

Breast cancer in women living with HIV

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Abstract. – With the introduction of HAART, the life expectancy of the patients infected with HIV almost approached that of the general population. The incidence of certain HIV-Associated cancers as Kaposi Sarcoma (KS) and Non-Hodgkin Lymphoma (NHL) decreased, while an increase in Non-AIDS-Defining cancers (NADCs) has been documented. HIV infection is a risk factor for numerous cancers in PLWH. Breast cancer is the most common cancer worldwide among all women. The association between HIV infection and breast cancer has not been thoroughly investigated: when compared to the general population, people living with HIV/AIDS (PLWHA) have a similar or slightly lower risk of breast cancer. Screening tests are essential weapons to fight cancer burden and more effective therapeutic and preventive strategies are needed, especially among PLWHA. Further and more comprehensive studies are needed to better characterize breast cancer among PLWH.

Key Words:

Breast Cancer, Screening, Human immunodeficiency virus (HIV), Epidemiology.

Introduction

The introduction of ART has had a significant impact on people living with HIV/AIDS (PLWHA) survival, turning HIV infection into a chronic condition. As a consequence, long-term morbidities, including malignancies, represent a new challenge to manage¹⁻²⁶.

Cancer is a burden worldwide, of interest the epidemiology in PLWHA has changed in the last 20 years. In fact, the incidence of the three classically AIDS-defining cancers (Kaposi's Sarcoma, Cervical cancer and Non-Hodgkin Lymphomas) has significantly decreased, while an increase in Non-AIDS-Defining cancers (NADCs) that typi-

cally occur at older ages has been documented²⁷⁻³⁸.

Several studies suggest a synergistic carcinogenic effect of aging and HIV, as a matter of fact, beyond the "classic" risk factors such as smoking, alcohol and age, it is important to consider the HIV-related risk factors, such as immunodeficiency, chronic persistence of infection and viral infections often associated with HIV (Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Papilloma Virus (HPV)³⁹⁻⁴⁷.

Human Immunodeficiency Virus (HIV) leads to progressive immunosuppression that has been associated with an increased cancer risk. Decreased immune surveillance and increased immune activation play an important role in cancer development. Moreover, HIV may have a direct role in carcinogenesis, inhibiting tumor suppressor genes and activating cellular proto-oncogenes^{48,49}.

Furthermore, susceptibility to the effects of carcinogens may be greater in PLWHA than in HIV-uninfected individuals, maybe due to the endothelial alterations associated with HIV infection, which may be permissive for tumor growth⁵⁰. As well, HIV-associated immunosenescence may also be associated with increased cancer risk^{51,52}.

Predictors for NADCs in HIV-infected patients include old age, lower CD4+ cell count, smoking habits and socioeconomic disadvantage^{28,29}. On the other hand, while antiretroviral therapy has been shown to be protective against ADC it was not against NADCs. In fact, the incidence of certain NADCs in HIV patients has been reported to have increased in the combination antiretroviral therapy (ART) era⁵⁰.

Breast Cancer Epidemiology

Breast cancer is the most common cancer worldwide among all women, it represents the 12% of all new cancer cases in the world and the 25% of

