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Cervical Cancer in Human Immunodeficiency Virus (HIV) Positive Patients

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Abstract

The clinical management of cervical cancer in human immunodeficiency virus (HIV) positive patients is associated with challenges mainly due to the state of their immunity. They are managed like their HIV seronegative counterparts with surgery or chemoradiotherapy. HIV, cervical cancer, radiotherapy and chemotherapy lower immunity through reduction in CD4 cell counts.

A perspective on the management of HIV positive patients with cervical cancer is hereby provided.

Available studies were reviewed and peculiar characteristics of HIV patients with cervical cancer were examined. Strategies for managing such patients were identified.

HIV positive patients are younger and have more aggressive disease. They have more treatment related toxicities, poorer disease control with higher rates of incomplete and treatment delays than their HIV negative counterparts. Highly active anti-retroviral therapy (HAART) improves treatment outcome in such patients.

HIV positive patients with cervical cancer should be commenced on HAART at diagnosis. There should be closer monitoring of CD4 cell counts and viral load while on oncology treatment towards early recognition of need for prophylaxes against opportunistic infections. The dosage of the treatment modalities should also be adjusted according to CD4 cells count status. Possible interactions between anti-retroviral therapy (ART) with chemotherapy and radiotherapy should not be overlooked.

Keywords: HIV, cervical cancer, radiotherapy, chemotherapy

1. Introduction

Cancer of the uterine cervix is the most common gynecological malignancy and occurs worldwide [1]. Close to eighty percent of cervical cancers occur in the developing countries [2]. Chronic persistent infections with high-risk HPV subtypes play an important role in the carcinogenesis of cervical cancer. Human immunodeficiency virus (HIV) infection lowers immunity and is epidemic in some developing countries especially in sub-Saharan Africa. Cervical cancer is very common in HIV seropositive patients and is associated with an aggressive course and poor treatment outcome [3]. The associated compromise in immunity caused by HIV infection poses serious challenges to the clinical management of HIV positive patients diagnosed with cervical cancer. The main modalities of managing cervical cancer are surgery, chemotherapy and radiotherapy with most patients requiring combination therapy. These treatment modalities lead to reduced immunity in patients which is further reduced if one or two modalities are combined. In a patient with immunological challenges due to HIV infection, these treatment modalities can therefore worsen the immunological competence of the individual leading to poorer treatment tolerance, undue treatment toxicity and poor treatment outcome. At present, HIV positive patients diagnosed with cervical cancer are being managed using guidelines for managing HIV seronegative patients diagnosed with cervical cancer. The outcome of treatment in HIV positive patients are worse compared with HIV negative patients and HIV positive patients present late and are less likely to complete oncology treatment [4]. Infection with HIV has also been noted to increase mortality among cancer patients generally [5]. There is therefore need to consider additional therapeutic measures applicable to cervical cancer patients who are HIV positive.

The aim of this chapter is to highlight special features associated with HIV positive patients diagnosed with cervical cancer and provide a perspective on management strategies for these patients. This was done through a review of the evidence from basic, epidemiological and clinical studies which formed the basis for the recommendations for the management of HIV positive patients diagnosed with cervical cancer.

2. Peculiarities of cervical cancer in HIV positive patients

2.1. Epidemiology of cervical cancer

Cervical cancer occurs worldwide. The incidence of cervical cancer is still high in developing countries whereas it has decreased significantly in the developed countries over the last several decades. Close to eighty percent of cervical cancer occur in the developing countries [2]. The highest incidence is in sub-Saharan Africa especially in Eastern African countries [6]. Furthermore, the mortality due to cervical cancer is about ten times higher in the developing countries where screening and treatment modalities are neither common nor easily accessible. In developed countries, screening is the main factor responsible for the decrease in the incidence and mortality rates of cervical cancer.

2.2. Risk factors for cervical cancer

The most important risk factor for the development of cervical cancer is infection with human papilloma virus [HPV] [7]. In particular, chronic persisting infections with high-risk HPV subtypes play an important role in the carcinogenesis of cervical cancer. The subtype mostly implicated in cervical cancer aetiology is types 16 followed by 18. Other subtypes are also implicated but to a lesser extent. Human Immunodeficiency Virus (HIV) infection causes low immunity in those infected. In HIV positive patients, some less carcinogenic subtypes of HPV have been reported to play an important role in the aetiology of cervical cancer (Table 1).

