

Proposal of model for personalized early adapted cancer screening in people living with HIV: experience of “Gaetano Martino” Hospital University of Messina

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Abstract. – Human immunodeficiency virus (HIV) infection has historically been related to the development of specific cancers, some of which are so closely linked to the infection, such as Kaposi’s Sarcoma (KS), that they have earned the name Acquired Immuno-Deficiency Syndrome (AIDS)-defining cancers (ADCs). While the development of antiretroviral therapy (ART) has decreased the incidence of AIDS-defining cancers, the resulting aging of people living with HIV (PLWH) highlighted an increased occurrence of other forms of cancer.

At the “Gaetano Martino” hospital in Messina, we developed a multidisciplinary approach

by creating a bridge between the Oncology Unit and the Infectious Diseases Unit to carry out screening and a more rapid diagnostic and therapeutic journey for cancers in PLWH.

The goal is to improve the diagnosis of various types of cancer by involving other professionals, such as gastroenterologists and gynecologists, to ensure faster access to treatment and, therefore, a greater chance of survival. In addition, our multidisciplinary approach has also included vaccine screening, offered by the “Gaetano Martino” hospital and useful for preventing the development of specific forms of cancer in the entire population and particularly in PLWH.

Key Words:

Screening cancer, HIV, AIDS cancer, non-AIDS cancer, Multidisciplinary team.

Introduction

The global burden of cancer in people living with HIV (PLWH) has increased significantly in recent years, and cancer is now the leading cause of death in people living with HIV¹.

Cancers associated with HIV-induced immunodepression include Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and invasive cervical cancer. The development of these oncologic diseases is mostly due to the reduction of CD4+ count and infection with other pathogens, such as Human Herpes Virus 8 (HHV-8), which is the main cause of KS, and Human Papilloma Virus (HPV), which is most commonly responsible for cervical cancer. These cancers are characteristic of the later stages of the disease, known as acquired immunodeficiency syndrome (AIDS), and are commonly referred to as "AIDS-defining cancers" (ADCs)².

The introduction of Antiretroviral Treatment (ART) has significantly reduced the number of cases of ADC and effectively halted the progressive damage to the immune system caused by HIV³.

Meanwhile, other cancers have also been observed in PLWH. This may be due to the aging of the HIV-positive population but also to the underlying but ever-present inflammation. In fact, despite the advent of antiretroviral treatment (ART), residual amounts of viral replication are always present in HIV patients, determining low but persistent inflammatory mechanisms that contribute to HIV persistence. This chronic, silent inflammation confers inherent fragility to PLWH and may be a substrate for carcinogenesis, including the development of non-AIDS-defining cancers (NADCs)⁴ (Table I).

NADCs do not appear to be associated with a normal CD4+ count. However, they appear to be related to co-infections with other viruses, which are more common in PLWH: hepatitis B virus (HBV) or hepatitis C virus (HCV) associated with hepatocellular carcinoma (HCC), HPV associated with oropharyngeal cancer, HPV associated with anal cancer, Epstein-Barr virus (EBV) associated with classical Hodgkin's lymphoma, melanoma and others^{5,6}.

In most cases, these co-infections are due to shared transmission routes with HIV⁷. Cancer screening is therefore essential, especially in the case of NADCs and their alarming rise in incidence^{8,9}.

ART resulted in higher HIV-specific overall survival rates and, therefore, older PLWH with a higher rate of occurrence of any disease, including cancer, like the general population. According to Chammartin et al¹⁰, continuous monitoring of the CD4+ count, CD8+ count, and CD4+/CD8+ ratio is required in PLWH, as a CD4+ count < 350/mm³, for example, correlates with a higher incidence of ADC and NADC. PLWH age earlier than the general population due to innate cellular senescence caused by the virus itself, antiretroviral therapies, and silent underlying HIV-related inflammation¹¹. The aim is to provide personalized cancer screening tests for people living with HIV that differ from those recommended in the Italian National Health System guidelines.

Due to the above-mentioned predisposition of HIV-infected individuals to cancer, it is extremely important to screen all HIV-infected patients for cancer and to create a standardized workflow involving different professionals¹².

Patients and Methods

The Infectious Diseases Unit at "Gaetano Martino" Hospital in Messina, Italy, followed about

Table I. Definition of the most frequent cancers in PLWH divided into AIDS-defining cancers (ADCs) and Non-AIDS-defining cancers (NADCs).

AIDS-defining cancers	Non-AIDS-defining cancers
Kaposi Sarcoma Aggressive B-cell non-Hodgkin lymphoma Cervical cancer	Anal cancer Hepatocellular carcinoma Oral cavity/pharynx cancer Lung cancer Hodgkin lymphoma

PLWH: people living with HIV.

