Drug interactions between HIV-associated lymphoma treatment and antiretroviral therapy

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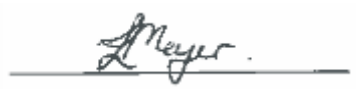
I, Lana Meyer, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's degree qualification MMed at the University of the Free State is my independent work, and I have not previously submitted it for a qualification at another institution of higher education.



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Contents

Abstract

Despite the large-scale roll-out of ART in the mid-1990s, HIV and HIV-associated diseases remain a major health problem in South Africa. HIV-associated lymphoma contributes significantly to the morbidity and mortality of the HIV-positive population. The majority of HIV-associated lymphomas are diffuse large B cell lymphomas (DLBCL), which have been reported to occur 60 to 200 times more commonly in patients with HIV than in the general population.

Drug interactions are inevitable when treating HIV-associated lymphoma and can alter the efficacy of treatment and ultimately patient outcomes. Therapeutic questions have been raised pertaining to the need to find a balance between the administration of effective cytotoxic treatment and the effect it has on immune function. Complications such as infections and chemotherapeutic toxicity can occur. Dosing schedules may need to be adapted and certain combinations may be prohibited.

The aim of this study was to conduct a critical overview of drug interactions between antiretroviral therapy used in the treatment of HIV and antineoplastic drugs used in the treatment of HIV-associated lymphoma. The purpose was to develop a quick reference tool to serve as a guide for clinicians to assist in identifying important drug interactions.

Known drug interactions between 19 antiretroviral drugs and 13 antineoplastic agents used in the treatment of HIV and HIV-associated lymphoma respectively were investigated. Standard antiretroviral therapy (ART) regimens proposed by the national protocol were compared to drugs used in the following antineoplastic regimens: ABVD, CODOX-M-IVAC, CALGB9251, hyper-CVAD, dose adjusted R-EPOCH and R-CHOP. Data were obtained during March and April 2019 from three different internet-based drug interaction checkers, namely Medscape Drug Interaction Checker (https://reference.medscape.com/drug-interactionchecker), Lexicomp Online (https://www.wolterskluwercdi.com/lexicomp-online/) and RxList (https://www.rxlist.com/drug-interaction-checker.htm). Interactions were classified as not clinically significant, no interaction,

decreased or increased effect, contraindicated, increased toxicity, increased toxicity of both drugs due to synergism and loss of virological response.

In total, 117 drug interactions were identified, of which 105 were deemed clinically significant. No interactions were found when the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine, abacavir and emtricitabine were used. The integrase inhibitors raltegravir and dolutegravir and the fusion inhibitor enfuvirtide also had no documented drug interactions. Chemotherapeutic agents that were found to have no significant drug reactions include cytarabine, rituximab and dacarbazine.

Important drug interactions between the non- nucleoside reverse transcriptase inhibitors (NNRTIs) tenofovir and zidovudine and antineoplastic drugs were noted. Toxicity of tenofovir may be increased with concomitant use of bleomycin and ifosfomide. Caution must be taken when using zidovudine in combination with methotrexate, ifosfamide, vincristine and vinblastine, as the toxicity of both drugs is increased when used in combination.

Efavirenz, a NNRTI, was found to have many interactions with antineoplastic drugs, the most significant being decreased levels of doxorubicin. Many drug interactions were noted between protease inhibitors and antineoplastic drugs. Anthracycline-associated cardiomyopathy may be induced when used concurrently with protease inhibitors.

In general, rilpivirine is known to have a good side-effect profile. However, it must be noted that when combined with dexamethasone, this combination may lead to a loss of virologic response. Other significant interactions with drugs not included as standard ART is discussed in the article.

Tailoring drug therapy according to individuals' specific requirements and proper medication reconciliation is critical when treating patients with HIV-associated lymphomas. Clinicians need to be aware of important interactions between antiretroviral therapy and antineoplastic drugs. Therapeutic monitoring and close interaction between role-players in the management of these

patients is crucial. Communication between the clinic issuing the antiretroviral therapy, the attending haematologist or oncologist and the patient is vital to continuity of care. A quick referencing tool was developed as a guide to clinicians involved in the treatment of HIV-associated lymphoma.

Keywords:

ART, HIV-associated lymphoma, chemotherapy, drug interactions, treatment regimens

List of abbreviations

3TC	lamivudine
ABC	abacavir
ABVD	doxorubicin, bleomycin, vinblastine and dacarbazine
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphoblastic leukemia
ART	antiretroviral therapy
ARV	antiretroviral (agent)
ATV	atazanavir
AZT	zidovudine
BL	Burkitt lymphoma
CALGB9251	cyclophosphamide and prednisone followed by ifosfamide/ cyclophosphamide, methotrexate, vincristine, dexamethasone, doxorubicin/etoposide/cytarabine and triple intrathecal chemotherapy consisting of methotrexate, cytarabine and hydrocortisone
cART	combination antiretroviral therapy
CHOP	cyclophosphamide, hydroxydaunomycin, oncovin (vincristine), and prednisone
CODOX-M-ICVAC	cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, cytarabine etoposide and intrathecal methotrexate
d4T	stavudine
DDI	didanosine
DLBCL	diffuse large B cell lymphoma
DRV	darunavir
EBV	Epstein-Barr virus
EFV	efavirenz
ETR	etravirine
FTC	emtricitabine

HAART	highly active antiretroviral therapy
HHV	human herpes virus
HIV	human immunodeficiency virus
Hyper-CVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone with or without rituximab, alternating with high dose methotrexate and cytarabine
INSTI	integrase strand transfer inhibitor
IVAC	ifosfamide, cytarabine, etoposide, intrathecal methotrexate
LPV/R	lopinavir/ritonavir
MOPP	mechlorethamine, vincristine, procarbazine and prednisone
MTX	methotrexate
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
PCNSL	primary central nervous system lymphoma
PEL	primary effusion lymphoma
PI	protease inhibitor
R-CHOP	rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone
R-EPOCH	rituximab, etoposide, vincristine, doxorubicin, prednisone, cyclophosphamide
RPV	rilpivirine
SQV	saquinavir
TDF	tenofovir

Chapter 1: Literature review

1. Introduction

In addition to human immunodeficiency virus (HIV) infection itself, HIV-associated lymphoma remains a considerable burden to these patients and contributes significantly to morbidity and mortality in HIV-positive patients. The spectrum of illnesses associated with HIV are related to the direct effects of the virus on the host immune system, opportunistic infections prevalent in immunodeficiency, co-infections associated with HIV and complications related to antiretroviral therapy.[1] The most common HIV-associated lymphomas are diffuse large B-cell lymphomas (DLBCL), which include primary central nervous system lymphoma (PCNSL) and Burkitt lymphoma (BL). Classic Hodgkin lymphoma, primary effusion lymphoma (PEL) and plasmablastic lymphoma occur at a much lower incidence rate.[2] Approximately 70–90% of lymphomas occurring in the HIV-positive population are clinically suggestive of DLBCLs or highly aggressive Burkitt-like lymphomas.[3] Up to 80% of these patients have stage IV disease at the time of presentation, most commonly with extra-nodal sites involving the gastrointestinal tract, liver, lung, bone marrow and central nervous system.[4] The degree of immunosuppression, as measured by a patient's CD4 count, correlates with their risk of developing AIDS-defining cancers.[5] Chronic antigen stimulation in HIV has been indicated to promote the emergence of monoclonal B cells.[2]

Furthermore, oncogenic viruses, such as Ebstein-Barr virus (EBV), have been found in 40% of patients with HIV-associated lymphoma.[2] In the general population, between 20% and 50% of Hodgkin disease is caused by EBV. This percentage increases to between 75% and 100% in patients with HIV, demonstrating increased oncogenic virus activity in the immunosuppressed patient.[6] Human herpesvirus-8 (HHV-8) also occurs commonly in the HIV-positive population. This virus is associated with cytokine and chemokine dysregulation, which may play a permissive role in the development of lymphoma. Genetic abnormalities such as activation of the MYC gene and BCL6 mutations, have also been reported in HIV-associated lymphoma.[2]

2. The use of combined ART and chemotherapy

Therapeutic controversy exists when it comes to finding a balance between administering immunosuppressive and potentially toxic chemotherapy and antiretroviral agents (ARVs). Although drug interactions leading to potentially toxic side-effects are a serious risk in the treatment of HIV-associated lymphoma, it is believed that uncontrolled viral replication during the time of chemotherapy in a patient in whom ART is withheld, will adversely affect immune function.[2] It has been shown that continuing highly active antiretroviral therapy (HAART) during

chemotherapy is safe in patients with HIV-associated lymphoma.[4] A study by Coutinho et al.[7] included 305 patients, of whom 93 were HIV-positive, diagnosed with DLBCL and treated with rituximab, cyclophosphamide, doxorubicin vincristine and prednisone (CHOP). It was found that the patients in the HIV-positive group had significantly longer disease-free survival (five-year survival 94% versus 77%; p=0.03) and overall survival (78% and 64% for HIV-positive and negative patients, respectively; p=0.03). It was concluded that that HIV-positive patients in the era of combination antiretroviral therapy (cART) have good outcomes when treated with standard chemotherapy, and that the choice of chemotherapy for lymphoma does not have to be influenced by a patient's HIV status.[7]

Reduction in the intensity of chemotherapy is often undesirable due to the aggressive nature of HIV-associated lymphomas. Patients with adequate immune function due to ART have a decreased risk of developing treatment-related infectious complications, which allows for optimal chemotherapy usage[6]. Boué et al.[8] determined that rituximab in combination with CHOP produced a two-year survival rate in patients with AIDS-related non-Hodgkin lymphoma, without increasing their risk of life-threatening infections.[8] Patients with intact immunity also have more favourable tumour biology.[2]

The underlying mechanisms of drug interactions are mediated via pharmacodynamic or pharmacokinetic effects. Pharmacodynamic interactions occur when a drug interferes with the absorption, distribution, metabolism or excretion of another drug. Pharmacokinetics refer to the relationship between drug concentrations at the site of action and the resulting effect, including the time course and the intensity of therapeutic and adverse effects.[9]

3. Antiretroviral therapy

Currently, five classes of ART are available for the treatment of HIV in South Africa and include nucleoside reverse transcriptase inhibitors (NRTIs), non- nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors and the entry inhibitors.[10]

3.1. Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs are analogues of DNA nucleotides. The HIV reverse transcriptase enzyme cannot distinguish between host DNA and the nucleotide analogues. By incorporating the analogue into the DNA chain, DNA synthesis is terminated, resulting in non-functional DNA. NRTIs require intracellular phosphorylation. They lack activity against free extracellular virus and have a slow onset of action.[11] NRTIs form the backbone of first-line ART and treatment with a combination of two drugs from this class is current standard care. The preferred combination consists of tenofovir (TDF) and either emtricitabine (FTC) or lamivudine (3TC).[10] NRTIs can all be administered orally

and cross the blood-brain barrier. This class of drugs is eliminated primarily by renal excretion.[12] The NRTIs available in South Africa are tenofovir (TDF), lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), zidovudine (AZT), stavudine (d4T) and didanosine (DDI).[10]

3.2. Non-nucleoside reverse transcriptase inhibitors (NRTIs)

NNRTIs are a structurally diverse group of compounds that bind to the reverse transcriptase molecule, thereby inactivating it.[11] NNRTIs are rapidly absorbed after oral administration and are directed against activity of the cell-associated and free HIV virions. These drugs are suitable for daily dosing due to their long half-life. NNRTIs are administered orally with good bioavailability and are extensively metabolised before undergoing renal and faecal excretion.[12] The NNRTIs available in South Africa include efavirenz (EFV), nevirapine (NVP), rilpivirine (RPV) and etravirine (ETR).[10]

3.3. Protease inhibitors (PI)

Protease inhibitors (PI) are substrate analogues for the HIV aspartyl protease enzyme involved in the processing of viral proteins. Once bound to the enzyme active site, the enzyme is blocked from further activity and inhibits the viral maturation process, leading to decreased functional virion formation. PIs are metabolised by cytochrome P450 enzymes before undergoing faecal excretion.[12] The PIs available in South Africa are atazanavir (ATV), lopinavir/ritonavir (LPV/r), darunavir (DRV) and saquinavir (SQV), although the latter is rarely used.[10]