HIV seronegative (worldwide)		HIV -1 seropositive (single report)	
HPV subtype	%	HPV subtype	%
16	54.4	52	14.7
18	16.5	35	9.4
58	5.1	58	9.4
33	4.7	51	8.6
45	4.4	16	7.8
31	3.6	31	7.5
52	3.4	53	6.7
35	1.9	18	6.4
39	1.3		
59	1.3		

Table 1. Most frequent HPV types among women with invasive cervical cancer by any histology. Sources: HIV negative: ICO HPV Information Centre (2014); HIV-1 positive: [8]. Subtypes 52 and 35 that are less carcinogenic in HIV negative patients are more important in HIV positive patients.

2.3. Human Immunodeficiency Virus (HIV) infection

Immunodeficiency is an important cofactor for persisting infections with HPV. It increases the virulence and aggressiveness of HPV thereby accelerating the progression to malignant transformation of the endo-cervical epithelial cells.

Human immunodeficiency virus (HIV) lowers immunity and is epidemic in most developing countries. Cervical cancer is very common in HIV seropositive patients and has an aggressive course with poor treatment outcome [3]. Regions of high prevalence of cervical cancer corresponds with regions of high prevalence of HIV infection (Figures 1& 2).

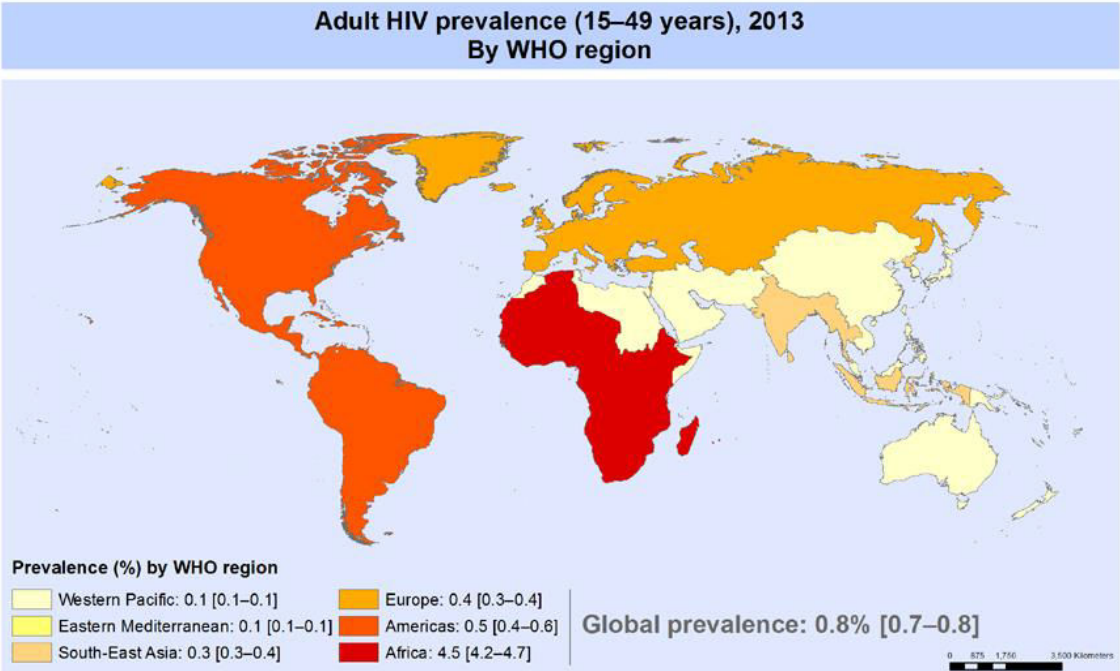


Figure 1. Adult HIV prevalence by WHO region (WHO 2013) <http://www.who.int/gho/hiv/en/>. Sub-Sahara Africa has the highest prevalence rate of 4.5% while Western Pacific and Eastern Mediterranean have the least with 0.1% prevalence.