200 patients with HIV infection, with an average of 10 new diagnoses in the last 2 years.

We currently have a dedicated HIV outpatient clinic run by three physicians, one professor, two residents, and a dedicated nurse.

Our patients are seen bimonthly or semi-annually, depending on the viro-immunological status of the patient according to current guidelines, with blood checks and a complete physical examination. During the examination, we perform a full and complete inspection of skin or mucosal lesions.

HIV viremia and CD4+, CD8+, and CD4+/CD8+ counts are determined at each appointment. Inflammatory markers such as C-reactive protein (CRP), interleukin-2 (IL-2) and lactate dehydrogenase (LDH), serum electrolytes, liver function enzymes, renal function markers, urine chemistry/physical examination, vitamin D, osteocalcin, parathyroid hormone, thyroid markers, prostate-specific antigen (PSA) in men, serology for syphilis, leishmania, toxoplasma, tuberculosis, viral hepatitis, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are checked infrequently. Women are also routinely tested for human chorionic gonadotropin (hCG), especially women receiving long-term antiretroviral therapy.

Over the years, we have established a workflow for our patients involving the oncology department,

initially for the diagnosis and treatment of oncologic diseases; then, we expanded our approach to other departments to provide comprehensive cancer care. Our patients need to follow a different diagnostic screening journey than the general population who follow the National Health Service guidelines. For PLWH, the timing of cancer screening must be advanced, or, in some cases, the first stage and other more comprehensive screening must be avoided to prevent false positives and negative results. In addition, all PLWHs are instructed to get vaccinated as early as possible. “Gaetano Martino” Hospital offers PLWH a comprehensive and fully accessible immunization pathway. At “Gaetano Martino” Hospital in Messina, we have formed a multi-healthcare provider working group to ensure comprehensive screening for our patients (Figure 1).

Results

Kaposi Sarcoma

Kaposi’s sarcoma (KS) is a multifocal lympho-angioproliferative, low-grade mesenchymal tumor associated with Kaposi’s sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus-8 (HHV-8). KS can be divided into four subclinical types: classical KS, which is

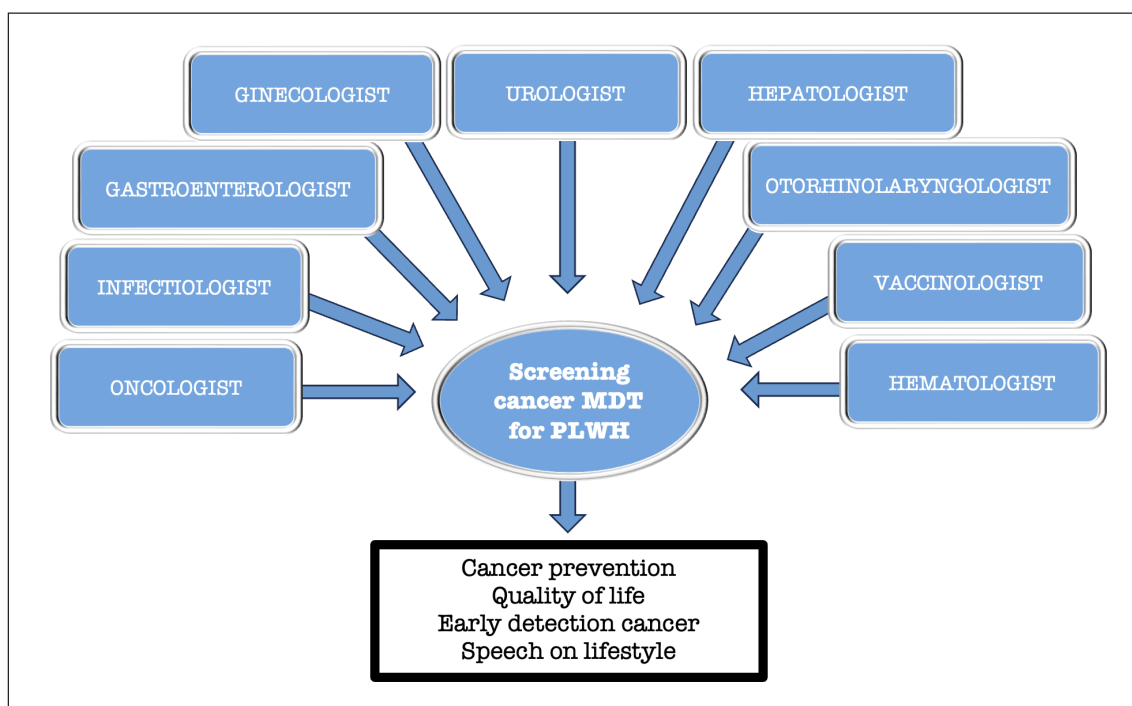


Figure 1. Multidisciplinary Team (MDT) involved in cancer screening for people living with HIV (PLWH).

typical of Mediterranean regions and is extremely indolent; HIV-associated KS, which is very common in the pre-ART era; endemic KS, which is similar to classical KS and is prevalent in areas of sub-Saharan Africa; and transplant-associated KS^{13,14}. KS is considered an ADC, and despite the decline in its incidence in the post-ART era, it remains the most common HIV-related cancer in many regions, especially in regions with less access to antiretroviral drugs. In African countries, for example, the incidence of KS is particularly high in older male patients not receiving ART¹⁵. The typical risk factor is immunosuppression, which is characterized by low CD4⁺ cell counts.