all cancers⁵³. Of note, it is the most common cause of cancer-related deaths among women, representing the 15% of total cancer deaths⁵⁴. Although the relationship between HIV and certain cancers has been deeply characterized, there is little evidence about breast cancer among PLWHA. When compared to the general population, PLWHA have a similar or slightly lower risk of breast cancer⁵⁵. Breast cancer has previously been described as occurring less frequently in women with AIDS compared to the general population⁵⁶. Goedert et al⁵² have shown that although HIV-infected women have a lower cancer risk, over time, it has almost approached the incidence in the general population. There are no reliable data about the role of HIV infection on the risk of breast cancer and the stage; the histological and molecular characteristics seem to be independent factors. However, more side effects occur during the treatment of the neoplasm, probably caused by the drug interactions between chemotherapy and HAART⁵⁷. Hurley et al⁵⁸ found that chemotherapy was poorly tolerated in patients with HIV, suggesting that HIV/AIDS and ART may negatively affect chemotherapy tolerability with a greater degree of lymphocytopenia and neutropenia. Parameswaran et al⁵³ similarly reported that 56% of patients with HIV and breast cancer in New York required a dose reduction in chemotherapy, compared with 30% of uninfected patients. Breast cancer is a result of a complex interplay of genetic, metabolic, immunologic and environmental factors. Several studies suggest an accelerating or detrimental effect of HIV in the natural evolution of breast cancer. Furthermore, similar genetics, signaling pathways and common receptors to both HIV and breast cancer^{59,60} have been suggested as the possible cause of this complex interplay. The common expression of genes and receptors does not establish a link between HIV and breast cancer, but may suggest a possible role of HIV in the natural history of this tumor. However, several data suggest that HIV infection promotes tumor growth acting on immune signaling, angiogenesis and metastasis⁶¹⁻⁶⁵. HIV infection and ART are known to be associated with a variety of metabolic disorders, including metabolic syndrome. Several studies confirm an overall increase in the incidence of metabolic syndrome in patients with HIV receiving ART⁶⁶, particularly relevant for patients with HIV and breast cancer.

Biomarkers

Biomarkers are used for breast cancer and they are classified as predictive and prognostic mar-

kers⁶⁷. Predictive markers provide information about the therapy and its efficacy, while prognostic markers offer information about biological characteristics that may influence the prognosis of the disease. Numerous biomarkers have been investigated for clinical applications. P53 was observed in approximately 15% of breast cancer patients, but it is not specific to breast cancer⁶⁸. CA15-3 is a biomarker for advanced breast cancer with limited sensitivity for early-stage cancer. It can be applied to monitor therapy and recurrences⁶⁹⁻⁷¹. HER2 levels were observed higher in about 30% of patients with breast cancer. It is helpful for monitoring disease relapse, cancer progression and choosing appropriate therapy. BRCA1 and BRCA2 are commonly used to evaluate breast cancer susceptibility⁷². They are involved in repair of DNA double-strand breaks that are responsible for breast cancer. Gene mutations lead to instability of the genome and the result is an increased risk of breast cancer⁷³. MicroRNAs (miRNAs) such as miR-21, are new markers with high specificity and sensitivity⁷⁴.

Screening

Factors involved in increased cancer risk among HIV-infected people are immunosuppression, chronic inflammation, long-term exposure to antiretroviral agents⁷⁵⁻⁸⁰.

The growing burden of non-AIDS-defining cancers requires cancer prevention and early detection among PLWHA^{39,53}. Early detection has been associated with a reduction in breast cancer mortality and breast cancer screening allows the detection of breast cancer in an asymptomatic phase and at an early stage⁸¹. PLWHA should be screened for cancer at earlier ages than HIV-uninfected individuals and screening should be performed more frequently⁸². Screening tests for breast cancer include clinical and self-breast examination, mammography, screening ultrasonography, magnetic resonance imaging (MRI), and breast tomosynthesis⁸³. The importance of self-examination is usually under evaluated. In our opinion, it is worthy to spend some time during the routine medical visits of PLWHA teaching a correct self-examination and explaining its importance. Mammography, however, is the best-studied method to reduce mortality from breast cancer, with a 77-95% and 94-97% of sensitivity and specificity, respectively⁷⁸⁻⁸⁴. The false-positive and false-negative rates of mammography are relatively high and the sensitivity could be reduced in high dense breasts and