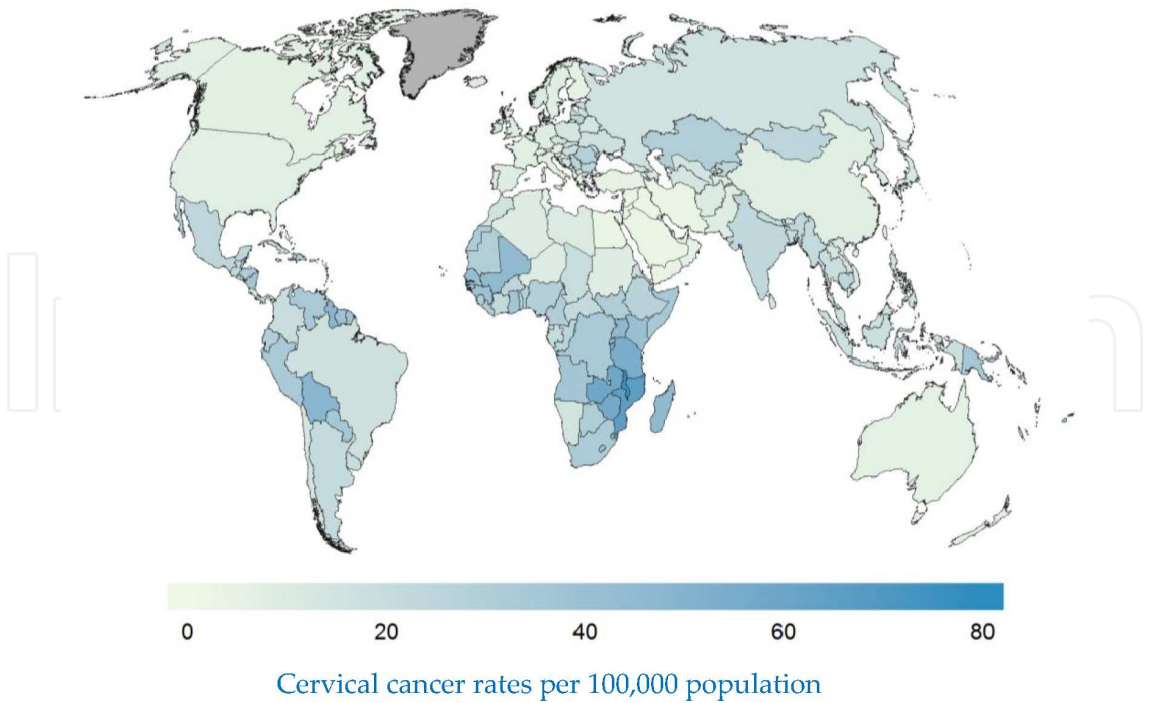


Figure 2. Estimated Cervical Cancer Incidence Worldwide in 2012 (GLOBOCAN 2012)

2.4. HIV infection and cervical cancer

Cervical cancer is one of the malignancies commonly diagnosed in people living with HIV. Other commonly associated malignancies in HIV setting include lymphomas, Kaposi's sarcoma, anal carcinoma and other HPV associated malignancies like vulval and penile cancers. Worldwide, cervical cancer incidence is higher among HIV positive women compared with HIV negative women. In a North American multi-cohort collaboration prospective study involving 13,690 HIV positive and 12,021 HIV negative women, it was found that HIV positive women had 7 times more incidence of cervical cancer than their HIV negative counterparts [9]. In a study in West Africa to assess the relationship between HIV infection and cervical cancer, HIV infected women had higher rates of 22/132 (16.7%) than controls 10/120 (8.3%) ($p = 0.048$) [10].

Cervical cancer has been observed to occur in younger age ranges among HIV positive patients than with HIV negative women (about 10 years younger) and the disease is also noted to have a more aggressive course with metastasis to unusual sites like the skin and brain. Recurrences are much earlier and frequent than in HIV negative women [11, 12]. HIV positive women are also noted to have cervical cancer at higher CD4 counts compared with the low CD4 counts associated with other AID associated malignancies like Kaposi's sarcoma and lymphomas [13].

2.5. Screening for cervical cancer

Screening for cervical cancer is an effective strategy for reducing the incidence and mortality of cervical cancer. The availability of effective screening corresponds with reduced incidence and mortality of the disease. It is the main reason why the incidence of cervical cancer in developed world is less compared with developing (poor resource countries) where screening programs are not available. The recommended schedule of screening of sexually active female populations by The American Cancer Society is summarized in Table 2.