Skin and mucosal involvement are most frequently observed in KS. The skin lesions in KS range from pinkish-purple patches and papules to rapidly progressing ulcerated plaques and nodules with or without spread to the viscera. Visceral involvement, although less common, is the most dangerous as it is often misdiagnosed due to the absence of symptoms in the early stages¹³. Diagnosis of KS requires a skin biopsy to detect markers such as CD34 and CD31.

In the last three years in our hospital “Gaetano Martino” in Messina, three patients were diagnosed with KS, two with mucocutaneous and one with pulmonary KS, who were then diagnosed with HIV infection at AIDS stage and started ART and chemotherapy for KS. Two of them were admitted to other departments of our hospital because of the oncological disease and then tested for HIV; the third was admitted to the infectious diseases department with a diagnosis of KS and a positive HIV test. After his discharge, he began chemotherapy for KS with pegylated liposomal doxorubicin (PLD). Subsequently, the skin lesions increased in volume and became painful, so the patient was evaluated by the oncology radiation therapy unit to decide on possible targeted radiation therapy. During these treatments, the patient continued ART correctly and achieved optimal viral load suppression. Collaboration between the oncology department and the infectious diseases department has been key to the treatment and follow-up of patients currently on ART and recovering quickly.

HPV-Related Oropharyngeal, Anal, and Cervical Cancer

HPV is responsible for various forms of cancer, the most common being cervical cancer. Cervical cancer is the fourth most common cancer in women.

Risky sexual behaviors that lead to HIV infection also expose women to other sexually transmitted infections (STIs), such as HPV. Some high-risk HPV serotypes (16 and 18) are known to be closely linked to the development of cancer.

Among PLWH, risky sexual behavior is often more prevalent, especially among men who have sex with men (MSM), sex workers, and prisoners. Risk factors also include smoking, multiple births, and the combined use of oral contraceptives. HIV-induced immunosuppression plays an important role in the development of cancer in people with HR-HPV infection, with a permissive mechanism that promotes the accumulation of genetic damage and progression from dysplasia to cancer¹⁶.

HPV DNA integrates into the host's genome and can be found in many epithelia, depending on the route of transmission.

Invasive cervical cancer is asymptomatic in the early stages. If it penetrates deep into the tissue, it can occasionally cause blood loss, which is usually not related to the menstrual cycle.

As with cervical cancer, anal cancer is preceded by high-grade squamous intraepithelial lesions (HSILs). Although the lesions are easier to localize than cervical cancer, they may also be small and/or located in the inner mucosa, contributing to a delay in diagnosing the early lesion that may develop into cancer. The incidence of HPV-associated anal cancer is very high in PLWH, especially in MSM. Careful screening is required to detect and treat them early. PLWH with anal cancer who are eligible for chemoradiation therapy have the same outcomes and toxicities as non-HIV-infected patients if they are on regular ART and have a CD4 cell count > 200/mm³¹⁷⁻¹⁹. Similar to anal cancer, oropharyngeal cancer is easily localized when visible, making a good inspection and examination of the oral mucosa extremely important.

Fortunately, the introduction of vaccines against HPV, especially the protection against HPV serotypes 6/11/16/18/31/33/45/52/58, has helped to reduce HPV transmission in non-HPV-infected individuals and disease progression in infected individuals.

The guidelines of the Italian health system recommend a Pap test every 3 years for all women between the ages of 25 and 30 and the HPV DNA screening test every 5 years for women between the ages of 30 and 64 (Figure 2).