3.4. Integrase inhibitors

Integrase inhibitors are a newer class of drug that targets the HIV enzyme integrase. This enzyme is responsible for integrating viral genetic material into the host DNA. Raltegravir is not metabolised by cytochrome P450, but primarily by hepatic glucuronidation encoded by the *UGT1A1* gene. It is excreted partly unchanged in both urine and faeces.[13] Raltegravir was the first approved integrase inhibitor, targeting the strand transfer step of HIV integration. Regimens containing raltegravir have potent antiviral effects and were found to be superior to optimised background regimens for patients with resistance. In patients who were treatment-naïve, raltegravir showed non-inferiority to efavirenz when administered with TDF and 3TC/FDC. As raltegravir is metabolised by glucuronidation and not hepatically, the risk for drug interactions is decreased. Drug resistance develops relatively frequently after virological failure by the mechanism of substitution of gene coding for the HIV-1 integrase enzyme.[14]

Dolutegravir is a second-generation integrase strand transfer inhibitor (INSTI) that has been found to induce more rapid and sustained virological suppression than a combination of efavirenz and raltegravir. It has been shown to be superior to efavirenz-based ART in the SINGLE (study 114467) trial.[10] It also has a higher barrier to resistance[15] and has been shown to retain activity in a number of INSTI-resistant phenotypes of HIV-1. Dolutegravir is well tolerated and has a modest drug interaction profile. However, caution should be taken when co-administering this agent with antacids as they significantly decrease dolutegravir exposure. Dolutegravir metabolises via uridine diphosphate glucuronosyltransferase 1A1 and cytochrome P450 (CYP)3A4, neither inhibiting or inducing CYP isoenzymes.[16] In the South African guidelines, dolutegravir is included as part of the initial ART regimen for previously untreated patients. Both of the integrase inhibitors are included in second- and third-line regimes.[10]

3.5. Entry inhibitors

Entry inhibitors interfere with receptor-mediated entry of HIV into the host cell. Two subclasses have been developed, namely fusion inhibitors and CCR5 antagonists.[10] Enfuvirtide is a fusion inhibitor that mimics the structure of the HR2 region of glycoprotein 41 (gp41). Gp41 is a glycoprotein of the HIV envelope that is used by the virus to fuse the viral envelope with the host cell membrane. Enfuvirtide is used as a subcutaneous injection and is catabolised via peptidases in the liver and kidneys. It is renally cleared.[17]

Maraviroc is a C-C motif chemokine receptor type 5 (CCR5) antagonist. It binds to the external part of the CCR5 transmembrane receptor that serves as a co-receptor for viral entry into host cells. Binding of this inhibitor prevents HIV gp120 from access to the co-receptor, thereby preventing the fusion process.[18] Maraviroc is metabolised via CYP3A to inactive metabolites in the liver. The unchanged drug is excreted in urine and faeces.[17] Maraviroc has been found to have an excellent safety profile,[19] and can be considered in third-line therapy but its use is limited by cost at this stage. It can also only be used after tropism testing has proven that the patient's virus has sole tropism for the CCR5 receptor.[10]

4. Antineoplastic agents

Antineoplastic agents encompass a wide variety of drug classes. A number of different regimens are available for the treatment of HIV-associated lymphoma. The treatment regimens presented below are in common use for the treatment of HIV-associated lymphoma.

4.1. ABVD

ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) is the preferred therapy for most patients with advanced HL.[20] In a study by Canellos et al.,[20] ABVD for 6 to 8 months was found to be as effective as MOPP (mechlorethamine, vincristine, procarbazine and prednisone) alternating with ABVD or MOPP alone. It has been reported to be less myelotoxic that the other two regimens studied.[21]

4.2. CODOX-M-IVAC

CODOX-M-IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, cytarabine etoposide and intrathecal methotrexate), also referred to as the Magrath regimen, traditionally has been the most frequently used chemotherapy for Burkitt lymphoma.[22] Results from a phase II study conducted by Mead et al.,[23] where low-risk patients were treated with modified CODOX-M and high-risk patients received treatment with alternating CODOX-M and IVAC, showed an overall two-year event-free survival of 64.6% (95%CI 50.4% to 78.9%) and two-year overall survival was 72.8% (95%CI 59.4% to 83.3%). For the high-risk group, the two-year event-free and overall survival was 59.5% and 69.9%, respectively. This study confirmed the high cure rate of CODOX-M-IVAC.[23]

4.3. CALGB9251

CALGB9251 (cyclophosphamide and prednisone followed by ifosfamide/cyclophosphamide, methotrexate, vincristine, dexamethasone, doxorubicin/etoposide/cytarabine and triple intrathecal chemotherapy consisting of methotrexate, cytarabine and hydrocortisone) was developed by the Cancer and Leukemia Group B (study 9251) as a six-cycle high intensity treatment regimen for adult B cell acute lymphoblastic leukemia (ALL). It has also been proven to be effective for the treatment of Burkitt lymphoma.[24]

4.4. Hyper-CVAD

Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone with or without rituximab, alternating with high dose methotrexate and cytarabine) has been used successfully for the treatment of BL with a three-year overall survival rate of 49%.[25,26]

4.5. R-EPOCH

Dose-adjusted R-EPOCH (rituximab, etoposide, vincristine, doxorubicin, prednisone, cyclophosphamide) is highly effective in the treatment of BL.[27] This regimen can also be used as an alternative in patients with DLBCL.[28] Dose-adjusted R-EPOCH can be used for plasmablastic lymphoma[29] and PEL.[30] EPOCH is also indicated for the treatment of plasmablastic lymphoma.[31]

4.6. R-CHOP

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) is widely used as the standard therapy for patients with DLBCL.[32] CHOP has also been used in the treatment of PEL.[33]

4.7. Treatment of primary central nervous system lymphoma (PCNSL)

The treatment of PCNSL lymphoma preferably involves high-dose methotrexate combination chemotherapy with the addition of rituximab. PCNSL has one of the worst prognoses of all lymphomas due to its aggressive nature. Systemic high dose methotrexate seems to be the most effective treatment, producing a two-year survival rate of 60–65%.[34]

5. Drug interactions between ART and antineoplastic agents

Drug interactions can, for example, lead to lower steady-state drug concentrations, which poses a particular challenge in infusional regimens.[2] Although it has been widely shown that standard treatment should be given to HIV-infected patients with non-AIDS defining cancers such as Hodgkin lymphoma, concerns do arise when combining ART and chemotherapy. Overlapping toxicities, chemotherapeutic effects on the immune system and drug interactions remain a perturbing matter. Myelosuppression, neuropathies and gastrointestinal side-effects occur with both the use of ART and chemotherapy.[35] Zidovudine can be related to myelosuppression, while neuropathy is known to occur with the use of Didanosine, and stavudine and it is well known that tenofovir and indinavir can be nephrotoxic. All PIs, zidovudine and didanosine have been related to nausea and vomiting. Diarrhoea has been reported with the use of lopinavir. All PIs, NRTIs and NNRTIs pose a risk of hepatotoxicity.[35]

It is well known that many chemotherapeutic agents also have the potential for serious drug toxicity.[2] High-dose methotrexate (MTX), defined as a dose higher than 500 mg/m^2, and is used to treat a range of adult and childhood cancers. Although it is generally used without significant

toxicity, nephrotoxicity due to crystallisation of MTX in the renal tubular lumen may occur. This can lead to treatment delays, reduced renal function and significant morbidity. One of the sequelae of impaired renal clearance is prolonged exposure to toxic concentrations of MTX, which could result in non-renal adverse events, including myelosuppression, mucositis, dermatologic toxicity and hepatotoxicity.[36] Myelosuppression has been found to occur in up to 28% of patients and usually results from delayed MTX excretion secondary to nephrotoxicity.[37]

Myelosuppression and gastrointestinal disturbance are common toxicities when cytarabine is used. Neurotoxicity resulting in myelopathy that may be incompletely irreversible has also been reported in patients receiving intrathecal cytarabine. Intravenous therapy has been associated with peripheral neuropathy, seizures, cerebral dysfunction and an acute cerebellar syndrome with an incidence of up to 14%.[38]

Bleomycin is an effective anti-tumour agent, but should be used with caution as it poses a risk of pulmonary toxicity. Although it has not been found to have important effects on bone marrow, the gastrointestinal tract, renal or hepatic function or the central nervous system, some pulmonary function impairment has been documented. Irreversible pulmonary fibrosis is a rare but fatal complication of bleomycin therapy.[39]

The anthracycline doxorubicin can be associated with severe cardiotoxicity, which could limit its use in the clinical setting.[40]

Infusion-related toxicity, which appears to be cytokine-mediated, has been reported with the use of rituximab. This includes the development of transient hypoxaemia, hypotension and dyspnoea.[41] Haematologic toxicity is the main concern with the use of etoposide.[42]

The most common effects of cyclophosphamide toxicity include haemorrhagic cystitis, immunosuppression and alopecia. In very high doses it can also be cardiotoxic. Cyclophosphamide has also been linked to a potential for the development of bladder malignancy.[43] Renal injury is a well-documented effect of ifosfomide toxicity. It also shares a toxicity profile with cyclophosphamide regarding myelosuppression and urotoxicity. Ifosfamide-related central nervous system toxicity is characterised by encephalopathy.[44] Dacarbazine has been implicated as a toxin causing veno-occlusive disease.[45]

The vinca alkaloids can cause peripheral neuropathy, with vincristine being the drug most commonly implicated. Infrequent neurological complications, such as alterations in mental status and seizures, have also been reported. Neutropenia also limits the use of the vinca alkaloids and is most commonly encountered with the use of vinblastine. Patients can also present with anaemia and thrombocytopaenia. Gastrointestinal side-effects and autonomic dysfunction have also been reported.[46]

Corticosteroid toxicity can lead to many adverse clinical effects, which include, but is not limited to hyperglycaemia, increased risk of infections, gastritis and gastrointestinal bleeding, proximal myopathy, peripheral oedema and psychiatric events. In a retrospective analysis,[47] hospital charts of 59 patients with intracranial malignancy or epidural spinal cord compression were reviewed to determine the frequency of clinically important steroid toxicities. Thirty patients (51%) developed at least one steroid toxicity. Furthermore, eleven patients (19%) required hospitalisation for diagnosis and management of steroid-related complications.[47]

Interactions between ART and chemotherapy that are well known to work through the CYP3A4 enzyme, include enzyme inhibition via the following ART: delavirdine, ritonavir, amprenavir, atazanavir, indinavir, amprenavir, indinavir, lopinavir, nelfinavir and saquinavir. This enzyme is induced by nevirapine and efavirenz, which will influence the use of the chemotherapeutic agents paclitaxel, docetaxel, erlotinib, sunitinib, sorafenib, etoposide, vincristine, vinblastine, vinorelbine and cyclophosphamide. CYP2C9 is inhibited by efavirenz and ritonavir, which will affect treatment with cyclophosphamide. CYP2c19 is inhibited by efavirenz and amprenavir and will interfere with the metabolism of cyclophosphamide, ifosfamide and thalidomide. CYP2B6 is inhibited by efavirenz, nelfinavir and ritonavir and induced by nevirapine. This will influence therapeutic levels of cyclophosphamide and ifosfamide. Ritonavir is an inhibitor of CYP2E1 that is involved in the metabolism of etoposide and dacarbazine.[35,48]

Due to the serious potential for drug interactions and side-effects, clinicians need to use their best judgement when treating patients with HIV and malignancy.[6] This may require drug tailoring in which case-proper medication reconciliation will be of utmost importance. From this perspective, taking proper drug histories, verifying that patients are on the correct doses of appropriate medications and documenting all the changes made to treatment regimens, are of utmost importance. For example, it will be crucial that when an ART regimen is adapted, the patient will carry a document stating the reason why his/her treatment was changed and also contain instructions to the local clinic on how to continue with the patient's treatment in future. Frequently reviewing all prescription, traditional and over-the-counter medications is also vital to prevent possible drug interactions.[49]

6. Aim of the study, methodology and endpoints

This study aimed to investigate the possible drug-drug interactions between standard therapies used for the treatment of HIV-associated lymphoma and the commonly used ARTs in a South African context. The antiretroviral agents included were the NRTIs 3TC, ABC, DDI, d4T, FTC, TDF and AZT. The NNRTIs EFV, NVP, RPV and ETR were included in this study. The PIs ATV, DRV, RTV and LPV/r were included. The integrase inhibitors investigated were RAL and DTG. The CCR5 inhibitor maraviroc and the fusion inhibitor enfuvirtide were included in this study.

The following chemotherapeutic agents were evaluated for possible drug interactions with the abovementioned ARTs: methotrexate and cytarabine (antimetabolites), bleomycin and doxorubicin (cytotoxic antibiotics), rituximab (monoclonal antibody), etoposide (topoisomerase II inhibitor), cyclophosphamide, ifosfamide and dacarbazine (alkylating agents), vincristine and vinblastine (antimicrotubular agents), prednisone and dexamethasone (corticosteroids).