Population	Recommended screening method
Age <21 years	No screening
Age 21-29 years	Cytology alone every 3 years
Age 30-65 years	HPV and cytology contesting every 5 years (preferred) Cytology alone every 3 years (acceptable)
Age > 65 years	No screening following adequate negative prior screening
After hysterectomy	No screening
HPV vaccinated	Follow age specific recommendations (same as unvaccinated women)

Table 2. Recommended screening scheme for cervical cancer (adapted from Saslow (2012) [14])

In HIV infected individuals the progression of HPV infection to carcinogenesis is accelerated and there is need to shorten the period of screening in women living with HIV so as to diagnose cervical squamous epithelial changes early. In a report of long term follow up of participants using cervical cytology, Massad and colleagues (2008) reported high grade squamous epithelial lesion of 4.4 in 1000 person-years in HIV positive patients against 1.3 in 1000-person years among HIV negative women. At ten years observation period, the cumulative risk of abnormal cytology was 77% in HIV positive individuals as against 50% in HIV negative individuals [15]. In another report of a cervical cytology follow up of 409 HIV positive women, progression of cervical lesions occurred in 39 cases. In 24 (61.5%) cases, the first diagnosis was benign cellular changes (BCC) and 21 out of the 24 cases had low-grade squamous intraepithelial lesion (LSIL) after one year. In 11 (28.2%) out of the 204 cases, the first diagnosis was BCC, and 9 cases had high-grade intraepithelial lesion (HSIL) after 1 year. In 2 (5.0%) out of the 204 cases, the first diagnosis was LSIL and the second was HSIL at one year interval. Two (5.0%) had the first diagnosis as HSIL, and the second as invasive carcinoma at 2-yr interval [16]. Cervical intraepithelial neoplasia (CIN) has also been reported to be more common in HIV positive women with CD4 cell count < 200 cells /ul [17]. Cervical cancer has also been noted to occur in younger women with HIV infection than in those without, and the peak incidence has been reported to be a decade earlier [18]. These results point to the need for shorter screening intervals for HIV positive women. In addition, the diagnosis of abnormal cervical cytology has been shown to be unrelated with current intake of highly active anti-retroviral therapy (HAART) [19]. It could therefore be beneficial to commence cervical cancer screening at an earlier age possibly at age 19 years with a screening interval of 2 years for those with CD4 count \geq 200 cells/ul and yearly for those with CD4 count < 200 cells/ul irrespective of HAART status.

2.6. Pathophysiology of HIV infection

HIV infection lowers immunity through the destruction of CD4 lymphocytes. The first target of HIV in the host system is the CD4 T cells. The HIV cell envelope binds to the CD4 cell receptor causing further activation of co-receptors that will eventually lead to the fusion of the host and viral cell membranes. The virus then gets totally into the host cell. This process leads to the destruction of CD4 cells through various mechanisms as the virus multiplies in the host system [20, 21].

The level of destruction is related to the level of HIV viral load in the patients system. CD4 cell count and viral load are the recommended tests to measure HIV positive patients' immune status which can also indicate the rate of destruction of immune cells [22]. Progressive reduction in CD4 cell population reduces the ability of the body to ward off infective agents leading to occurrence of opportunistic infections in HIV infected individuals. Dormant infections such as Herpes zoster can also be reactivated under conditions of depressed immunity. These opportunistic infections add to the deterioration of the clinical states of HIV infected patients leading to poor treatment outcome. Opportunistic infections are common if CD4 cells count is below 200 cells/ul [23]. The list of common infections associated with depressed immunity is presented in Table 3.

Infective Agents	Species
Viral	Human Herpes viruses (Herpes simplex types 1 & 2, varicellazoster virus, Epstein-Barr virus, Cytomegalovirus), Measles, Respiratory syncytial virus, Influenza, Adenovirus
Bacterial	Legionella pneumophila, Listeria monocytogenes, Salmonella typhimurium, Mycobacterium tuberculosis, Atypical mycobacterium
Parasitic	Pneumocystis pneumonia, Toxoplasma gondii, Cryptosporidia spp,
Fungal	Candida spp, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immiti

Table 3. Common opportunistic infections associated with depressed T cell immunity Adapted from Mackall (2000) [23].