It is imperative that PLWH are also screened for HPV infection and cancer, just as people with

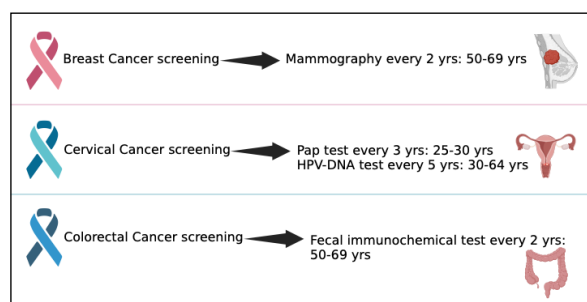


Figure 2. Current cancer screening programs recommended by the Italian National Health System.

an HPV infection or cancer diagnosis should also be screened for HIV and other STIs. In accordance with the Italian guidelines for the diagnosis and treatment of HIV infection, we perform an anal Papanicolaou (PAP) smear once a year on MSM PLWH and, if the results are abnormal, we refer patients to the Endoscopy Gastrointestinal Unit to perform a digital anal rectal examination (DARE) and, if suspected, a high-resolution anoscopy with acetic acid test.

At the same time, we work together with the gynecology department and carry out an annual screening with a PAP test and, if necessary, a colposcopy for our patients with HIV infection. However, to avoid the risk of underestimating earlier forms of HPV infection, it would be advisable to carry out an HPV DNA screening test for PLWH²⁰. In addition, all women with cervical cancer or other sexually transmitted diseases who come to the gynecologist are also screened for HIV. Very often, we also work with our gynecologist colleagues to screen for cancer and STIs in women who migrate to lower-income countries and go to the doctor for a known HIV infection or pregnancy. We also promote the vaccination offered by our hospital to our patients, which is particularly well received by the female population. These vaccines are very effective when administered to both boys and girls before first sexual intercourse but are strongly recommended for women and MSM for the prevention of HPV-associated diseases²¹.

Hepatocellular Carcinoma

The risk of developing HCC in PLWH is mainly related to co-infection with viral hepatitis (HBV and HCV) and high alcohol consumption. However, since the introduction of ART and the spread of more correct social norms of behavior, co-infection rates between HIV and viral hepatitis (HBV and/

or HCV) have decreased²². The increasing age of PLWH and the prevalence of comorbidities such as obesity, diabetes mellitus, and dyslipidemia have led to an increased rate of liver metabolic disorders leading to non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Some drugs in the ART regimen may adversely affect the outcomes of patients with dyslipidemia and/or insulin resistance and should, therefore, be modified to avoid metabolic complications²³. The cost-effectiveness of screening PLWH for HCC is controversial. Apart from HBV infection or cirrhosis, there is no evidence of a higher risk of HCC in HIV-infected patients²⁴.

Nevertheless, PLWH with HCC have a lower survival rate compared to non-HIV-infected patients^{24,25}, and a study by Torgersen et al²⁶ conducted in 35,659 PLWH has shown that high HIV RNA levels and long-term viremia are associated with a higher risk of developing HCC without underlying cirrhosis. Therefore, a screening campaign for prevention or early diagnosis certainly makes sense.

The treatment options for HCC do not differ between HIV-infected and non-HIV-infected patients, and the survival rate remains the same in both groups. However, a statistically significant difference in palliative treatment was found between the two groups^{24,25}. Liver ultrasonography (US) every six months is the current screening method used in all patients at risk of developing HCC, as recommended by international guidelines. It is often performed in conjunction with liver elastography (Fibroscan[®]), which is helpful in determining the stage of liver fibrosis. HIV patients with HCC may also benefit from a liver transplant if they have end-stage liver disease^{27,28}. Di Benedetto et al^{29,30} have described several cases in which the results of these patients were excellent, even compared to the HIV-negative population. Guerrini et al³¹ published at the same time a recent experience from a single center in which 110 liver transplants were analyzed, including 32 in HIV-positive patients. The results were outstanding. The 5-year overall survival rate between HIV-negative and HIV-positive patients was 71.6% and 69.9%, respectively.

In our hospital, we carry out a US test twice a year on our patients who are co-infected with HIV and HBV and/or HCV. In addition, HCV RNA, HBV DNA, alpha-fetoprotein, and liver function enzymes are tested regularly. It is also important to promote weight loss and diet in overweight PLWH.

Ultrasound screening is carried out in consultation with the Hepatology department. Liver elastography is usually reserved for patients with untreated HBV and/or HCV infection and is also performed by the Hepatology department. Newly diagnosed or known HCV-infected patients who have never been treated or have relapsed after previous therapy are referred to the Hepatology department and then included in the HCV network of Sicily to initiate specific antiviral therapy and follow-up.

Cooperation with the Oncology Unit is then required for patients who develop HCC to ensure the best treatment option for each patient, from liver resection and radiofrequency ablation (RFA) to trans-arterial chemoembolization (TACE) and systemic treatments.

Patients undergo a preliminary examination to assess the stage of the HCC, the feasibility of a possible resection, and the presence of metastases.