Drug interactions were identified and graded according to their clinical significance as stated by three internet-based drug interactions checkers (i) Medscape Drug Interaction Checker;[50] (ii) Lexi-Comp Inc. (Lexi-Drugs);[51] and (iii) RxList.[52] The more serious or clinically significant interactions were reported should a discrepancy occur between interaction checkers. The results of this study were documented in table format that was designed to serve as a quick reference tool for a physician working in the field of haematology-oncology, with the intention to be practically applicable.

This study did not test the instrument in actual clinical situations and further research is needed in a clinical setting. Furthermore, the researcher acknowledges the need for a database that is frequently updated as new drugs become available.

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Chapter 2: Journal article

Title

Drug interactions between HIV-associated lymphoma treatment and antiretroviral therapy

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Title

Drug interactions between HIV-associated lymphoma treatment and antiretroviral therapy

Abstract

Background: Drug interactions are inevitable when treating HIV-associated lymphoma in patients on antiretroviral agents (ART). These interactions can alter the efficacy of treatment and ultimately have an impact on patient outcomes. Patients infected with HIV have a 60- to 200-fold increased incidence of HIV-associated lymphomas. Therapeutic questions have been raised pertaining to the need to find a balance between the administration of effective cytotoxic treatment and its effect on immune function. Complications such as infections and chemotherapeutic toxicity may occur. Dosing schedules may need to be adapted and certain combinations may be prohibited.
Objectives: The aim of this study was to conduct a comprehensive overview of the known drug interactions between antiretroviral therapy used in the treatment of HIV, and antineoplastic drugs used in the treatment of HIV-associated lymphoma.
Methods: This descriptive study investigated known drug interactions between 19 antiretroviral drugs commonly used in South Africa and 13 antineoplastic agents commonly used in the treatment of HIV and HIV-associated lymphoma. Data were obtained from the three different databases.
Results: A total of 117 documented drug interactions were found between chemotherapeutic and antiretroviral agents. These interactions ranged from those that are clinically not significant to those that would require contraindication of the concomitant use of certain drugs. The results are presented in table format to serve as a quick reference tool in a clinical setting.
Conclusion: The proposed reference tool on drug interactions between ART and chemotherapeutic agents could aid clinicians in making choices regarding the simultaneous treatment of HIV and HIV-associated lymphoma.

Keywords: antiretroviral treatment; chemotherapeutic agents; ART; drug interactions; HIV-associated lymphoma

Introduction

The human immunodeficiency virus (HIV) belongs to the lentivirus group of the family Retroviridae. The subtype HIV-1 is the most prevalent global strain and HIV-2 primarily occurs in West Africa.[1] Retroviruses produce the enzyme reverse transcriptase that enables viral RNA to transcribe into the host DNA, thus incorporating itself into the host cell genome. The spectrum of illnesses associated with HIV are related to the direct effects of the virus on the host immune system, the co-infections associated with HIV, and the drugs used to treat this infection.[1] Since the advent of antiretroviral therapy (ART) in 1996, HIV has transformed from a progressive illness with a fatal outcome to a manageable chronic disease, with ART aimed at suppressing replication of the virus.[2]

Lymphoma as a complication of HIV carries a significant risk of both morbidity and mortality. Lymphoma occurs frequently in patients with HIV, with HIV-positive patients having a 60- to 200-fold increased incidence of non-Hodgkin lymphoma (NHL), the most common being Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma (PEL) and plasmablastic lymphoma (PL).[2] Although not classically an AIDS-defining malignancy, Hodgkin lymphoma is more prevalent in HIV-infected individuals.[3] HIV infection leads to chronic antigen stimulation, which in turn is suggested to promote the emergence of monoclonal B cells.[2] Oncogenic viruses, such as Epstein-Barr virus (EBV), has been found in 40% of patients with HIV-associated lymphomas, putting these patients at an increased risk of developing malignancy. Human herpesvirus-8 (HHV-8) is also commonly found in HIV-positive patients. Cytokine and chemokine dysregulation is associated with the HHV-8, which may play a permissive role in the development of lymphoma. Genetic abnormalities such as activation of the MYC gene and BCL6 mutations, have also been found in HIV-associated lymphoma.[2]

The advent of combination antiretroviral therapy in the mid-1990s has led to a decreased incidence of HIV-associated lymphomas and improved prognosis in patients diagnosed with such malignancies. This could be ascribed to improved immune function and better control of viral replication of HIV.[2] Effective ART has significantly improved the HIV-related prognostic factors allowing the use of curative chemotherapy in these patients. Patients with adequate immune function due to ART are at a decreased risk of developing treatment-related infectious complications, which allows for optimal chemotherapy usage.[3] It has also been shown that tumour biology is more favorable in patients with intact immunological function. Combination ART has improved the survival rate of patients with HIV-associated DLBCL and Burkitt lymphoma, particularly when used in combination with rituximab.[2] Current ART regimens usually encompass the use of nucleoside reverse transcriptase inhibitors (NRTI), with either non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or an integrase inhibitor.[4] Curability in these cases is similar to the HIV-negative population.[2]

Therapeutic questions have been raised regarding the need to find a balance between the administration of effective cytotoxic treatment and its effect on immune function. The implications of continuing ART during curative chemotherapy for aggressive lymphomas has been debated extensively. Uncontrolled viral replication during chemotherapy may adversely affect immune function, while chemotherapy renders patients at an increased risk of infection-related complications of HIV.[2]

A significant number of drug interactions can be expected due to the large numbers of both potent ART used to treat HIV and chemotherapeutic agents used to treat HIV-associated lymphoma. Drug interactions occur when one drug alters the pharmacological effect of another drug.[5] Such an interaction may result from pharmacokinetic interactions (absorption, distribution, metabolism and excretion) or from interactions at pharmacodynamic level. The pharmacological effect of one or both drugs may either be increased or decreased, or a new and unanticipated adverse effect may be produced. Consequently, the efficacy of the drugs used can either be augmented or impeded, ultimately influencing patient outcomes.[5]

The aim of this study was to investigate known drug interactions between standard available treatment for HIV-associated lymphoma and antiretroviral therapy in the public sector, South Africa. The results are presented in a format that can serve as a referencing tool to be used in centers treating HIV-associated malignancies.

Methods

A comprehensive overview of data collected from three well-known drug-interaction databases was performed to identify drug interactions. These databases included (i) Medscape Drug Interaction Checker,[6] (ii) Lexicomp Online,[7] and (iii) RxList.[8] Information was retrieved during March and April 2019.

Approval to conduct the study was obtained from the Health Sciences Research Ethics Committee, University of the Free State (ethics number UFS-HSD2018/0940/3010). No other major ethical considerations were identified as no patient information was included in this study. The analysis of data was done by the principal author.

Nineteen antiretroviral drugs that form part of the HIV clinical guide proposed by the South African Department of Health were included in this study,[9] and comprised drugs representing the first-, second- and third-line antiretroviral therapy combinations, and also drugs used specifically in patients with HIV and a creatinine clearance of less than 50 mL/min. Drugs from the novel classes of integrase, fusion and CCR5 inhibitors have also been included. Recommended first-line ART is tenofovir (TDF) in combination with emtricitabine (FTC) / lamivudine (3TC); and either efavirenz (EFV) or dolutegravir as the third antiretroviral agent. In patients with an HIV viral load of less than 100 000 copies/mL, rilpivirine (RPV) may be used as the third antiretroviral agent.[9]

Two nucleoside reverse transcriptase inhibitors (NRTIs) with a protease inhibitor are recommended for second-line therapy. Zidovudine with FTC/3TC, or TDF with FTC/3TC in combination with a ritonavir-boosted protease inhibitor, are used as second-line therapy. Patients who require third-line therapy are prescribed two NRTIs, FTC/3TC with either TDF or AZT, as well as darunavir (DRV/r). In patients with an estimated glomerular filtration rate of less than 50 mL/min, TDF is substituted for abacavir (ABC).[9]

Dolutegravir, an integrase inhibitor, has a favourable drug profile and can be used in many ART regimens. The SINGLE study proved better safety and efficacy of dolutegravir plus abacavir-lamivudine than a regimen consisting of efavriens-tenofovir-emtricitabine.[10] The fusion inhibitor enfuvirtide has been shown to provide significant immunological benefit in virological suppression.[11] Maraviroc, a powerful selective CCR5 antagonist is the first in its class of oral agents and is known to have favourable pharmacological properties.[12] Antiretroviral drugs included in the analysis are summarised in Table 1.

Table 1. Antiretroviral agents included for analysis in the study.

Class	Abbreviation	Full name of agent
Nucleoside reverse transcriptase inhibitors (NRTIs)	3TC	Lamivudine
	ABC	Abacavir
	DDI	Didanosine
	d4T	Stavudine
	FTC	Emtricitabine
	TDF	Tenofovir
	AZT	Zidovudine
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	EFV	Efavirenz
	NVP	Nevirapine
	RPV	Rilpivirine
	ETR	Etravirine
Protease inhibitors (PI)	ATV	Atazanavir
	DRV	Darunavir
	RTV	Ritonavir
	LPV/R	Lopinavir/Ritonavir
Integrase inhibitors	RAL	Raltegravir
	DTG	Dolutegravir
Entry inhibitors		
CCR5 inhibitors		Maraviroc
Fusion inhibitors		Enfuvirtide

Antineoplastic drugs included in this study are commonly used in treatment regimens for HIV-associated lymphomas in the South African setting. Drugs that would be used in the following treatment protocols were included: (i) ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine);[13] (ii) CODOX-M-IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, cytarabine, etoposide and intrathecal methotrexate);[14] (iii) CALGB9251 (cyclophosphamide and prednisone followed by ifosfamide/cyclophosphamide, methotrexate, vincristine, dexamethasone, doxorubicin/etoposide/cytarabine and triple intrathecal chemotherapy consisting of methotrexate, cytarabine and hydrocortisone);[15] (iv) hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone with or without rituximab, alternating with high-dose methotrexate and cytarabine);[16] (v) dose adjusted R-EPOCH (rituximab, etoposide, vincristine, doxorubicin, prednisone, cyclophosphamide);[17] and (vi) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone).[18–20] The antineoplastic drugs included in the study are listed in Table 2.

Table 2. Antineoplastic agents included for analysis in the study.

Class	Full name of agent
Antimetabolites	Methotrexate
	Cytarabine
Cytotoxic antibiotics	
Glycopeptide	Bleomycin
Anthracycline	Doxorubicin
Monoclonal antibodies	Rituximab
Topoisomerase II inhibitors	Etoposide
Alkylating agents	Cyclophosphamide
	Ifosfamide
	Dacarbazine
Anti-microtubule agents (Vinca alkaloids)	Vincristine
	Vinblastine
Corticosteroids	Prednisone
	Dexamethasone

The potential interactions that were identified were classified according to the legend shown in Table 3, with an indication whether these interactions were clinically significant (CS) or not clinically significant (NCS)

Table 3. Legend for grading of seriousness of drug interactions.

Symbol	Interpretation
( )	Not clinically significant/significance unknown/minor significance
Ɵ	No interaction
▲	Increased effect
▼	Decreased effect
†	Contraindicated
!	Increased toxicity
X	Increased toxicity of both drugs due to synergism
0	Loss of biological response

Results

One-hundred and seventeen drug interactions were identified and graded according to the legend represented in Table 3. Results of the interactions are summarised in Table 4. Most of the interactions were identified on RxList,[8] followed by Medscape[6] and Lexicomp Online,[7] namely 96/117 (82.1%), 76/117 (65.0%%) and 52/117 (44.4%), respectively. Thirty-nine interactions were identified on all three checkers, 30 on two separate checkers and 48 on a single checker.

Reactions that were reported as having minor or unknown clinical significance are portrayed in round brackets in Table 5. All the other interactions were accepted to be clinically significant. Where interaction checkers differed with regard to clinical significance, the most severe reaction was documented on the clinical tool.

An interaction between lopinavir and ritonavir was identified on Medscape,[6] which has not been described in this study as it is a known synergistic action.

Table 4. Interactions identified on interaction checkers (MS= Medscape;[6] LC = Lexicomp Online;[7] RL = RxList[8]).