2.7. Clinical aspects of HIV infection and cervical cancer

The higher the HIV viral load, the more likely the compromise in the immune status. Cervical cancer patients with HIV have been reported as having lower levels of CD4 cells count than HIV sero positive patients without cervical cancer. In a report by Leita0 and colleagues (2008) comparing the CD4 cells count and viral load in 15 HIV positive cases with cervical cancer with 60 HIV positive patients without cervical cancer controls, the median CD4 count for cases was 208 cells/IL (range, 18-1102 cells/IL) while that for controls was 445 cells/IL (range, 20-1201 cells/IL) ($p = 0.03$). The median viral load was 16,918 copies/mL (range, 50-214,915 copies/mL) for cases while that for control was 1430 copies/mL (range, 50-571,000 copies/mL) for controls ($p = 0.15$ [24]). In the WHO staging of HIV, the association of HIV with cervical cancer is classified under stage IV as with other AIDS defining malignancies indicating severity and warrants the commencement of anti-retroviral therapy [25]. HIV infection is also noted to be associated with high grade cervical cancer which leads to rapid progression of the disease.

2.8. Management of cervical cancer

The management of cervical cancer follows a multimodality approach. Relevant clinical examinations and investigations to assess the stage of the disease and the suitability of the patient for the modes of therapy have to be done. The choice of treatment depends on the stage of the disease and the performance status of the patient. The treatment choice usually involves surgery, radiotherapy and chemotherapy either alone or in combinations.

The treatment is usually chosen based on the stage of the disease. Treatment follows guidelines that operate in various countries and regions. The European Society for Medical Oncology (ESMO) guidelines (2012) is outlined in Table 4. [26]

2.9. CD4 cell count and cervical cancer treatment

Chemotherapy leads to suppressed immunity especially through the reduction of CD4 and CD8 cell counts in HIV positive patients. The effect is more marked on CD4 cells. The recovery is slow and better with CD8 than CD4 cells. The recovery of CD4 cells depends on the state of the thymus gland as they are thymus dependent. The thymus gland undergoes involution in the adults and hence recovery of CD4 cells count is usually very slow in those with involute thymus gland. The effect of chemotherapy is more marked with

Stage	Treatment	Issue
IA1	Conization or simple hysterectomy ± salpingo-oophorectomy and PLND if LVSI	Conservative surgery
IA2	Conization/radical trachelectomy or modified radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB1, IIA	Radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB2, IIB–IV	Combination CT/RT with cisplatin	NACT to large bulky tumors prior to CT/RT

PLND- pelvic lymphadenectomy; LVSI- lymphovascular space invasion; CT- computed tomography; NACT- neoadjuvant chemotherapy; RT- radiation therapy

Table 4. Cervical cancer treatment according to Stage (ESMO guideline 2012).

alkylating agents, purine nucleoside analogues and steroids [23]. In a study to assess the activity of the thymus gland after chemotherapy, it was reported that in younger patients aged between 18-49 years, the thymus function was evident in 63% of the participants compared with 0% of their counterparts aged 70-91years three months post treatment [27]. Pelvic radiotherapy has been reported to lower immune cells significantly in HIV sero negative patients. These cells include CD4 T- lymphocytes, B cells and Helper T cells. The reduction could be up to 50% in some instances [28, 29].

The advent of highly active anti-retroviral therapy (HAART) has improved the immunological status of HIV positive patients and control the increase in viral load [30]. HAART leads to rapid reduction in HIV viral load and sometimes to clinically undetectable level [31]. In a study to assess the effects of combination chemotherapy on immune status of HIV associated lymphoma patients, Powles (2002) reported that there was a significant drop in CD4 T cells. Following completion of treatment, the recovery of CD4 T-cells was faster in patients receiving HAART than in those without HAART [32]. The treatment with HAART does not however prevent the development of cervical cancer in HIV positive patients [33].

Patients with compromised immunity usually suffer more treatment toxicities as well. Chemo-radiotherapy used in the treatment of cervical cancer affect the immune status of patients. Chemotherapy leads to immune cells suppression and the toxicity following radiotherapy is increased in patients with compromised immunity [18]. HIV positive patients not on HAART are therefore more likely to experience compromised immunity than those on HAART. With decreasing immune status among HIV positive patients, the rate of decrease of CD4 cells can be unpredictable and such patients can suffer from opportunistic infections that will further complicate their conditions.