Patients receive psychological support and are given comprehensive information about the nature of the disease, treatment options, and mortality rate. Vaccination screening for PLWH also includes vaccination against HBV. Although it has been mandatory for all newborns in Italy since 1991, it is possible that the antibody titer has fallen drastically after a few years. In any case, a small percentage of the Italian population is not vaccinated against HBV. Therefore, every PLWH is examined by the vaccination center of our hospital, which carries out a comprehensive consultation, both if they have already been vaccinated and if they have ever been vaccinated. For cancer patients, the consultation is also extended to other vaccinations (herpes zoster virus, seasonal influenza, pneumococcal infection, and SARS-CoV-2)³².

Hodgkin and Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) are lymphomas defined by the acquired immunodeficiency syndrome and lymphomas not defined by the acquired immunodeficiency syndrome, respectively. They are due to a clonal expansion of malignant lymphoid cells. Viruses such as EBV or HIV are often involved in the pathogenesis. NHL is the most common type of lymphoma in PLWH. As with other cancers, the incidence has decreased following the introduction of ART. However, the incidence of HL has increased in the post-ART period, partly due to the lower incidence of NHL but also due to the stimulation of B cells by immune reactivation in people on ART³³.

Burkitt lymphoma is an aggressive non-Hodgkin lymphoma that can be divided into three forms: endemic, sporadic, and immunodeficiency-related. About 40% of HIV-related BL is associated with EBV^{34,35}.

A bridge between infectious diseases, oncology, and hematology is an important point in the diagnosis of PLWH and hematological diseases at our center. People with hematologic diseases are always tested for HIV. Unfortunately, when lymphoma manifests itself, the infection is often at an advanced stage. However, it is essential to screen every patient newly diagnosed with HIV for signs that could indicate hematologic disease. Therefore, in our hospital, an ultrasound examination of the lymph nodes is performed in every patient with a new diagnosis and at regular intervals after starting ART, especially in patients diagnosed at a late stage of infection or AIDS. The thymus gland is also scanned with a chest X-ray or CT scan.

Lung Cancer

Lung cancer is emerging as a leading cause of death in PLWH, in addition to the already known risk related to smoking and baseline inflammation³⁶. Data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) multi-cohort show that lung cancer incidence continues to increase among HIV-infected individuals but also suggest that the underlying risk of lung cancer is decreasing, possibly due to changes in smoking habits³⁶. Abstaining from smoking is an important detail for these individuals, as smoking is more common in HIV patients than in the general population³⁷ and would also reduce the incidence of other cancers. PLWH appears to develop lung cancer at a younger age than people who are not infected with HIV. The risk factors, in addition to smoking behavior, are the underlying inflammation and increased risk of lung infections, which contribute to the stimulation of the immune system and lung cells³⁸. Although overall survival rates are poor, survival rates of PLWH with lung cancer on ART are similar to those in the general population³⁹.

In our center, the incidence of lung cancer in people with HIV infection is, fortunately, low. Last year, a woman was admitted to our "Gaetano Martino" hospital in Messina with a diagnosis of lung cancer that had not yet been diagnosed and treated. The woman was also tested for HIV, which came back positive and was started on ART and, consequently, chemo-radiotherapy

with the collaboration of the oncology department. The woman was also examined by our pulmonologists and thoracic surgeons for a possible surgical resection of the cancer. Screening for lung cancer is a highly controversial topic. To date, it has neither been approved nor is it reimbursed by the Italian healthcare system. The National Lung Screening Trial (NLST) was the first study to demonstrate the benefit of low-dose chest CT (LDCT) as a screening method in high-risk individuals (between 55 and 74 years of age, smokers or former heavy smokers)⁴⁰. Passiglia et al⁴¹ have published a meta-analysis highlighting the benefit of LDCT in individuals with a history of cigarette smoking. Therefore, the most recent Italian guidelines recommend that annual LDCT should only be performed in patients with significant smoking cessation.

Gastrointestinal Cancer

Knowledge about gastrointestinal (GI) cancers in PLWH is sparse. However, an increased incidence of GI tumors in PLWH has been demonstrated⁴². The explanation for this increased incidence lies in the same factors as for the other types of NADCs after the introduction of ART, namely underlying inflammation, risk factors such as smoking, and a diet high in fatty acids, but above all in the increased life expectancy in PLWH on ART and it is known that age is a major risk factor for the development of some tumor types. Contrasting data concern the different outcomes between HIV-positive and negative patients. A clinical case-control study⁴² showed poorer performance status and shorter survival in HIV patients, in contrast to a recent meta-analysis by O'Neill et al⁴³ that demonstrated a similar risk and mortality rate for colorectal cancer in PLWH and non-HIV-infected individuals, as mentioned above, aging in HIV-infected individuals has resulted in a similar risk for some cancers as in the general population⁴⁴. The guidelines of the Italian National Health System recommend a fecal immunochemical test every 2 years for all persons between 50 and 69 years of age, followed by a colonoscopy if positive, to diagnose early stages of colorectal cancer (Figure 2).