	Drug	MS	LC	RL		Drug	MS	LC	RL
1	MTX and AZT increase each other's toxicity	√	0	√	29	Etoposide will increase RTV	0	0	√
2	MTX increased by RTV	0	√	0	30	Etoposide increased by LPR/r	√	√	√
3	MTX increased by LPV/r	0	√	0	31	Etoposide will increase LPV/R	0	0	√
4	Bleomycin increases TDF* toxicity	√	0	0	32	Ifosfamide and TDF toxicity increased	√	0	0
5	Doxorubicin# decreases d4T	√	√	√	33	Ifosfamide and AZT toxicity increased	√	0	√
6	Doxorubicin# toxicity increased by AZT	√	0	0	34	Ifosfamide toxicity increased by EFV	√	√	√
7	Doxorubicin# decreases effect of AZT	√	√	√	35	Ifosfamide levels decreased by EFV	0	√	0
8	Doxorubicin# enhances toxic effect of AZT	0	√	0	36	Ifosfamide toxicity increased by NVP	√	0	√
9	Doxorubicin# decreased by EFV	√	√	√	37	Ifosfamide level decreased by NVP	0	√	0
10	Doxorubicin# decreased by NVP	√	0	√	38	Ifosfamide increases toxicity of ETR	0	0	√
11	Doxorubicin# decreased by ETR	√	√	√	39	Ifosfamide toxicity increased by ETR	√	√	√
12	Doxorubicin# increased by ATV	√	√	√	40	Ifosfamide decreased by ETR	0	√	0
13	Doxorubicin# increases level of ATV	0	0	√	41	Ifosfamide will decrease the level of ATV	0	0	√
14	Doxorubicin# increased by darunavir	√	√	√	42	Ifosfamide decreased by ATV	√	√	√
15	Doxorubicin# increased level of darunavir	0	0	√	43	Ifosfamide decreased by DRV	√	√	√
16	Doxorubicin# increased by RTV	√	√	√	44	Ifosfamide decreases DRV	0	0	√
17	Doxorubicin# increased by LPV/R	√	√	√	45	Ifosfamide decreased by RTV	√	√	√
18	Etoposide decreased by EFV	√	√	√	46	Ifosfamide increased by RTV	√	0	0
19	Etoposide will decrease EFV	0	0	√	47	Ifosfamide decreased by LPR/r	√	√	0
20	Etoposide decreased by NVP	√	0	√	48	Ifosfamide increased by LPV/r	0	0	√
21	Etoposide decreases NVP	0	0	√	49	Cyclophosphamide decreased by EFV	0	√	0

	Drug	MS	LC	RL
22	Etoposide decreased by ETR	√	√	√
23	Etoposide will decrease ETR	0	0	√
24	Etoposide increases ATV	0	0	√
25	Etoposide increased by ATV	√	0	√
26	Etoposide increases DRV	0	0	√
27	Etoposide increased by DRV	√	0	√
28	Etoposide increased by RTV	√	√	√

	Drug	MS	LC	RL
50	Cyclophosphamide decreased by NVP	0	√	0
51	Cyclophosphamide toxicity increased by ATV	0	√	0
52	Cyclophosphamide toxicity increased by DRV	0	√	0
53	Cyclophosphamide level increased by RTV	√	0	√
54	Cyclophosphamide toxicity increased by RTV	0	√	0
55	Cyclophosphamide will increase RTV	0	0	√
56	Cyclophosphamide level increased by LPV/r	√	0	√

Table 4. continued

	Drug	MS	LC	RL		Drug	MS	LC	RL
57	Cyclophosphamide toxicity increased by LPV/r	0	√	0	86	Prednisone will decrease EFV	√ ncs	0	√ ncs
58	Cyclophosphamide will increase LPV/r	0	0	√	87	Prednisone decreased by EFV	√	0	√
59	Vincristine and DDI increased toxicity	√	0	0	88	Prednisone decreased by NVP	√	0	√
60	Vincristine toxicity increased by AZT	√ ncs	0	0	89	Prednisone decreases NVP	0	0	√
61	Vincristine decreased by EFV	√	√	√	90	Prednisone decreased by ETR	√	0	√
62	Vincristine will decrease EFV	0	0	√	91	Prednisone decreases ETR	√	0	√
63	Vincristine decreased by NVP	√ ncs	0	√ ncs	92	Prednisone increased by ATV	√	√	√
64	Vincristine will decrease NVP	0	0	√ ncs	93	Prednisone decreases ATV	√ ncs	0	√ ncs
65	Vincristine decreased by ETR	√ ncs	√ cs	√ ncs	94	Prednisone increased by DRV	√	√	√
66	Vincristine will decrease ETR	0	0	√ ncs	95	Prednisone decreases DRV	√	0	√
67	Vincristine increased by ATV	√ ncs	√ cs!!	√ ncs	96	Prednisone increased by RTV	√	√	√
68	Vincristine will increase level of ATV	0	0	√ ncs	97	Prednisone decreases RTV	√	0	√
69	Vincristine increased by DRV – severe	√	√	√	98	Prednisone increased by LPV/r	√	√	√
70	Vincristine increases DRV	0	0	√ cs	99	Prednisone decreases LPV/r	√	0	√
71	Vincristine increased by RTV	√	√	√	100	Prednisone decreases maraviroc	√	0	0
72	Vincristine increased by LPV/r	√	√	√	101	Dexamethasone decreased by EFV	√	√	√
73	Vinblastine toxicity increased by AZT	√ ncs	0	0	102	Dexamethasone decreases EFV	√ ncs	0	√ ncs
74	Vinblastine decreased by EFV	√ ncs	√ cs	√	103	Dexamethasone decreased by NVP	√	0	√
75	Vinblastine will decrease EFV	0	0	√	104	Dexamethasone decreases NVP	0	0	√
76	Vinblastine decreased by NVP	√ ncs	0	√	105	Dexamethasone decreases RPV: loss of virological response	√	√	√
77	Vinblastine decreases NVP	0	0	√	106	Dexamethasone will decrease ETR	√	0	√

78	Vinblastine decreased by ETR	√ ncs	√ cs	√
79	Vinblastine decrease ETR	0	0	√
80	Vinblastine increased by ATV	√ ncs	√	√
81	Vinblastine increase ATV	0	0	√
82	Vinblastine increased by DRV	√	√	√
83	Vinblastine increase DRV	0	0	√
84	Vinblastine level increased by RTV	√	√	√

107	Dexamethasone decreased by ETR	√	√	√
108	Dexamethasone increased by ATV	√	√	√
109	Dexamethasone will decrease ATV	√ ncs	0	√ ncs
110	Dexamethasone increased by DRV	√	√	√
111	Dexamethasone will decrease DRV	√	0	√
112	Dexamethasone will decrease RTV	√	0	√
113	Dexamethasone increased by RTV	√	√	√

Table 4. continued

	Drug	MS	LC	RL		Drug	MS	LC	RL
114	Dexamethasone increased by LPV/r	√	√	√	116	Dexamethasone decreases maraviroc	√	0	√
115	Dexamethasone will decrease LPV/r	√	0	√	117	Dexamethasone decreased by maraviroc	0	0	√

Total number of interactions	77	52	96
Interactions found on all 3 checkers		39	
Interactions found on 2 checkers		30	
Interactions found on 1 checker		48	

√ = interaction identified; 0 = no interaction identified; ncs = not clinically significant; cs = clinically significant; * Tenofovir DF (disoproxil fumarate); # conventional doxorubicin and not liposomal doxorubicin;

Antineoplastic agents and NRTIs

Nine interactions were identified between antineoplastic agents and NRTIs, and all were deemed to be clinically significant.

Antimetabolites and NRTIs

A reaction leading to increased toxicity with concomitant use of methotrexate and zidovudine was identified.[21] Miller et al.[21] reported considerable toxicity when combining methotrexate and zidovudine in 31 patients with either adenocarcinoma of the pancreas or hepatocellular carcinoma. Severe haematologic toxicity developed in 50% of patients whose haemoglobin levels dropped to below 8 g/dL. Seventy percent of patients developed agranulocytosis.[21]

Cytotoxic antibiotics and NRTIs

When TDF and bleomycin are administered simultaneously, clinically significant increased toxicity of TDF will occur. It has been suggested that renal function be monitored as the combination of bleomycin and TDF can lead to decreased renal excretion of nephrotoxic agents.[22]

Stavudine has a decreased effect when used in conjunction with doxorubicin. Doxorubicin was found to interfere with the phosphorylation of d4T, thereby decreasing its efficacy.[23]

With the concomitant use of zidovudine and doxorubicin, the toxic effects of doxorubicin were found to increase and use of the combination is contraindicated.[24]

Increased genotoxicity was found in a murine study by Yadav[25] when a combination of doxorubicin, zidovudine and cyclophosphamide were used in combination, compared to retrospective controls where these drugs were used as monotherapy. The effects of zidovudine may also be decreased.[24]

Alkylating agents and NRTIs

When ifosfamide and TDF are used together, the toxic effects of both are increased due to pharmacodynamic synergism. Both ifosfamide and tenofovir are implicated to be toxic to the proximal tubule of the kidney and can cause the development of renal Fanconi syndrome.[26] The risk and severity of adverse effects can be increased when zidovudine is used with ifosfamide. [27]

Anti-microtubule agents and NRTIs

The toxic effects of both vincristine and didanosine are increased when used in combination. Vinblastine and vincristine also have increased toxic effects when used with zidovudine.[28] These interactions, however, were reported as not clinically significant.[6]

Antineoplastic agents and NNRTIs

Thirty-nine interactions were found between NNRTIs and antineoplastic agents. Of these interactions, one was found to represent an absolute contraindication; this being the use of nevirapine and ifosfamide.[29] Thirty-three reactions were deemed clinically significant.

Cytotoxic antibiotics and NNRTIs

Doxorubicin has been shown to have a decreased therapeutic effect when used in conjunction with efavirenz, nevirapine and etravirine, which was regarded as clinically significant.[30]

Topoisomerase II inhibitors and NNRTIs

The effects of etoposide and efavirenz, nevirapine and etravirine are decreased when used simultaneously,[31] which has been deemed clinically significant.

Alkylating agents and NNRTIs

Increased toxicity of ifosfamide was identified when used in combination with either efavirenz or nevirapine.[32] This was found on two interaction checkers. One checker, however, states that efavirenz decreases the level of ifosfamide. Synergism causes an increase in both the toxicities of ifosfamide and etravirine when used together, with these reactions being deemed clinically significant.[33] Lexicomp Online,[7] however, mentions that etravirine can either increase toxicity of ifosfamide or decrease the levels thereof. Some discrepancy exists regarding the interactions between nevirapine and ifosfamide, and therefore, an apparently unpredictable interaction between these drugs has been identified. The Mayo Clinic recommends that this combination should be avoided.[27] The therapeutic effect of cyclophosphamide is decreased when used with efavirenz or nevirapine, which represents clinically significant interactions.[34]

Anti-microtubule agents and NNRTIs

When vincristine is used in combination with efavirenz, nevirapine or etravirine, the therapeutic effects of both components are reduced.[35] These ART agents also reduce the efficacy of vinblastine and vice versa.[36]

Corticosteroids and NNRTIs

Prednisone decreases the effect of efavirenz, nevirapine and etravirine, while these antiretrovirals all decrease the efficacy of prednisone, which is regarded as clinically significant.[37]

Efavirenz and dexamethasone decrease each other's therapeutic effect. Nevirapine or etravirine used with dexamethasone leads to a clinically significant decreased therapeutic effect of both.[37] The use of rilpivirine and dexamethasone is contraindicated, as dexamethasone can lead to a loss of virologic response to rilpivirine.[37]

Antineoplastic agents and other antiretroviral drugs

Fifty-six interactions were identified between the antineoplastic agents and the PIs, integrase and fusion inhibitors. Two of these interactions are absolute contraindications. Four interactions have either minor or unknown clinical significance.

Antimetabolites and PIs

The effects of methotrexate have been reported to increase when used with lopinavir/ritonavir,[38] an interaction that is regarded as clinically significant.

Cytotoxic antibiotics and PIs

Doxorubicin has been found to have an increased effect when used with all the PIs. It also increases the effects of atazanavir and darunavir.[39]

Topoisomerase II inhibitors and PIs

The effects of all the PIs and etoposide are increased when used in conjunction.[38]

Alkylating agents and PI

Decreased effects of ifosfamide have been noted when used with PIs, while the levels of ATV and DRV may also be decreased.[32] The toxic effects of cyclophosphamide are increased when combined with all the PIs. The effects of ritonavir and lopinavir/ritonavir are also increased when used with cyclophosphamide.[40]

Anti-microtubule agents and PIs

The effects of both vincristine and vinblastine are increased when used with the PIs, which has been found to be clinically significant. The use of both vincristine and vinblastine with darunavir is contraindicated and therapy modification is advised.[41]

Corticosteroids and PIs

When used in conjunction, the effect of the corticosteroids prednisone and dexamethasone, will be increased and the effect of all the PIs will be decreased. Busse et al. reported that ritonavir significantly increased prednisolone exposure.[37]

Corticosteroids and entry inhibitors

The concentration of the CCR5 inhibitor maraviroc is decreased when used with corticosteroids.[34]

Table 5. Quick reference guide for the identification of drug interactions between antiretroviral and chemotherapeutic agents.