2.10. Management of cervical cancer in HIV positive patients

Decisions on the management of cervical cancer in HIV positive patients are not straight forward. This is because of the immune concerns about such patients. Contributory factors to immune compromise in such patients include the cancer, the HIV infection and the modalities of treatment – chemotherapy and radiotherapy. There is the fear that oncology treatment will worsen the immune status of treatment. Standard treatment as with HIV seronegative patients are recommended. Radiation treatment of HIV positive patients with cervical cancer however, has been reported to be associated with a seven fold increase in multi-systemic toxicities compared with HIV sero-negative patients [18]. HIV patients with malignancy have also been reported to have impaired ability of the mucosa to repair radiation damage. In treating oropharyngeal tumour with radiation, it was reported that HIV positive patients had mucosal reaction with lesser doses of radiation than HIV negative patients [34]. With regards to cervical cancer, it is likely that the tissues with mucosal lining close to the treatment fields like urinary bladder and gastro intestinal tract (GIT) might be affected in a similar way. This pattern of mucosal reaction is attributable to low immune status of the patients.

Close to about 10% of HIV positive patients are also reported to be co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) or with both [35]. HIV positive patients diagnosed with cervical cancer should therefore be routinely screened for HBV and HCV. A study in sub-Saharan Africa reported that among HIV-infected individuals, mean HBV and HCV prevalence rates were 15% and 7%, respectively [36]. Such co-infections have been reported to accelerate the progression of HIV infection [37]. Such infections also warrant extra caution in using HAART drugs that are metabolised in the liver to minimise liver toxicity that may occur [38]. Chemotherapy and radiotherapy may also activate viral hepatitis in such patients leading to complications of therapy [39].

Essential measures to improve treatment tolerance and optimal outcome in HIV positive patients with cervical cancer include early commencement of HAART (at diagnosis) based on WHO recommendation of commencement of anti-retroviral therapy (ART) in WHO HIV stage IV patients. Other studies have also recommended the commencement (at diagnosis) of ART in all patients diagnosed with cancer based on the study results that show better outcome of treatment in such patients. Such patients are noted to have better CD4 cell count and viral load responses compared with those not on ART and are more likely to complete oncology treatment on schedule [40, 41, 42]. Generally, early commencement of ART in HIV positive individuals has been recently shown to be of benefit. In a randomized trial in Cote d'Ivoire West Africa, in which 2,056 participants with HIV-1 infection were included in the analysis (Temprano Trial), it was reported that ART reduced the possibility of severe illness by 44% in people starting treatment immediately at diagnosis, as compared to those starting ART only when their CD4 levels drop to below 500/mm³. The study also reported that prophylaxis against tuberculosis with isoniazid initiated among people living with HIV with a CD4 count greater than 500/mm³ reduced the risk of severe illness by 35%, compared with those without such treatment. Early initiation of isoniazid was also not associated with increase in the development of resistance to isoniazid [43].

Regular monitoring of CD4 cell count and viral load assay is needed towards early intervention in case of derangements below critical levels. Msadabwe (2009) reported the CD4 cells count trend during treatment and up to three months after treatment of HIV positive patients with cervical cancer treated with chemoradiotherapy. The average initial CD4 cells count was 321.06 cells /mm² at commencement of treatment. This gradually dropped to 62.56 cells/mm² at the end of treatment giving a mean difference of 258.2 cells /mm². There was however, gradual rise after treatment but by 3 months which was the end of the follow up period of the study, the pre-treatment level was not reached. The average count at the end of three months was one third of the pre-treatment value [44]. Significant drop in CD4 cells following radiotherapy applies to both HIV negative and HIV positive patients especially if the radiation fields are around areas with large lymphoid tissues such as the chest and pelvis. In HIV seronegative patients treated for early stage breast cancer and stage I seminoma with radiotherapy, it was reported that the CD4 cells count dropped by about 200 cells/ul and that pre-treatment levels could not be attained after six years follow up [45]. Monthly CD4 cells count assay is therefore needed to monitor the trend in CD4 cells count during treatment and at three monthly intervals after treatment to ensure adequate CD4 count levels. This practice will enable the early commencement of prophylaxis against opportunistic infections if CD4 cells count is below critical levels so as to reduce morbidity in the patients. The recommended CD4 levels for commencement of appropriate prophylaxis are presented in Table 5.