In our hospital, “Gaetano Martino” in Messina, we have not seen any cases of colorectal cancer or other GI cancers in the last three years. However, people already administered ART must undergo annual screening for GI tumors, such as fecal immunochemical tests, fecal calprotectin, and possibly colonoscopy and esophagogas-

troduodenoscopy in suspected cases. In PLWH with high-risk sexual behavior, often concomitant anu-rectal ulcerative lesions, sometimes even bleeding, the fecal immunochemical screening test may be affected by high false-positive rates, so colonoscopy every 2 years may be preferred. In patients with a new diagnosis of HIV infection, both tests are always performed. A consultation with a gastroenterologist is carried out annually for our patients.

Prostate Cancer

Prostate cancer (PC) is the most common malignant disease in men. The blood test for prostate-specific antigen (PSA) is not officially recommended as a screening test by the Italian health system. However, it is recommended to be performed annually in men aged 50 and over. The data, endorsed by the European Association of Urology, come from two primary randomized controlled trials⁴⁵⁻⁴⁷ that confirm the benefits of prostate cancer screening in terms of PCa-specific survival and overall survival (OS). In addition, while screening may be associated with the detection of a greater number of localized tumors, it may also result in a higher proportion of indolent cancer cases being identified. Prostate-specific antigen (PSA) is specific for the organ but not specific for cancer. Therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis, and other non-malignant diseases. As a result, PLWH having anal intercourse (RAI) may experience an unanticipated increase in prostate-specific antigen (PSA). According to a survey of a population in the United States, a small number of patients are advised to avoid anal stimulation prior to a PSA test⁴⁸. The conventional transrectal ultrasound examination (TRUS) is not a reliable method for detecting prostate cancer⁴⁹. According to worldwide recommendations⁵⁰, multiparametric prostate MRI is considered a very sensitive method for the detection of clinically relevant prostate cancer. It is recommended as the examination of choice when prostate cancer (PCa) is suspected. In addition, it can facilitate the identification of prostate cancer by targeting prostate biopsies to the suspicious area, as recommended in the EAU guidelines for 2023. Therefore, HIV-infected individuals who engage in risky sexual behavior are susceptible to contracting other sexually transmitted infections (STIs), which may increase the likelihood of developing prostate cancer. Conversely, the frequency of sexual activity in these individuals

may have a protective effect against prostate cancer⁵¹. The evidence on the incidence of PC in PLWH people and the general population is contradictory. Some studies⁵² indicate a lower incidence of PC in PLWH, while others indicate a higher incidence compared to people without HIV infection. It should be noted that the incidence of PC in people living with HIV (PLWH) appears to have increased over time, but this increase is similar to that observed in the general population. Although the incidence of PC is similar, the mortality rate among people living with HIV is higher than in the general population. This could be due to inadequate screening and the presence of additional risk factors, as well as the underlying inflammation in HIV-infected individuals. Given the elevated likelihood of developing PC metastases and the difficulty in detecting them in the absence of symptoms, screening is crucial, even in the absence of clinical signs. At “Gaetano Martino” hospital, we administer an annual injection of PSA to our HIV+ patients.

Breast Cancer

The incidence of breast cancer (BC) is not increased in HIV-infected individuals compared to the general population, although it accounts for a

large proportion of malignant disease diagnoses. Nevertheless, HIV and breast cancer share common signaling pathways and receptors, and the virus has been shown to play a role in accelerating cancer development, particularly by acting on immune signaling, upregulation of angiogenesis, and metastatic spread^{5,53}. Screening campaigns for the early detection of breast cancer have been shown to increase risk awareness in the population significantly. It is, therefore, essential to increase screening for PLWH and promote breast self-examination. In our hospital, screening with ultrasound breast examination or mammography, when indicated, is performed according to current recommendations for the general population. Mammography is performed every two years for women > 50 years old (Figure 2). In discussions with oncologists, our patients are often encouraged to adhere to the screening campaign and always perform a breast self-examination.