Antineoplastic agent		Antiretroviral agents																		
		NRTIs							NNRTIs				PIs				IIs		Other	
		3TC	ABC	DDI	d4T	FTC	TDF	AZT	EFV	NVP	RPV	ETR	ATV	DRV	RTV	LPV/R	RAL	DTG	Mara-viroc	Enfu-virtide
Antimeta-bolite	MTX	Θ	Θ	Θ	Θ	Θ	Θ	**X**	Θ	Θ	Θ	Θ	Θ	Θ	▲ MTX	▲ MTX	Θ	Θ	Θ	Θ
	Cytarabine	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ
Cytotoxic antibiotics	Bleomycin	Θ	Θ	Θ	Θ	Θ	**!** TDF	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ
	Doxorubicin	Θ	Θ	Θ	▼ d4T	Θ	Θ	**!** Doxo ▼ AZT	▼ Doxo	▼ Doxo	Θ	▼ Doxo	▲ Doxo ATV	▲ Doxo ATV	▲ Doxo	▲ Doxo	Θ	Θ	Θ	Θ
Mono-clonal antibodies	Rituximab	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ
Topoiso-merase II inhibitors	Etoposide	Θ	Θ	Θ	Θ	Θ	Θ	Θ	▼ Etop EFV	▼ Etop NVP	Θ	▼ Etop ETR	▲ Etop ATV	▲ Etop DRV	▲ Etop RTV	▲ Etop LPV/r	Θ	Θ	Θ	Θ
Alkylating agents	Ifosfamide	Θ	Θ	Θ	Θ	Θ	**!** Ifos	**X**	! Ifos	! Ifos	Θ	**X**	▼ Ifos ATV	▼ Ifos DRV	▼ Ifos	▼ Ifos	Θ	Θ	Θ	Θ
	Cyclophos-phamide	Θ	Θ	Θ	Θ	Θ	Θ	Θ	▼ Cyclo	▼ Cyclo	Θ	Θ	**!** Cyclo	**!** Cyclo	**!** Cyclo ▲ RTV	**!** Cyclo ▲ LPV/r	Θ	Θ	Θ	Θ
	Dacarbazine	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ	Θ
Anti-micro-tubule agents	Vincristine	Θ	Θ	**X**	Θ	Θ	Θ	**!** (Vinc)	▼ Vinc EFV	▼ (Vinc) (NVP)	Θ	▼ Vinc (ETR)	▲ Vinc (ATV)	† Vinc ▲ DRV	▲ Vinc	▲ Vinc	Θ	Θ	Θ	Θ
	Vinblastine	Θ	Θ	Θ	Θ	Θ	Θ	**!** (Vinb)	▼ Vinb EFV	▼ (Vinb) NVP	Θ	▼ Vinb ETR	▲ (Vinb) ATV	† ▲ Vinb DRV	▲ Vinb	▲ Vinb	Θ	Θ	Θ	Θ
Cortico-steroids	Prednisone	Θ	Θ	Θ	Θ	Θ	Θ	Θ	▼ Pred (EFV)	▼ Pred NVP	Θ	▼ Pred ETR	▲ Pred ▼ (ATV)	▲ Pred ▼ DRV	▲ Pred ▼ RTV	▲ Pred ▼ LPV/r	Θ	Θ	▼ Marav	Θ
	Dexamethas one	Θ	Θ	Θ	Θ	Θ	Θ	Θ	▼ Dexa (EFV)	▼ Dexa NVP	†0 RPV	▼ Dexa ETR	▲ Dexa ▼ (ATV)	▲ Dexa ▼ DRV	▲ Dexa ▼ RTV	▲ Dexa ▼ LPV/R	Θ	Θ	▼ Marav Dexa	Θ

Θ = no interaction, ( ) = not clinically significant/ significance unknown/ minor significance, ▲ = increased effect name of drug mentioned denotes which drug is affected, ▼ = decreased effect name of drug mentioned denotes which drug is affected, † = contraindicated, ! = increased toxicity, X = increased toxicity of both drugs due to synergism, 0 = loss of biological response.

Discussion

Significant drug interactions were identified in this descriptive study. The implications of these interactions are discussed according to the commonly used drug regimens in the South African public health sector.

Drug tailoring for patients on first-line ART

With regard to first-line ART, both the NRTIs FTC and 3TC have no documented interactions and can be used safely with any antineoplastic agent. Tenofovir should be used with caution in patients receiving bleomycin, as tenofovir toxicity can be increased. This effect has implications for patients with Hodgkin lymphoma for whom ABVD is considered. Tenofovir and ifosfamide also have an increased synergistic therapeutic effect that will lead to increased drug toxicity in patients with Burkitt lymphoma on a CALGB9251 regimen.

Multiple drug interactions occur when efavirenz is used. Efavirenz decreases the concentration of doxorubicin, which has implications for patients receiving ABVD, CODOX-M-IVAC, CALGB9251, hyper-CVAD, dose-adjusted EPOCH, R-CHOP and CHOP. It therefore is evident that EFV as part of first-line treatment will have to be substituted for another drug.

It has, however, been found that PRV used in combination with dexamethasone is absolutely contraindicated due to a loss of virologic response to RPV. This alternative is therefore regarded as unusable for patients on CALGB9251 and hyper-CVAD protocols. Alternatives that could be considered are prednisone instead of dexamethasone, or substitution of RPV with dolutegravir, which has been found to be a safe option with no drug interactions.

From the data obtained from our study, we can therefore recommend that patients with all forms of HIV-associated lymphoma who are on a regimen containing efavirenz be considered for a possible switch to dolutegravir.

Drug tailoring for patients on second-line ART

FTC and 3TC can safely be used in any chemotherapy regimen. TDF, however, has significant interactions with bleomycin.

AZT in combination with methotrexate leads to increased toxicity of both these drugs due to pharmacodynamic synergism. This may be problematic in patients with Burkitt lymphoma who are on CODOX-M-IVAC, CLAGB9251 or hyper-CVAD. Although daEPOCH would be a logical alternative, it has been reported that AZT increases doxorubicin toxicity.[7] This poses a major clinical dilemma as doxorubicin is included as part of the recommended treatment for Hodgkin lymphoma, all the regimens for Burkitt lymphoma, DLBCL, PEL and plasmablastic

lymphoma. We propose strict monitoring for signs of anthracycline cardiotoxicity and appropriate preventative management.

AZT used in combination with ifosfamide leads to increased toxicity of both drugs, which will be problematic with the CODOX-M-IVAC and CALGB9251 regimens used for treatment of Burkitt lymphoma. Consequently, alternative regimens should be considered. AZT increases the drug level of vincristine that could lead to toxic effects. It has implications for the treatment of Burkitt lymphoma, DLBCL, PEL and PL. We therefore recommend considering an alternative antiretroviral agent in these circumstances. AZT may lead to vinblastine toxicity, with vinblastine being used as part of ABVD. Alternative ART should be considered.

PIs pose major challenges for the clinician treating HIV-associated lymphoma. All four PIs that have been studied were found to increase the effects of doxorubicin, putting the patient at increased risk of cardiotoxicity. Doxorubicin forms part of all the chemotherapy regimens. This complicates treatment for all patients on second- or third-line ART. Further investigation into this situation in necessary. Using PIs will require an increase in the dose of etoposide needed, which will have an impact on all patients treated with CODOX-M-IVAC, CALGB9251 and EPOCH. In this regard, hyper-CVAD appears to be a better option for patients with Burkitt lymphoma.

PIs decrease the levels of ifosfamide which forms part of CODOX-M-IVAC and CALGB9251. HyperCVAD again seems to be a better option for Burkitt in this regard. PIs increase the levels of cyclophosphamide. This has an impact on all patients with Burkitt lymphoma as ifosfamide forms part of all the frequently used regimens. The use of R-CHOP is burdened by the same interaction. PIs increase the levels of both vincristine and vinblastine. The concomitant use of darunavir and anti-microtubule agents is absolutely contraindicated. This finding influences all the described chemotherapeutic regimens.

All PIs will increase the level of corticosteroids and vice versa. The use of PIs in patients with HIV associated lymphoma cannot be advocated and alternative ART should be considered.

Drug tailoring for patients on third-line ART

Darunavir forms the backbone of third-line ART, although it has significant interactions with many drugs, thus complicating the use of all of the PI class drugs. Darunavir increases the levels of doxorubicin that forms part of all the current HIV-associated lymphoma treatment regimens. Close therapeutic monitoring and preventative measures to decrease anthracycline-related cardiotoxicity is of utmost importance.

Darunavir increases the effects of etoposide. Hyper-CVAD will therefore be a preferred regimen for patients with Burkitt lymphoma. The darunavir/etoposide interaction also has to be kept in mind in patients receiving dose-adjusted EPOCH for either Burkitt lymphoma or

PL. Darunavir decreases the level of ifosfamide, and therefor alternative regimens to CODOX-M-IVAC or CALGB9251 should be considered for treatment of Burkitt lymphoma.

Darunavir increases the toxic effects of cyclophosphamide, which will affect patients on CODOX-M-IVAC, CALGB9251 and hyper-CVAD. From an interaction point of view, dose-adjusted EPOCH will therefore be the safest option for patients with Burkitt lymphoma. Darunavir causes toxicity of both anti-microtubule agents, vincristine and vinblastine. The concomitant use of these agents is contraindicated and alternative ART should be prescribed in patients who require treatment with ABVD, CODOX-M-IVAC, CALGB9251, hyper-CVAD, R-CHOP and dose-adjusted EPOCH.

Due to significant risk of toxicity of vincristine and vinblastine when used simultaneously with darunavir, we recommend that an alternative to PIs be considered in these patients. Darunavir increases the availability of both prednisone and dexamethasone, an interaction that should be kept in mind in patients receiving CALGB9251, hyper-CVAD, dose-adjusted EPOCH and R-CHOP. Possible dose adjustment is warranted to be investigated.

Corticosteroids may decrease the effect of darunavir, which should be taken into account if patients develop worsening immunological function. Due to multiple adverse drug interactions, we cannot advocate the use of darunavir in patients on chemotherapy as no regimen has been found to be without significant interactions.

Drug tailoring for renally adjusted ART

No interactions between abacavir (which is the substitute for tenofovir) and antineoplastic agents were found.

Other significant drug interactions of noteworthy value

In patients on nevirapine, it should be borne in mind that this agent has been found to decrease the required doses of doxorubicin, etoposide, cyclophosphamide, vincristine, vinblastine, prednisone and dexamethasone. Therefore, dose adjustment might be necessary. Nevirapine will also increase the toxic effects of ifosfamide in patients on CODOX-M-IVAC and CALGB9251 protocols.

The entry inhibitors and fusion inhibitors as newer antiretroviral drug classes were found to have minimal drug interactions. No interactions were identified with the integrase inhibitors raltegravir or dolutegravir. The fusion inhibitor enfuvirtide also had no drug interactions. Maraviroc reportedly has decreased levels when used with corticosteroids. These drugs seem to be good alternatives for patients where drug interactions limit other commonly used regimens.

It is unequivocal that we have to progress in a direction where therapy will require to be tailored according to each patient's specific needs. A close relationship between the treating

haematologic oncologist or oncologist and an infectious disease specialist will be crucial if we intend to give patients with HIV-associated lymphoma the best possible care.

Given the fact that multiple medication safety issues are bound to develop when individual drug tailoring is done, proper medication reconciliation will be of utmost importance. From this perspective, it entails taking proper drug histories, verifying that patients are on the correct doses of appropriate medications and documenting all the changes made to treatment regimens. For example, it will be crucial that when an ART regimen is adapted, the patient will carry a document stating the reason why his/her treatment was changed and also instructions to the local clinic on how to continue with the patient's treatment going forward. Frequently reviewing all prescription, traditional and over-the-counter medications is also vital to prevent potential drug interactions.[42]

Therapeutic monitoring of drug levels, dose adjustments or single drug switches might be necessary in many instances. This implores the need for further studies in this regard. Although the authors can make recommendations on treatment options with regard to drug interactions, it cannot comment on either the efficacy of specific antiretrovirals or chemotherapy regimens. Based on experience and resources, the clinician may still choose to continue with a certain regimen despite the interactions described in this report. We aspire to sensitise doctors to the reality of these potential interactions, and ensure appropriate monitoring of patients for drug side-effects.

This study has been limited by the fact that the RxList[8] interaction checker did not include didanosine. Furthermore, it was found that the interaction checker from RxList[8] in some instances provided conflicting information and on later review was found to be malfunctioning. This particular challenge that we experienced demonstrates the need for an instrument that allows a compilation of information from a variety of sources that is regularly updated as information may change over time. This study did not test the instrument in actual clinical situations. Furthermore, it should be kept in mind that in a resource-limited setting, such as the South African public health sector, prescribing will often be led by cost and drug availability. The study did not evaluate levels of evidence and therefor is unable to predict what the relevance of these theoretical interactions will be in a clinical environment, which is a question that should be investigated in further studies.