Pathogen	Initiate Prophylaxis	Preferred agent	Discontinuation of Prophylaxis
Mycobacterium avium complex (MAC)	CD4 <50 cells/mm3	Azithromycin 1200mg orally once weekly or Clarithromycin 500mg orally twice weekly	CD4 count increase to >100 cells/mm3 for ≥3 months in response to ART
Toxoplasma gondii encephalitis (TE)	CD4 <100 cells/mm3 and Positive serology for Toxoplasma (IgG+)	Trimethoprim/ Sulfamethoxazole (TMP/SMX) double strength daily	Patient receiving ART with increase in CD4 count to >200 cells/mm3 for ≥3 months
Pneumocystis pneumonia (PCP)	CD4 <200 cells/mm3 or a history of oropharyngeal candidiasis	Trimethoprim/ Sulfamethoxazole (TMP/SMX) Single strength daily or double strength three times weekly.	CD4 count >200 cells/mm3 for >3 months in response to ART · Adequate viral suppression · If PCP occurred with CD4 >200 cells/mm3, prophylaxis should be maintained

Table 5. Criteria for initiating and discontinuing prophylaxis for opportunistic infections in HIV positive patients [adapted from NIH- AIDS Information 2015]. [46]

Other steps include testing for viral load every six months. This will ensure early diagnosis of drug resistances as increasing viral load while patient is on ART may indicate onset of drug resistance which should be promptly investigated and appropriate ART changes made.

External beam radiation therapy should be delivered at a daily dose of 1.8Gy per fraction to HIV positive patients to minimize toxicity [47]. Patients with CD4 cells count less than 200

cells/ul should be treated with 1.5Gy per fraction while the dose of weekly cisplatin should be given at a reduced dose of 30-35mg/m². These modifications have been reported to result in treatment tolerance similar to HIV negative patients [45]. Patients with CD4 cells count less than 150 cells /ul may however, not be able to withstand long course of radiation therapy and should be given short course treatments depending on performance status. The rate of completion of chemotherapy has been reported to be 30-45% among HIV positive patients compared with 64-89% among HIV negative patients[48, 49].

The above measures could help in improving the rate of completion of treatment in HIV positive patients. Renal dysfunction not myelo- suppression or gastrointestinal toxicity has been reported in a retrospective study, to be the main cause of chemotherapy suspension in HIV positive patients treated for cervical cancer and that chemotherapy was the most difficult section to be completed in HIV positive patients [4]. Carboplatin chemotherapy may be preferred to cisplatin in order to improve chemotherapy completion rate in HIV positive patients. Patients with CD4 cells count less than 200 cells/ul should however, not receive chemotherapy.

2.11. Drug interactions between chemotherapy and anti-retroviral agents

Platinum compounds commonly used in the chemotherapy of cervical cancer are cisplatin and carboplatin. Patients with persistent or recurrent and metastatic disease can have paclitaxel added to their treatment regimen [50]. On the other hand, anti-retroviral therapy in HIV treatment consists of combinations of three different drugs from at least two different drug classes (Table 6).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Protease Inhibitors	Entry and Integrase Inhibitors
Abacavir (ABC)	Delavirdine (DLV)	Atazanavir (ATV)	Dolutegravir (DTG)
Didanosine (ddI)	*Efavirenz (EFV)	Darunavir (DRV)	Elvitegravir (EVG)
Emtricitabine (FTC)	Etravirine (ETR)	Fosamprenavir (FPV/ FOS-APV)	Maraviroc (MVC)
*Lamivudine [3TC)	Nevirapine (NVP)	Indinavir (IDV)	Raltegravir (RAL)
*Stavudine (d4T)	Rilpivirine (RPV)	Lopinavir	
*Tenofovir (DF/TDF)		Nelfinavir (NFV)	
Zidovudine AZT/ZDV		Ritonavir (RTV)	
		Saquinavir (SQV)	
		Tipranavir (TPV)	

*Drugs commonly used for first line treatment of HIV infections.

Table 6. Major HIV drug classes. At least three drugs from two drug classes are selected for the treatment of HIV when ART is indicated Sources: NIH-NIAID, 2015; hiv-druginteractions.org 2015). [51]

Commonly used first line drugs are stavudine or tenofovir, lamivudine [Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and efavirenz [Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) [4]. Various other second line combinations are used in cases of drug resistance development or intolerable side effects of the first line combination drug regimen. Pharmacokinetic enhancers like Cobicistat [COBI] can be included with some of the combinations to increase the effectiveness of the treatment. Most HIV positive patients diagnosed with cervical cancer who are on HAART are likely to be placed on regimen containing the above drugs [52, 53].