Summary of Multidisciplinary Workflow for Screening Cancer and Vaccination in PLWH

We suggest that a multidisciplinary approach may be the key to the early detection of HIV infection and cancer (Figure 3). After

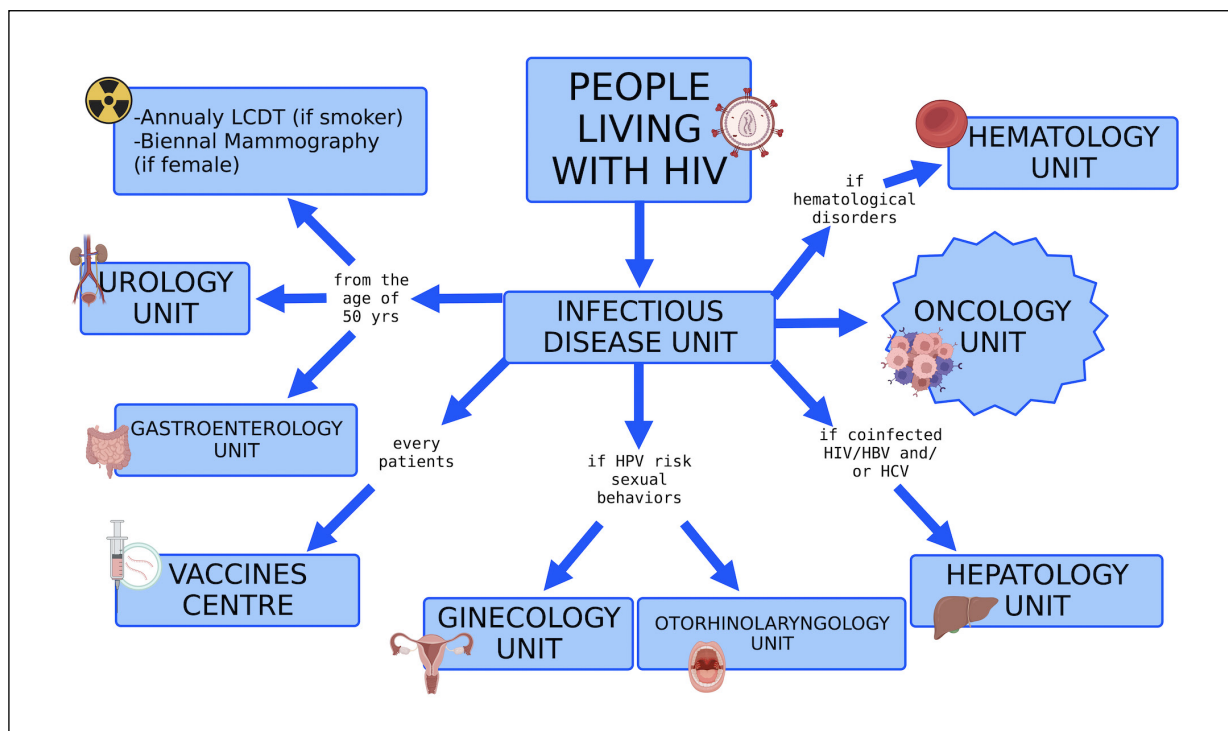


Figure 3. Multidisciplinary workflow for cancer screening and vaccination dedicated to PLWH developed at “Gaetano Martino” hospital in Messina.

a confirmed HIV diagnosis, the patient starts antiretroviral therapy (ART) and begins regular checks for infectious diseases. Every patient is referred for a full vaccination screening (HBV, HPV, HZV, COVID-19, influenza, and others) at the vaccine center. All patients with risk factors for HPV infection are encouraged to have an annual cervical Pap test or HPV DNA test for women and an annual anal Pap test in the gynecology department for men. If these tests are positive, patients should have further examination, such as a colposcopy and/or anoscopy (performed in the gastroenterology department). In addition, a rhino-otolaryngologic examination is required in the Department of Otorhinolaryngology. In the presence of co-infection with HIV/HBV and/or HCV, HBV DNA, HCV RNA, liver function enzymes, and a six-monthly liver ultrasound are performed in the hepatology department for each PLWH and, if HCC

develops, an assessment for radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) is performed. Any hematologic disease will be evaluated in the hematology department, where a bone marrow aspiration may be performed. Every PLWH over the age of 50 undergoes the following examinations: annual PSA test (especially in the presence of sexual risk factors such as MSM) and, if suspected, examination in urology for a prostate biopsy, annual fecal immunochemical test (FIT) and colonoscopy with possible biannual biopsy in the case of a positive or false FIT in gastroenterology, annual low-dose computed tomography of the breast (LDCT) in PLWH who are heavy smokers or heavy smokers, and finally, in women, a biennial mammogram. The entire screening program for PLWH described above is organized by the Oncology Unit and the Infectious Disease Unit, which coordinate and evaluate the results.

Table II. Our workflow explanation for personalized adapted screening cancer in PLWH.

