely, dose adjust and/or consider alternate therapy.
○ Circle: potential weak interactions; monitor therapy.
X Cross: contraindications to concomitant therapy.

DDIs can occur when paclitaxel is administered with ARV drugs that are CYP3A4 inhibitors or inducers. It has interactions with 17 of the 21 ARVs studied, as shown in Table 4, warranting close monitoring of therapy with potential need for dose adjustment.

Platinum agents form the backbone of treatment in a wide variety of malignancies, including cervical and anal cancer, and have mild to moderate CYP450 interactions. Table 4 demonstrates that cisplatin in particular has multiple DDIs, predominantly with NRTIs and PIs. Of particular note is cisplatin's interaction with the WHO recommended two first-line NRTIs, emtricitabine and tenofovir, primarily due to renal clearance interactions which are an important clinical consideration but beyond the scope of this study.

Dolutegravir based cART, combined with NNRTIs such as abacavir and lamivudine, did not show any significant DDIs with the NCCN recommended first-line systemic treatment for NHL, cervical cancer, or KS[50]. However, this is based on limited evidence, with little to no pharmacokinetic studies in humans, and does not account for other potential mechanisms of interaction, such as overlapping toxicities. We therefore recommend clinicians assess the choice of ARV and anticancer drug on a patient by patient basis using up to date drug interaction tools as previously described[33].

Discussion

Concomitant administration of ARV and anticancer drugs can lead to a number of complex DDIs in HIV positive patients with cancer that can complicate therapy. Interactions of ARV drugs with the CYP450 enzymes have been well-documented in the literature[20,24,28,30,45,53]. Among ARVs, almost all PIs and NNRTIs, are known to be metabolized by CYP3A4 and hence are prone to cause DDIs (Table 2A). Furthermore, these drugs can also interact through other mechanisms, including drug

transporters, glucuronidation, and pH-dependent drug absorption[14,15]. Other clinical considerations are overlapping toxicities, such as myelosuppression with zidovudine and cytotoxic chemotherapy drugs, pancreatitis with didanosine and asparaginase, peripheral neuropathy with didanosine or stavudine, and taxanes/platinums/vinca-alkaloids or cardiac QT interval prolongation with dasatinib and lopinavir[10].

The management and identification of DDIs constitute one of the major challenges in optimizing concomitant cancer and HIV treatment[10,25,54]. It requires a thorough understanding of the different CYP450 isozymes and drug transporters to predict and prevent clinically relevant drug interactions based on the known metabolic fate of the drugs (Tables 2A and B). This article was written to summarize much of the known data, in part as an aid to physicians caring for these patients. Further complicating matters, however, are unanticipated variation in drug metabolism from such factors as genetic factors, additional medications that patients may be taking, herbal or nontraditional medications, and food intake. To date, there has been discussion on the need to identify the impact of pharmacogenetic polymorphisms on these DDIs[14,18,55]. Further understanding of genetic variability will be an invaluable addition to improving rational drug prescribing[18,55]. This is not likely to be easily and cheaply available in SSA in the near future. There must also be an awareness of the use of over-the-counter medication and herbal remedies, as we aim to improve management of prescribed polypharmacy the addition of these unstudied agents further increases the risk of DDIs[21,56,57]. A number of herbal medicines have been found to interact significantly with ARVs[21]. The use of traditional and alternative medicines is widespread; the specifics of use however are limited due to sparse published reports and reviews[58]. One study in Ghana found 59% of patients on active cancer treatment used complementary or alternative medications and only 83% notified their doctor of these additional medications[56]. Traditional and alternative medicine use poses a potentially significant issue and deserves more prospective analysis. Fragmented health-care systems and inadequate human resources pose challenges for adequate “risk-benefit” assessments and documentation of drug prescriptions by clinicians[1,59]. In addition, FDCs can further hinder management by limiting capacity for dose-modification[53]. A great resource for physicians treating patients with HIV and cancer is the free and regularly updated webpage “HIV Drug Interactions Checker”[33]. This website allows users to quickly and efficiently check on known and potential interactions. In addition, the user can look for drug substitutes that may not interact.

Clinically, significant DDIs have been reported as affecting 20%-41% patients in the developed countries; however, data from developing countries are limited[53]. In SSA, patients often present late, with acute opportunistic infections, such as TB, and other AIDS-associated conditions, and require additional medications for supportive care and comorbid disease management, thus increasing the potential for clinically significant drug-interactions[1,53]. Moreover, drug resistance particularly to NNRTIs is rising in Africa; the prevalence of NNRTI resistance was > 10% in 75% of countries reporting data to WHO, with pretreatment HIV drug resistance to NNRTIs ranging from 8.1% in Cameroon to 15.4% in Uganda[36].