It is also necessary to keep in mind that these patients often are on other medications apart from or in addition to ART and approved lymphoma chemotherapy protocols, which may also cause significant drug interactions and alter the effects of the drugs prescribed by their attending physicians. HIV is often complicated by tuberculosis (TB), which is treated with drugs with well-known interactions due to enzyme induction or inhibition. Similarly, malignancy is often complicated by deep vein thrombosis (DVT) for which warfarin, a well-known "offender" when it comes to drug interactions, is prescribed. It is vital to appreciate that these are very complex patients to treat and each case needs to be evaluated on its own merit with the patient's clinical condition kept in mind.

It is proposed that the instrument be reviewed and updated frequently, and the database extended as new drugs become available in the ever-changing disciplines of both oncology and the treatment of HIV.

Conclusion

Despite easy access to ART and improved survival of patients living with HIV, HIV-related complications do occur. HIV-associated lymphoma remains a problem of national concern in South Africa. By means of evaluating data from three drug interaction databases, information was obtained regarding interactions between commonly used ART and antineoplastic agents used to treat HIV-associated lymphoma. This study has endeavoured to provide an easy-to-use, quick reference tool for doctors working with these two common conditions, which will promote the safe prescribing of suitable pharmaceutical agents to their patients.

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Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
L.M. and C.B. designed the study. L.M. collected, analysed and interpreted data under supervision of C.B. P.v.Z. and C.B. assisted with conceptualisation and approval of the protocol. L.M. prepared the initial draft of the article. All the authors viewed and approved the final version of the article.

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Appendices:

Appendix 1: Letter of approval from University of the Free State HSREC

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES

Health Sciences Research Ethics Committee

25-Sep-2018

Dear **Dr Lana Meyer**

Ethics Clearance: **Drug interactions between HIV-associated lymphoma treatment and antiretroviral therapy: a critical review**

Principal Investigator: **Dr Lana Meyer**

Department: **Internal Medicine Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is: **UFS-HSD2018/0940/3010**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki, The Belmont Report, The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56, CIOMS, ICH-GCP-E6 Sections 1-4, The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7595/7794 | E: ethicsfhs@ufs.ac.za
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Appendix 2: Letter of approval from the HOD, Internal Medicine

UFS·UV

18 July 2018

The Chairperson,
Ethics Committee,
Faculty of Health Sciences
University of the Free State

TO WHOM IT MAY CONCERN

RE: Drug interactions between HIV-associated lymphoma treatment and antiretroviral therapy: A critical review.

I hereby approve that Dr L Fourie, Registrar Internal Medicine conduct the study in the division Clinical Haematology, Department Internal Medicine.

Kind regards

Dr TRP Mofokeng
Head: Department of Internal Medicine

Department of Internal Medicine/Departement Interne Geneeskunde
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Appendix 3: Protocol

DRUG INTERACTIONS BETWEEN HIV-ASSOCIATED LYMPHOMA TREATMENT AND ANTIRETROVIRAL THERAPY: A CRITICAL REVIEW

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Introduction

1.1. Summary in layman's terms

Human Immunodeficiency Virus (HIV) is an acquired, chronic and potentially life-threatening virus that impairs cellular immunity. The consequence of impaired cellular immunity is an increased risk of both infections and cancers. The advent of anti-retroviral therapy (ART) has markedly increased the lifespan and improved the quality of life of patients living with HIV.

Lymphoma, a type of cancer affecting the lymphocyte portion of the body's white blood cells, is an important complication of HIV infection, leading to both significant morbidity and mortality. At the same time, HIV positive patients have a 60 to 200-fold increased incidence of HIV-associated lymphomas. Treatment of HIV-associated lymphomas has improved dramatically since the introduction of ART in the mid-1990s.

Increasing amounts of literature advocate the simultaneous use of ART and chemotherapy for HIV-associated lymphoma due to the aggressive nature of both these conditions and the urgency in treating both. Due to the large number of potent drugs used for both the treatment of HIV-associated lymphoma and HIV drug interactions are inevitable. These interactions may alter the efficacy of the treatment thus influencing patient outcomes.

The aim of this study will therefore be to investigate the drug interactions between commonly used ART in the treatment of HIV and antineoplastic agents used for the treatment of HIV-associated lymphoma. Interactions will be classified as indicate in Table 1 below.

Table 1. Classification of drug interactions

Clinically significant; severe	Increased effect
	Decreased effect
Clinically significant; minor	Increased effect
	Decreased effect
Undetermined effect of reaction	

This study hopes to provide an evidenced-based reference for doctors prescribing both ART and antineoplastic agents simultaneously, aiming to find a regimen that will be safe to use for the above-mentioned patient population.

Abbreviations used

AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral therapy
ARV	Anti-retroviral
BL	Burkitt lymphoma
CDE	Cyclophosphamide, Doxorubicin, Etoposide
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CODOX-M/IVAC	Cyclophosphamide, Doxorubicin, Vincristine, Cytarabine, Methotrexate
CYP450	Cytochrome P450
DLBCL	Diffuse large B cell lymphoma
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PCNSL	Primary central nervous system lymphoma
PEL	Primary effusion lymphoma
PI	Protease inhibitors

Definitions

HIV-associated lymphoma

HIV-associated lymphomas are predominantly aggressive B cell lymphomas. Many HIV positive patients present with these lymphomas as the initial manifestation of HIV and these lymphomas are AIDS defining. The most common HIV-associated lymphomas are the following:(1)

- Burkitt lymphoma
- Diffuse large B cell lymphoma
- Primary effusion lymphoma
- Plasmablastic lymphoma
- Hodgkin's lymphoma

Cytochrome P450

Cytochrome P450 genes produce enzymes involved in the synthesis and metabolism of various molecular chemicals. Cytochrome P450 enzymes play a role in the synthesis of steroid hormones, cholesterol and bile acids, prostacyclin and thromboxane A2.(2) These enzymes are also involved in the metabolism of medications and cellular toxins. Around 60 cytochrome P450 genes are found in humans, however 90% of drugs are metabolised by six of these – the most significant being CYP3A4 and CYP2D6.(2)

Cytochrome P450 enzymes are found mainly in the liver but also occur elsewhere in the body. Within cells they are found in the endoplasmic reticulum and mitochondria. The mitochondrial enzymes are primarily involved in the metabolism of internal substances whilst the enzymes in the endoplasmic reticulum metabolise primarily external substances such as medications and environmental pollutants.(2)

Cytochrome P450 enzymes are essential for the metabolism of many medications. Drugs can either induce or inhibit cytochrome P450 enzymes, resulting in clinically significant drug-drug interactions which may lead to unanticipated adverse reactions or therapeutic failure. Many drug interactions occur as a result of the alteration of CYP450 metabolism. Standard drug doses may lead to adverse effects related to elevated serum drug levels should a person have a CYP450 inhibitor added to their therapy. Likewise, a drug will prove less therapeutic if a CYP450 inducer speeds up drug metabolism.(2)

Pharmacodynamics

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of the therapeutic and adverse effects.(3)

Pharmacokinetics

Pharmacokinetics is defined as the study of the time course of drug absorption, distribution, metabolism and excretion. The application of pharmacokinetic principles ensures safe and therapeutic use of a drug.(3) The primary goals of clinical pharmacokinetics are concerned with enhancing drug efficacy whilst reducing drug toxicity. The development of correlations between drug concentrations and the corresponding pharmacological responses have enabled clinicians to apply pharmacokinetic principles to actual patient situations.(3)

Enzyme induction

The term enzyme induction describes the increase in the amount and/or activity of a drug metabolising enzyme as a result of an inducing chemical. The induction of an enzyme may result in either the inactivation or detoxification of an active or toxic substance. The production of an active or toxic metabolite from an inactive precursor can also occur.(4)

Enzyme inhibition

Enzyme inhibition occurs when an enzyme is unable to effectively metabolise its substrate because of interference by another substance.(4)

Glycoprotein 41 (gp41)

A glycoprotein of the HIV envelope. HIV enters a host cell by using gp41 to fuse the HIV envelope with the host cell membrane. (5)

Literature Review

Introduction

HIV is a virus belonging to the lentivirus group of the retrovirus family. Two subtypes, HIV-1 and HIV-2 exist, with HIV-1 being the most prevalent global strain and HIV-2 primarily existing in West Africa.(6) Retroviruses possess the enzyme reverse transcriptase which enables viral RNA to transcribe into the host DNA thus incorporating itself into the host cell genome.(6) The spectrum of illnesses associated with HIV are related to the direct effects of the virus on the hosts immune system, the co-infections associated with HIV and the drugs used to treat this infection.(6) Antiretroviral therapy is aimed at supressing viral replication of the HIV virus. Since the advent of ART in 1996, HIV has transformed from a progressive illness with a fatal outcome to a manageable chronic disease.(6)

Lymphoma as a complication of HIV carries a significant risk of both morbidity and mortality. These occur at a high frequency in patients with HIV, with HIV positive patients having a 60- to 200- fold increased incidence of NHL, the majority being DLBCL.(7) The advent of combination antiretroviral therapy in the mid-1990s has led to a decreased incidence of HIV-associated lymphomas and improved prognosis in patients diagnosed with such lymphomas. This can be ascribed to improved immune function and better control of viral replication of HIV. Before the advent of combined ART, the severity of immunodeficiency greatly influenced the prognosis of patients with HIV-associated lymphoma and HIV. Effective ART has significantly improved the HIV related prognostic factors allowing the use of curative chemotherapy in these patients.(1) Patients with adequate immune function due to ART are at a decreased risk of developing treatment related infectious complications which allows for optimal chemotherapy usage. It has also been shown that tumour biology is more favourable in patients with intact immunological function.(7)

Combination ART has improved the survival rate of patients with HIV associated diffuse large B cell lymphoma and Burkitt's lymphoma, particularly when used in combination with Rituximab. The curability in this era of ART has been found to be similar to the HIV negative population.(7) Current ART regimens usually encompass the use of reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside transcriptase inhibitor (NNRTI), protease inhibitor (PI) or an Integrase inhibitor.(8)

Therapeutic questions have arisen around the need to find a balance between the administration of effective cytotoxic treatment and the effect it has on immune function. Infectious complications, chemotherapeutic toxicity, dose intensity and drug interactions are important aspects to take into account when combining these 2 lines of treatment.(7) The implications of continuing ART during curative chemotherapy for aggressive lymphomas has been widely debated. Uncontrolled viral replication during chemotherapy will adversely affect immune functioning. That being said, chemotherapy renders patients at an increased risk of infection related complications of HIV.(7)

It is well known that due to the large number of potent ARTs used to treat HIV in conjunction with chemotherapeutic agents there is a significant amount of drug interactions which need to be taken into account. A drug interaction may either augment of hinder the efficacy of the drugs used, thereby altering efficacy and ultimately influencing patient outcomes. Drug interactions occur when one drug alters the pharmacological effect of another drug. The pharmacological effect of one or both drugs may either be increased or decreased or a new and unanticipated adverse effect may be produced. Drug interactions may result from pharmacokinetic interactions (absorption, distribution, metabolism and excretion) or from interactions at pharmacodynamic level. (9)

The use of combined ART and chemotherapy

Since the introduction of HAART, the prognosis of HIV-related lymphoma has improved and patients present with higher CD4 counts at diagnosis. HAART has been shown to significantly improve the survival and the quality of life in these patients and it is universally agreed that withholding treatment during chemotherapy would be to the detriment of these patients.(10)

Reduction in the intensity of chemotherapy is often undesirable given the aggressive nature of HIV related lymphoma. However, it is known that combining HAART with chemotherapy may lead to an increase in adverse drug interactions and toxicity. This could compromise remission and survival.(10)

Pharmacokinetic and drug-drug interactions can lead to lower steady state drug concentrations which pose a particular challenge in infusional regimens.(7) Some of the possible interactions between antiretroviral therapy agents and anti-neoplastic agents include the following (11)

- Additive haematological toxicity with Zidovudine containing regimens
- Enzyme inhibition interactions lead to possible etoposide, vincristine and
- cyclophosphamide toxicity
- Increased risk of anaemia and autonomic neurotoxicity with ART and CHOP
- Increased risk of severe infections and neutropenia with PI based ART and CDE

In a study done by the Centre of Cancer Research in 2002 the researchers opted to withhold antiretroviral therapy for the 16 weeks duration of chemotherapy in patients with lymphoma.(11) They found that the HIV dependent decrease in CD4 cells during the time of administering chemotherapy was negligible. Their results indicated that potential adverse effects of ART on lymphoma treatment were avoided and AIDS progression did not worsen

substantially during this period. The benefit of suspending ART was that possible adverse drug interactions were avoided. It was also found that patients did not develop new HIV mutations which is a known risk of poor ART compliance.(11)

However, many studies have been done using ART in combination with chemotherapy demonstrating favourable outcomes. A multicentre trial done in Germany to evaluate the safety and survival rate of patients treated with CHOP in combination with HAART for patients with HIV associated lymphoma.(10) From 1997 to 2001, 72 patients were stratified according to CD4 count, prior opportunistic infection and WHO performance status.(10) Complete remission and median survival were measured. This study showed that the survival of the patients in the standard risk group was very similar to that of patients who were HIV negative with aggressive lymphoma. The authors therefore recommended that standard CHOP and HAART could be safely administered in an outpatient setting as first-line modality for patients with HIV related lymphoma.(10)

A similar study done by Navarro, Ribera, Oriol and Vaquero studied 58 patients with AIDS-related NHL.(12) 41 of these patients were not on HAART at the time of diagnosis of NHL, whereas 17 patients were already on HAART at the time of diagnosis. HAART was found to be an independent prognostic factor for complete remission, overall survival and event free survival in patients with AIDS-related NHL.(12) A retrospective study done by Rodrigo et al. involved 14 patients with HIV- associated Burkitt's lymphoma. These patients were treated with CODOX-M/IVAC with or without Rituximab. It was found that this chemotherapy regimen had acceptable toxicity and good survival rates in the study population.(13)

It can be inferred from the above that there is a need to treat HIV and lymphoma simultaneously to ensure favourable patient outcomes. Due to the significant risk of drug interactions between HAART and antineoplastic agents these treatment regimens need to be designed with these in mind for optimal outcomes.