premenopausal women. However, it has many downsides: the use of ionizing radiation, relatively high false-positive and false-negative rates, and uncomfortable examination^{85,86}. The sensitivity of mammography is related to the age, radiologist's experience and technique quality⁸⁵. Breast ultrasonography is a cost-effective and widely available exam, which detects tumors by using acoustic waves. It increases cancer detection rates for subjects with high breast cancer risk and high breast density⁸⁶. Breast MRI has been recommended for subjects with high breast cancer risk, but it has not been recommended for the general population due to its high false-positive rate, high cost and the need for experienced radiologists⁸⁴. The aim of screening tests is to reduce the mortality of women who are at risk. When available, they represent an effective weapon in cancer prevention, together with an early onset of therapy, lifestyle changes, coinfection treatment and vaccinations³⁹. Screening recommendations vary by country and institution. According to the European guidelines, all women between 50 and 70 years old have to perform a mammogram every two years. In some Italian regions, screening recommendations usually range between 45 and 49 years old, and every two years from 70 to 74. It is advisable to perform a mammogram to women under 40 at high risk^{86,87}. High-risk women are those with genetic factors (Li Fraumeni syndrome, BRCA1, BRCA2), familiarity, iatrogenic factors (a history of chest irradiation between the ages of 10-30 years for lymphomas and other tumors, hormonal therapy) and individual factors (atypical hyperplasia, pregnancy in old age, premature menarche, late menopause)⁸⁸. The Guidelines for general population may be applied to women living with HIV⁸⁷.

Materials and Methods

On January 7th, 2019, we performed a review of the literature to identify the possible links existing between Human Immunodeficiency Virus (HIV) infection, HAART and breast cancer.

We searched PubMed applying the keywords "Breast Cancer", "HIV infection", "Screening", "HAART" to identify potentially relevant articles.

We included only recent articles written in English, and we found 98 publications. We excluded 10 articles after reading title and abstract. At the end of the assessment, we included in our review the 88 full-text articles.

Discussions

Highly Active Antiretroviral Therapy (HAART) has significantly increased the survival of PLWHA, turning this infection into a chronic disease. As a consequence, we assisted to an increase in the incidence of non-AIDS defining cancer, typically occurring at older ages. HIV infection is a risk factor for numerous cancers: breast cancer is one of them, representing a major worldwide public health problem. When compared to the general population, PLWHA have a similar or slightly lower risk of breast cancer, but several data suggest a role of the virus in carcinogenesis, therapy and outcomes. For this reason, the importance of a correct management of patients should not be underestimated. Screening tests are essential weapons to fight cancer burden and more effective therapeutic and preventive strategies are needed, especially among PLWHA. Infectious specialists have to persuade the patients about the importance of screening and early diagnosis. Moreover, it is worthy to spend some time during the routine medical visits of PLWHA teaching a correct self-examination and explaining its importance. PLWHA should undergo a screening for breast cancer at younger age and more often than the general population. The different screening tests showed no differences in sensitivity and specificity between PLWHA and HIV-negative subjects, so the recommended tests for the screening of breast cancer in PLWHA should be the same that we use for the general population. What should be improved are their frequency and the adherence of our patients.

Conclusions

Cancer screening has to become an integral part of the clinical management of patients, especially if at high risk, such as PLWHA. Further and more comprehensive studies are needed to better characterize breast cancer among PLWHA and the role of HIV in the natural history of this tumor.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