Possibilities of drug interactions and potentiation of toxicities exist among these chemotherapy and ART drugs and these can affect treatment outcome. Paclitaxel is metabolized mainly by CYP 2C8 enzyme of the cytochrome P450 system to 6 alpha-hydroxypaclitaxel. Paclitaxel metabolites are inactive in comparison with the parent drug [54]. CYP 2C8 enzyme can be inhibited by some ART drugs such as Delavirdine, Ritonavir, Fosamprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir and Saquinavir. Concomitant intake of any of these agents can lead to increased toxicity of paclitaxel. On the other hand, Nevirapine is CYP 2C8 enzyme inducer and on concomitant intake of this agent with paclitaxel can lead to accelerated clearance of the active parent drug leading to ineffectiveness of paclitaxel [55].

Drugs	Stavudine	Tenofovir	Lamivudine	Efavirenz
Cisplatin	^a Potential interaction	^a Potential interaction	^b Potential interaction	No interaction
Carboplatin	^c Potential interaction	^d Potential interaction	^e Potential interaction	No interaction
Paclitaxel	No interaction	No interaction	No interaction	^f Potential interaction

^a Might increase risk of neuropathy as both drugs could cause neuropathy.

^b Cisplatin is eliminated through renal route via organic cation transporter 2 (OCT2) and human multidrug and toxin extrusion 1 (MATE1) enzymes. Cisplatin and lamivudine could compete for OCT2 which could slow their elimination. Lamivudine dose could be adjusted.

^c Carboplatin and stavudine administered together can increase the risk of peripheral neuropathy due to additive toxicity.

^d Both have nephrotoxic potential. Dose of tenofovir may need to be adjusted appropriately.

^e Lamivudine may affect renal function hence dose may need to be adjusted.

^f Efavirenz is a strong inhibitor of CYP2C8 enzyme mostly involved in the metabolism of paclitaxel. Co administration of these agents may increase the toxicity of paclitaxel.

NB. The above interactions are supported by very low levels of evidence.

Table 7. Cytotoxic and HIV drugs interactions relevant to HIV and cervical cancer (Source: HIV drugsinteraction.org. Accessed 2015 March 11).

There can be overlapping side effects between chemotherapy and ART drugs. Myelo-suppression is associated with most chemotherapeutic agents including paclitaxel and platinum compounds and this can also be induced by the ART drug zidovudine. Paclitaxel can also cause neuropathy likewise didanosine and stavudine. Care therefore has to be exercised in patients that take these drugs concomitantly or other alternatives should be given. Cisplatin and carboplatin can cause nephrotoxicity likewise the ART drug tenofovir while nausea and vomiting which is common with most chemotherapy drugs can also be induced by ART drugs in the classes of protease inhibitors, nucleoside and nonnucleoside reverse transcriptase inhibitors [50]. Patients on these agents should have effective management of nausea and vomiting with potent anti-emetics.

The possible interactions of cytotoxic drugs commonly used in cervical cancer chemotherapy with first line drugs used in the treatment of HIV infection are presented in Table 7 above.

Interactions between cytotoxic drugs used in the treatment of cervical cancer and first line ART drugs are quite favorable as contained in Table 7 with the associated levels of evidence. Combining the treatment modalities in HIV positive patients should therefore be tolerated by most patients.

3. Conclusion

The outcome of treatment in HIV positive patients diagnosed with cervical cancer is still poor especially in regions with high prevalence of HIV and cervical cancer. This could be improved through prompt commencement of such patients on ART at diagnosis. Close monitoring of the immune status (CD4 cell) and viral load is needed to ensure early diagnosis of depressed immune status and HAART treatment resistance. This could give early indication for commencement of appropriate prophylaxis against opportunistic infections and review of ART drug combinations. There is need to continue further search for other modes of treatment such as targeted therapies and radio sensitizers that can improve the effectiveness of managing HIV positive patients diagnosed with cervical cancer. Prospective studies are also needed to establish optimal radiation and chemotherapy doses in HIV positive patients diagnosed with cervical cancer.

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