ART drug classes: Mechanism of action and metabolism

NRTIs

NRTIs are analogues of DNA nucleotides. The HIV reverse transcriptase enzyme cannot distinguish between host DNA and the nucleotide analogues. By incorporating the analogue into the cDNA chain cDNA synthesis is terminated, resulting in a non-functional cDNA. (14) NRTIs require intracellular phosphorylation to exert antiretroviral activity. They lack activity against free extracellular virus and have a slow onset of action. (14) Usually two drugs from this class resembling different DNA nucleotides are used as the backbone of HAART(15) NRTIs can all be administered orally and cross the blood-brain barrier. This class of drugs is eliminated primarily by renal excretion.(16)

NNRTIs

NNRTIs are a structurally diverse group of compounds that bind to the reverse transcriptase molecule, thereby inactivating it.(14) NNRTIs are rapidly absorbed after oral administration and are directed against activity of cell-associated and free HIV virions. These drugs are often small chemical compounds with long half-lives and are suitable for daily dosing.(14)

The NNRTIs are hydrophobic compounds that have a high affinity for the hydrophobic binding site of HIV reverse transcriptase. Binding of the drug to the enzyme results in alteration of the structural conformation of important residues required for optimal ability of the enzyme to catalyse DNA polymerisation. (14) The NNRTIs are administered orally with good bioavailability. They are extensively metabolised before undergoing renal and faecal excretion.(16)

PIs

Protease inhibitors are substrate analogues for the HIV aspartyl protease enzyme involved in the processing of viral proteins. Once bound to the enzyme active site the enzyme is blocked from further activity, inhibiting the viral maturation process. This leads to decreased functional virion formation.(15) Protease inhibitors are metabolised by the Cytochrome P450 enzymes before undergoing faecal excretion.(16)

Integrase inhibitors

Integrase inhibitors are a newer class of drug that targets the HIV enzyme integrase. This enzyme is responsible for integrating viral genetic material into the host DNA. Raltegravir is not metabolised by the cytochrome P450 enzyme. It is metabolised primarily by hepatic glucuronidation by UGT1A1. It is partly excreted unchanged in urine and faeces.(17)

Entry inhibitors

Entry inhibitors interfere with receptor-mediated entry of HIV into the host cell. Two subclasses exist: fusion inhibitors and CCR5 antagonists. Enfuvirtide is a fusion inhibitor that mimics the structure of the HR2 region of gp41(a glycoprotein on the HIV envelope) that binds to the HR1 region and facilitates the fusion of the viral envelope with the host cell membrane. Binding of the inhibitor to the HR1 region prevents the HR2 region from access to the HR1 region and inhibits the fusion process.(15) Enfuviritide is used as a subcutaneous injection and is catabolised via peptidases in the liver and kidneys. It is renally cleared.(17)

Maraviroc is a CCR5 antagonist that binds to the external part of the CCR5 transmembrane receptor that serves as a co-receptor for viral entry into host cells. Binding of this inhibitor prevents HIV gp120 from access to the co-receptor, thereby preventing the fusion process.(15)Maraviroc is a substrate of CYP3A4, P-glycoprotein/ABCB1. It is metabolised

via CYP3A to inactive metabolites in the liver. The unchanged drug is excreted in the urine and faeces.(17)

Antineoplastic agents: Mechanism of action and metabolism

Antineoplastic agents encompass a wide variety of drug classes. A number of different regimens exist and treatment is often tailored according to the patient's specific needs.

Antimetabolites

Antimetabolites are structurally similar to natural substances such as vitamins, nucleosides or amino acids. They compete with the natural substrate for the active site on a receptor or an essential enzyme. Some are incorporated into DNA or RNA. They are more efficacious over the long term.(18) Antimetabolites can be divided into three classes:

Folic acid antagonists such as Methotrexate which inhibits dihydrofolate reductase blocking the formation of tetrahydrofolate from dihydrofolate. This reaction is needed for the generation of coenzymes necessary for the synthesis of purines, thymidylate, methionine and glycine.(18)Methotrexate can be given either orally or intramuscularly and has a rapid onset of action. It can also be administered intrathecally for the prevention of CNS disease. It is degraded by the intestine and the liver and is eliminated as the parent compound by the kidney.(16)

Pyrimidine analogues act by inhibiting the synthesis of nucleic acids, inhibiting enzymes involved in or interfering with DNA synthesis.(18) The pyrimidines include fluorouracil, which inhibits the synthesis of nucleic acids, cytarabine, which inhibits DNA polymerase, and gemcitabine, which incorporates into host DNA interfering with DNA synthesis and ultimately leads to apoptosis.(18) Cytarabine can be administered intravenously or subcutaneously. When used parenterally these drugs are extensively metabolised before undergoing renal excretion. (16)

Purine analogues are analogues of the natural purine bases and nucleotides. These drugs are able to inhibit nucleotide biosynthesis by incorporation into DNA. 6-Mercaptopurine is a derivative of adenine and thioguanine is a derivative of guanine. (18) Mercaptopurine and thioguanine are given orally. These drugs are primarily metabolised by the liver and GI mucosa. However, high doses of Mercaptopurine are partly excreted unchanged in the urine.(16)

Cytotoxic antibiotics

Anthracyclines: Daunorubicin and doxorubicin are antibiotics obtained from Streptomyces peucetius. (16).Anti-tumour antibiotics integrate with DNA and affect the topoisomerase II enzyme. Topoisomerase II is a DNA gyrase which splits the DNA helix and reconnects it to overcome torsional forces that interfere with replication. Anthracyclines stabilize the DNA

topoisomerase II complex, thereby inhibiting the reconnection of DNA strands. (18)Anthracyclines are administered intravenously and rapidly distributed to all body tissues except those of the CNS. They are extensively metabolised by the liver. It is excreted in both faeces and urine. (16)

Glycopeptides: Bleomycin is obtained from Streptomyces verticillus. The drug has its greatest effect on the neoplastic cells in the G2 phase of the cell cycle. Its cytotoxic action is mediated by free radical formation and DNA strand breakage. Bleomycin is administered intravenously and excreted renally. It undergoes enzymatic inactivation by a cytosolic cysteine proteinase enzyme called bleomycin hydrolase. (17)

Monoclonal antibodies

Monoclonal antibodies can be used for both the detection and the treatment of cancer. They can be derived from different sources: murine (mouse antibodies), chimeric (part mouse/part human), humanized (engineered to be mostly human), or fully human antibodies. The mechanism of action of monoclonal antibodies is varied and can either be direct or indirect. Direct effects include: induction of apoptosis, inhibition of receptor signalling and anti-idiotype antibody formation. Indirect effects include antibody-dependent cellular cytotoxicity and compliment mediated cellular toxicity. (18)

Rituximab was the first monoclonal antibody approved for cancer chemotherapy. It is a chimeric antibody and is highly effective in the treatment of relapsed or refractory B-cell NHL. It binds to the CD20 antigen on the B-lymphocyte. CD20 regulates an early step in cell cycle initiation. Rituximab binds to the antigen on the cell surface, thereby activating complement-dependent B-cell cytotoxicity. It also binds to Fc receptors, mediating cell killing through antibody dependent cellular toxicity. (16) Rituximab is administered intravenously or subcutaneously. (17) It is removed by opsonization via the reticuloendothelial system when bound to B lymphocytes, or by human antimurine antibody production (19)

Topoisomerase II inhibitors

Etoposide and vespid are semisynthetic derivatives of *Podophyllum peltatum*, a herbaceous perennial plant containing podophyllotoxin, which is used as a purgative and a cytostatic. They act by stabilizing bonds between topoisomerase II and DNA that cause strand breaks, thereby inhibiting DNA replication.(18) Etoposide can be given intravenously and orally. It is metabolised hepatically via the CYP3A4 to various metabolites. It is eliminated primarily unchanged in urine. (16)

Alkylating agents

The effect of these highly reactive compounds is produced by covalently linking an alkyl group (R-CH2) to a chemical species in nucleic acids or proteins. The number of cross links formed and the site at which they cross-link is drug specific. Most alkylating agents are

bipolar. They form bridges between a single strand or two separate strands of DNA, influencing the action of enzymes involved in DNA replication. This process interferes with cell replication or triggers apoptosis (18)

Cyclophosphamide and Isfosfamide are classified as nitrogen mustards under the bigger class of alkylating agents as chemotherapeutic agents. They are both prodrugs that must be converted to active metabolites by CYP450 enzymes. Both cyclophosphamide and Isfosfamide can be administered intravenously. These drugs are hepatically metabolised and partially excreted as unchanged drug in the urine and faeces. (16)

Anti-microtubule agents

Vincristine and vinblastine, the two prominently used vinca alkaloids, are classified under the group spindle poisons. They are extracted from the periwinkle plant. These drugs bind to tubulin, thereby inhibiting the assembly of the spindle during the metaphase of the cell cycle. This ultimately inhibits mitosis. The influence of these drugs on DNA repair is responsible for their toxicity. (18) Both vincristine and vinblastine are administered intravenously as their oral absorption is unreliable. Neither drugs penetrate the CNS in significant amounts. They are both extensively metabolised by CYP3A4 in the liver and undergo biliary excretion.(16)

Corticosteroids

Corticosteroids such as prednisone and dexamethasone inhibit T-cell proliferation and the expression of genes encoding various cytokines. In cancer treatment they are primarily used for their lymphocytotoxic effects and are effective in the treatment of lymphocytic leukaemia, lymphoma and multiple myeloma. (16) Prednisone is administered orally and is metabolised to the active metabolite prednisolone in the liver. Its conjugates are excreted in the urine.(17) Dexamethasone undergoes hepatic metabolism and is renally excreted. (17)

From the above literature review it is clear that the concomitant use of HAART and antineoplastic agents is of utmost importance in treating patients with HIV associated-lymphoma.

The aim of this critical review will therefore be to investigate the drug interactions between HAART and antineoplastic agents used for the treatment of HIV associated lymphoma and classifying these interactions. The outcome of this study will be to develop a quick reference tool that can be used to evaluate possible drug interactions.

Methodology

Study design

Grant and Booth, in an article "A typology of reviews", defines a critical review as a review that aims to demonstrate that literature has been extensively researched and critically evaluated for its quality.(20) According to these authors it goes further than merely describing identified literature and includes a degree of analysis and conceptual innovation. A critical review aims to present and analyse literature from multiple sources and manifests as a hypothesis or a model.(20)

This critical review will evaluate the drug interactions between ART used in South Africa and commonly used antineoplastic agents. The drug interactions will be classified using the following legend:

	Contraindicated/dangerous	CS
	Increased effect	CS/NCS
	Decreased effect	CS/NCS
	Toxic reactions	CS/NCS
	Isolated cases	CS/NCS
	Possible interactions	CS/NCS
	Beneficial augmentation	CS/NCS

CS: Clinically significant NCS: Not clinically significant

Figure 1: Legend classifying drug interaction

Measurement

The drugs that will be evaluated in this study are indicated in Tables 2 and Tables 3 below.