PLWH	Unit involved	Exams performed
Every PLWH	Vaccines Centre	Vaccinations screening: HBV, HPV, HZV, COVID-19, Flu and others
If HPV sexual risk behaviors	Ginecology Unit Otorhinolaryngology Unit Gastroenterology Unit	Annual anal Pap test: if positive → DARE and if suspected anoscopy with acetic test (performed by Gastroenterology Unit) Annual cervical Pap test or HPV-DNA test: if positive → colposcopy Rhinophybrlaryngoscopy If suspected anal cancer in MSM or female DARE and anoscopy with acetic test
If coinfectd HIV/HBV and/or HCV	Hepatology Unit	Check HBV-DNA, HCV-RNA, liver function enzymes, semetral US: if develop HCC evaluation for RFA or TACE
If hematological disorders	Hematology Unit	Evaluation signs and symptoms suggest hematological disease: if suspected bone marrow aspiration
Every PLWH from 50 yrs	Urology Unit Gastroenterology Unit	Annualy PSA (especially if sexual risk): if suspected rectal esploration and eventually prostatic MRI for evaluation biopsy Annualy FIT: if positive or false positive risk → biennal colonoscopy with eventual biopsy
If strong smoker or heavy smoker	Annual LCDT (from 50 yrs)	
If female	Biennal Mammography (from 50 yrs)	

PLWH: people living with HIV, HBV: hepatitis B virus, HPV: human Papilloma virus, HZV: herpes-zoster virus, DARE: digital anal rectal examination, US: ultrasound, HCC: hepatocellular carcinoma, RFA: radiofrequency ablation, TACE: transarterial chemoembolization; MRI: magnetic resonance imaging, FIT: fecal immunochemical test, LCDT: low-dose computed tomography.

Discussion

The multidisciplinary approach model introduced in our hospital, “G. Martino” in Messina, allows for the early detection of tumors in PLWH. Overall, we are seeing a dramatic decrease in the incidence of ADCs and a parallel increase in NADCs. In Spain, a higher cancer mortality rate has been observed in PLWH than in HIV-negative patients over the last 18 years⁵⁴. Shiels et al⁵⁵ described the projected cancer incidence in PLWH in the USA by 2030, when the most common malignancies in these patients will be prostate and lung cancer, as in the general population. In 2012, Zanet et al⁵⁶ described a small cohort of HIV-positive patients who had pancreatic cancer, were younger and had shorter survival than HIV-negative patients. Therefore, not only the multidisciplinary approach but also the influence of the individual in terms of primary prevention is crucial. In addition, our approach aims to sensitize PLWH to pay attention to and change high-risk sexual behaviors (e.g., condom use among MSM) to reduce the incidence of sexually transmitted diseases and thus the transmission of potentially oncogenic viruses such as HPV or to change the habits of injecting drug users by exchanging needles and syringes to reduce the transmission of HBV and/or HCV. At the same time, quitting smoking remains key to reducing the spread of lung cancer, now the most common malignancy in PLWH, while oral vitamin D supplementation may help as an antioxidant⁵⁷. The current eligibility criteria for clinical trials also need to be modernized. Uldrick et al⁵⁸ have described that in 80% of pivotal trials in adults with cancer, HIV infection is an exclusion criterion. In most cases, these are patients with stable infection. To avoid perpetuating these inequalities in PLWH, the following points should therefore be examined: immune status, concurrent ART, and the possible interaction between ART and medication and natural products⁵⁹⁻⁷⁵.

Conclusions

HIV infection and oncological diseases are closely linked, as the HIV history in the case of ADC shows. Emerging cancers are an alarming problem in HIV-infected individuals because the underlying inflammation, risky behaviors, and coinfection contribute to an increased risk

of developing cancer. ADCs have, therefore, declined in the post-ART era, but the risk of cancer in HIV-infected individuals is far from over. A multidisciplinary approach to PLWH is essential. A strong bridge between oncology and infectious diseases seems necessary to ensure rapid treatment and prevention for patients. Given the large number of oncological diseases that can affect PLWH, other disciplines must also be involved. Of course, this network of professionals works in two ways: HIV-infected people and cancer patients are granted rapid therapies, and at the same time, people with a new cancer diagnosis need to be screened for all risk factors, including HIV. At the “Gaetano Martino” hospital in Messina, we have already created a bridge between oncology and infectious diseases that has proved fundamental in providing personalized therapies and screening for many patients, involving a professional multidisciplinary team with a personalized workflow (Figure 3) (see Table II).

Authors' Contributions

Conceptualization: G.F.P., A.S., G.C., S.M., P.C. and M.B.; writing-original draft preparation: G.F.P., A.S., G.C., V.I.P., I.C., C.S., M.R., E.D.T., P.C., and M.B.; writing-review and editing: G.F.P., A.S., G.C., V.I.P., S.P., C.S., M.R., E.D.T., A.A., D.A.R., P.C., and M.B.; supervision: G.F.P., N.C., A.A., G.M., G.M., D.A.R., P.C., and M.B.. All authors have read and agreed to the published version of the manuscript.

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Funding

This research received no funding.

Ethics Approval and Informed Consent

Not applicable since no clinical data are reported.

Data Availability

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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