Comorbid conditions can be exacerbated by, and exacerbate, adverse drug effects. The burden of noncommunicable diseases is on the rise in SSA[60]. Many of these diseases are complicated by adverse effects of ARV and anticancer therapies. For example, chronic kidney disease is increasingly becoming a public health concern in SSA[61]. Adverse effects of ARV therapy on kidneys is a well-known complication[62,63]. Many anticancer agents are also known to cause acute kidney injury[64], and impaired renal clearance can significantly enhance the risk of DDIs[65].

Major DDIs are well described between several antituberculosis and ARV drugs; predominantly through CYP3A4 and ABCB1 pharmacokinetic interactions[66]. For example, rifampicin reduces dolutegravir exposure by 54%, which can be overcome by increasing the dolutegravir dose from 50 mg daily to 50 mg twice daily, the data for appropriately managing a patient who additionally requires paclitaxel for KS treatment is utterly lacking[66]. Moreover, physicians usually have limited or no capacity to assess these interactions through measurement of drug levels, or assessment of pharmacogenetic variations affecting metabolism[20].

Most traditional anticancer drugs have narrow therapeutic indices and minor changes in their doses can either result in sub-therapeutic effect or overdosing leading to adverse events[10,39]. At present, there is limited guidance on the combination of drug therapy for cancer and HIV[10]. This is partly because patients with HIV are usually excluded from early clinical trials to avoid potential drug interactions. Clinical guidance on how to safely and effectively administer cART and anticancer drugs is relatively sparse[10,25,54,]. A rethinking of this issue has been initiated at the U.S. National Cancer Institute (NCI)[67]. In 2008, the Cancer Therapy Evaluation Program of the NCI began an initiative to

include HIV-positive patients in clinical cancer trials unless there are compelling reasons to exclude these populations. Furthermore, the NCI-funded AIDS Malignancy Consortium is investigating such interactions in cancer drugs being developed. The results from these clinical trials will be a steppingstone to enhancing clinical decision-making capacity for dose modification to safely treat HIV-positive patients with cancer.

While this paper summarizes the main known interactions in a user-friendly way, it became quite evident that information on such interactions was sparse and difficult to find. In part for this reason, we chose to focus on drugs from the WHO Essential Medicines (EML) that are recommended as the most effective and safe to treat diseases and most cost-effective options for key public health problems. While the study was written with an eye to SSA, the information may also be of use to physicians in other low- and middle-income countries developing countries and also in resource-rich regions. This said, in surveying the literature for this study, it became apparent that there were substantial gaps in our knowledge, and this study also serves to highlight a need for additional research to better define these interactions and make the information available to physicians. As persons with HIV live longer and develop a wide variety of ADC, NADC, and incidental tumors, information about such interactions will become increasingly important to guide optimal therapy. These results also suggest that cancer prevention strategies are urgently warranted in this population, such as the reduction in liver cancer resulting from proactive treatment of hepatitis[68] and reduction in cervical cancer from HPV vaccination and effective cervical screening programs[69]. As we progress toward achieving the ambitious UNAID 90-90-90 target, we recognize that such strategies can reduce the number of patients impacted by the co-occurrence of HIV and cancer, and thus the treatment associated DDIs.

Conclusion

The impact of combined chemotherapy and cART for HIV-positive patients with cancer on a patient's survival, treatment tolerance, adherence, and development of drug resistance needs to be urgently evaluated. More safety, pharmacokinetic, and pharmacogenomic studies are needed in this area. While real challenges in health-care delivery exist in resource-limited settings, safe and effective cancer care can and must be provided in this context[1]. Attention to the prevalence of DDIs is a relatively simple and potentially cost-effective intervention that could lead to optimizing disease treatment, reducing drug resistance, and increasing drug adherence. Approaches to minimizing DDIs between ART and cancer therapy will be particularly valuable in resource-limited settings, which bear the largest burden of HIV-associated cancers.

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Conflicts of interest

Robert Yarchoan[6] is a coinventor on a patent involving the treatment of HIV with lamivudine or emtricitabine and a peptide vaccine. All rights, title, and interest to this patent have been assigned to the U.S. Department of Health and Human Services. The government conveys a portion of the royalties it receives to its employee inventors under the Federal Technology Transfer Act of 1986 (P.L. 99-502).

Supplementary data

Supplementary data are available at AIDS Reviews online (http://www.aidsreviews.com/). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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