Table 2. Anti-retroviral drugs included in study

Anti-retroviral drugs	
Class	Drug
NRTIs	3TC ABC DDI d4T FTC TDF AZT
NNRTIs	EFV NVP RPV ETR
PIs	ATV DRV RTV LPV/R
Integrase inhibitors	RAL
Entry inhibitors CCR5 inhibitors Fusion inhibitors	 Maraviroc Enfuvirtide

Table 3. Commonly used antineoplastic agents

Antineoplastic agents	
Class	Drug
Antimetabolites	Methotrexate Cytarabine
Cytotoxic antibiotics	Glycopeptide: Bleomycin Anthracycline: Doxorubicin
Monoclonal antibodies	Rituximab
Topoisomerase II inhibitors	Etoposide
Alkylating agents	Cyclophosphamide Ifosfamide Dacarabzine
Anti-microtubule agents (Vinca alkaloids)	Vincristine Vinblastine
Corticosteroids	Prednisone Dexamethasone

The drug interactions will be classified according to the abovementioned legend on Table 4 for easy referencing.

Table 4: Anti-retroviral drugs																			
		NRTIs							NNRTIs				PIs				Integrase Inhibitors		
		3TC	ABC	DDI	d4T	FTC	TDF	AZT	EFV	NVP	RPV	ETR	ATV	DRV	RTV	LPV/R	RAL	Maraviroc	
Antimetabolite	MTX																		
	Cytarabine																		
Cytotoxic antibiotics	Bleomycin																		
	Doxorubicin																		
Monoclonal antibodies	Rituximab																		
Topoisomerase II inhibitors	Etoposide																		
Alkylating agents	Ifosfamide																		
	Cyclophosphamide																		
	Dacarabzine																		
Anti-microtubule agents	Vincristine																		
	Vinblastine																		
Corticosteroids	Prednisone																		
	Dexamethasone																		

Data with regards to drug interactions will be obtained from the following databases:

- Drug interaction checker
  - https://reference.medscape.com/druginteractionchecker
- Drug interaction tool
  - http://www.umm.edu/health/medical/drug-interaction-tool
- Drug interactions checker
  - https://www.rxlist.com/drug-interaction-checker.htm

The available data on the drugs being investigated will be obtained from the above-mentioned resources. Grading of the expected drug interactions will be done accordingly. Should there be a discrepancy with regards to the interactions described from the above-mentioned sources, a fourth source will be used: Lexicomp available from up-to-date. The level of evidence will also be included in the tool.

Table 5: Classification of levels of evidence

Level of evidence	Type of study
1a	Systematic reviews (SR) or randomised control trials (RCT)
1b	Individual RCT with narrow confidence interval
2a	SR of cohort studies
2b	Individual cohort studies and low-quality RCT
3a	Systematic reviews of case-control studies
3b	Case-control studies
4	Case series and poor-quality cohort and case control studies
5	Expert opinion

Source: Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)

After completion of the review the tool will be validated by a panel of peers rating its usefulness in a clinical setting.

Time schedule

Table 6 Time schedule for completion of the study

Outcome	Time frame	Responsibility
Protocol submission	May 2018	Researcher
Ethics evaluation	May 2018	Ethics committee
Data analysis	June-September 2018	Researcher and biostatistics
Preparation of manuscript	October-December 2018	Research and study leader

Budget

There are no costs to the Free State Department of Health.

Time considerations

The protocol, as well as the data collection, analysis and preparation of the manuscript will not be done in working hours. It will therefore not cause any interference with the researcher's duties as a medical practitioner.

Ethical considerations

The Free State Department of Health, as well as the Head of the Department of Internal Medicine, Dr Mofokeng, will be approached to give consent for the study. The protocol will be simultaneously submitted to the National Health Research Database, as well as to the Health Sciences Research Ethics Committee of the University of the Free State for their consideration and approval.

Publication of findings

Findings will be submitted in a publishable article to a peer-reviewed journal and if accepted, be presented at the Faculty Forum in 2019.

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Appendix D. Instructions to authors of the named peer review articles

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Word limit	3500-5500 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Background, Objectives, Method, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Editorial

Editorials are by invitation only and are intended to provide expert comment on relevant topics within the focus and scope of the journal.

Word limit	800 words
References	10 or less

Case Report

A venue to document their experience with testing, diagnosis and treatment of a patient, animal or group. This can include the diagnosis and treatment of a patient, or a potential description of the implementation of an educational programme or healthcare-related intervention towards the improvement of human development

Word limit	500-800 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Introduction, Patient presentation, Management and outcome, and Conclusion
References	15 or less
Tables/Figures	no more than 4 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Review Article

Review articles provide a comprehensive summary of research on a certain topic, and a perspective on the state of the field and where it is heading. These articles are often meta-analyses comparing and combining findings of previously published studies.

Word limit	2500-4000 words (excluding the abstract and references)
References	15 or less
Structured abstract	250 words to include a Background, Objectives, Method, Results and Conclusion
Tables/Figures	data in the text should not be repeated extensively in tables or figures

Scientific Letter

Original research that is limited in scope can be submitted as a scientific letter rather than a full original research article.

Word limit	1500 words
References	6 or less
Tables/Figures	no more than 1 Table/Figure

Guidelines

A guideline provides evidence-based recommendations that will influence clinical research and practice. These can be consensus-based statements of reporting standards or clinical practice guidelines.

Word limit	1000 words

Opinion Papers

Short opinion pieces or personal perspectives (not research papers) that takes on a personal viewpoint of HIV and/or AIDS treatment, prevention and related topics relevant to clinical and public health practice as to provide a contextual and holistic view of practices across the continent. With rare exceptions, these essays are meant to express a personal viewpoint and should have no more than two authors.

Word limit	2000 words (excluding the structured abstract and references)
Unstructured abstract	250 words
References	15 or less
Tables/Figures	no more than 2 Tables/Figure
Ethical statement	should be included in the manuscript, if applicable

Cover Letter

The format of the compulsory cover letter forms part of your submission. Kindly download and complete, in English, the provided **cover letter**.

Anyone that has made a significant contribution to the research and the paper must be listed as an author in your cover letter. Contributions that fall short of meeting the criteria as stipulated in our policy should rather be mentioned in the 'Acknowledgements' section of the manuscript.
Read our **authorship** guidelines and **author contribution** statement policies.

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative change or differences on answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)
  Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.
  Research methods and design: This must address the following:
- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.

- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named.
Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Case Report full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract should be no longer than 250 words and must be written in the past tense. The abstract should give a concise account of the Introduction, Patient presentation, Management and outcome and significance of the matter. The abstract can be structured and should consist of four paragraphs labelled Introduction, Patient presentation, Management and outcome, and Conclusion.

- Introduction: Describe the context and the reason for publishing this patient study.
- Patient presentation: Describe your 3-stage assessment of the patient.
- Management and outcome: Describe the management plan, progress and final outcome.
- Conclusion: Summarise the lessons learnt and key implications or recommendations.

Introduction: Convey clearly what is particularly interesting about the patient that you want to describe to the reader. It is useful to begin by placing the study in a historical or social context. If similar cases have been reported previously, please describe them briefly. Clarify your aim or objectives in publishing this patient study.

Ethical considerations: Papers based on a case study that involves the treatment of humans must adhere to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Specify the recognised ethics committee from which approval for the case study was obtained; also state the serial number of the ethical clearance. Case studies must have the consent of the patient(s) or waiver of consent approved by an ethics committee.

Patient presentation: Describe your patient in detail with consideration of the following aspects:

- Describe the information that was gathered on the patient's medical problem(s) from the consultation, physical examination and results of any investigations.
- Describe the information that was gathered on the patient's perspective of their illness (loss of function, ideas, beliefs, concerns, expectations, or feelings)
- Describe the information that was gathered on the patient's context (family structure and function, occupational issues, environment)
- Provide a 3-stage assessment of the patient's clinical, individual and contextual issues.

Management and outcome: In this section, you should clearly describe the plan for care, as well as the care that was actually provided, how the patient's condition progressed over time and the final outcome.

Discussion: Summarise the key points, lessons learnt and discuss these in relation to the literature. Clarify the implications or recommendations that arise from this patient study.

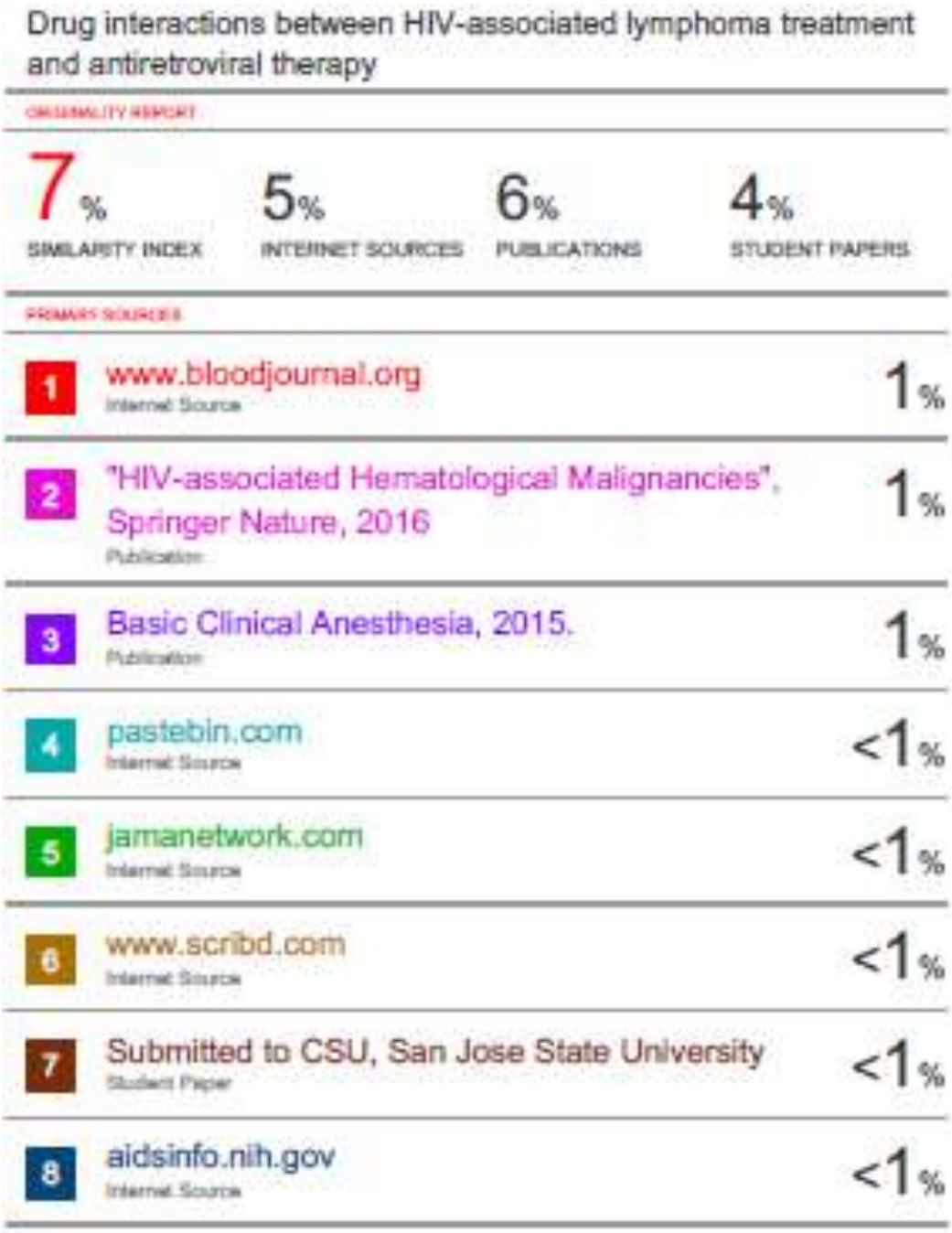
Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named.
Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant

- Disclaimer: a statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Appendix E. Summary report compiled in the Turnitin Plagiarism search engine



Drug interactions between HIV-associated lymphoma treatment and antiretroviral therapy

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Appendix F: Declaration from language editor

DECLARATION OF TECHNICAL AND EDITORIAL ASSISTANCE

TO WHOM IT MAY CONCERN

I hereby declare that with regard to the following document:

Author: Dr. Lana Meyer

Title: Drug interactions between HIV-associated lymphoma treatment and antiretroviral therapy

- I have performed the language editing (grammar, vocabulary and syntax).
- I assisted the author with the technical preparation of the manuscript, including layout and formatting.
- I verified the accuracy of the citations in the list of references.
- I obtained and verified the most recent active Uniform Resource Locator (URL) for internet-based references.

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