- 1) D'ARMINIO MONFORTE A, DIAZ-CUERVO H, DE LUCA A, MAGGIOLIO F, CINGOLANI A, BONORA S on behalf of the

- ICONA Foundation Study Group. Evolution of major non-HIV-related comorbidities in HIV-infected patients in the Italian cohort of individuals, naive for antiretrovirals (ICONA) foundation study cohort in the period 2004-2014. *HIV Med* 2019; 20: 99-109.
- 2) PINZONE MR, BERRETTA M, CACOPARDO B, NUNNARI G. Epstein-barr virus- and Kaposi sarcoma-associated herpes virus-related malignancies in the setting of human immunodeficiency virus infection. *Semin Oncol* 2015; 42: 258-271.
 - 3) PINZONE MR, DI ROSA M, CELESIA BM, CONDORELLI F, MALAGUARNERA M, MADEDDU G, MARTELOTTA F, CASTRONUOVO D, GUSSIO M, COCO C, PALERMO F, COSENTINO S, CACOPARDO B, NUNNARI G. LPS and HIV gp120 modulate monocyte/macrophage CYP27B1 and CYP24A1 expression leading to vitamin D consumption and hypovitaminosis D in HIV-infected individuals. *Eur Rev Med Pharmacol Sci* 2013; 17: 1938-1950.
 - 4) SMITH, J. A, NUNNARI G, PREUSS M, POMERANTZ R. J, DANIEL R. Pentoxifylline suppresses transduction by HIV-1-based vectors. *Intervirology* 2007; 50: 377-386.
 - 5) NUNNARI G, GUSSIO M, PINZONE M.R, MARTELOTTA F, COSENTINO S, CACOPARDO B, CELESIA B. M Cryptococcal meningitis in an HIV-1-infected person: Relapses or IRIS? Case report and review of the literature. *Eur Rev Med Pharmacol Sci* 2013; 17: 1555-1559.
 - 6) CELESIA BM, NIGRO L, PINZONE MR, COCO C, LA ROSA R, BISICCHIA F, NUNNARI G. High prevalence of undiagnosed anxiety symptoms among HIV-positive individuals on cART: a cross-sectional study. *Eur Rev Med Pharmacol Sci* 2013; 17: 2040-2046.
 - 7) CELESIA BM, ONORANTE A, NUNNARI G, MUGHINI MT, MAVILLA S, MASSIMINO SD, RUSSO R. Porphyria cutanea tarda in an HIV-1-infected patient after the initiation of tipranavir/ritonavir: case report. *AIDS* 2007; 21: 1495-1496.
 - 8) GUARNERI C, TCHERNEV G, BEVELACQUA V, LOTTI T, NUNNARI G. The unwelcome trio: HIV plus cutaneous and visceral leishmaniasis. *Dermatol Ther* 2016; 29: 88-91.
 - 9) MADEDDU G, MAMELI G, CAPOBIANCO G, BABUDIERI S, MAIDA I, BAGELLA P, ROCCA G, CHERCHI PL, SECHI LA, ZANETTI S, NUNNARI G, DESSOLE S, MURA MS. HPV infection in HIV-positive females: the need for cervical cancer screening including HPV-DNA detection despite successful HAART. *Eur Rev Med Pharmacol Sci* 2014; 18: 1277-1285.
 - 10) MAGGI P, DI BIAGIO A, RUSCONI S, CICALINI S, D'ABBRACCIO M, D'ETTORRE G, MARTINELLI C, NUNNARI G, SIGHINOLFI L, SPAGNUOLO V, SQUILLACE N. Cardiovascular risk and dyslipidemia among persons living with HIV: a review. *BMC Infect Dis* 2017, 17:551
 - 11) RAFFI F, ESSER S, NUNNARI G, PÉREZ-VALERO I, WATERS L. Switching regimens in virologically suppressed HIV-1-infected patients: Evidence base and rationale for integrase strand transfer inhibitor (INSTI)-containing regimens. *HIV Med* 2016, 17: 3-16.
 - 12) LEDDA C, CICIÙ F, PUGLISI B, RAMACI T, NUNNARI G, RAPISARDA V. Attitude of health care workers (HCWs) toward patients affected by HIV/AIDS and drug users: a cross-sectional study. *Int J Environ Res Public Health* 2017; 14: E284
 - 13) D'ETTORRE G, CECCARELLI G, ANDREOTTI M, SELVAGGI C, GIUSTINI N, SERAFINO S, SCHIETROMA I, NUNNARI G, ANTONELLI G, VULLO V, SCAGNOLARI C. Analysis of Th17 and Tc17 frequencies and antiviral defenses in gut-associated lymphoid tissue of chronic HIV-1 positive patients. *Mediators Inflamm* 2015; 2015: 395484
 - 14) MADEDDU G, FIORI ML, ENA P, RIU F, LOVIGU C, NUNNARI G, BAGELLA P, MAIDA I, BABUDIERI S, MURA MS. Mucocutaneous leishmaniasis as presentation of HIV infection in sardinia, insular italy. *Parasitol Int* 2014; 63: 35-36.
 - 15) DAVE RS, MCGETTIGAN JP, OURESHI T, SCHNELL MJ, NUNNARI G, POMERANTZ RJ. siRNA targeting vaccinia virus double-stranded RNA binding protein [E3L] exerts potent antiviral effects. *Virology* 2006; 348: 489-497.
 - 16) PINZONE MR, CECCARELLI M, VENANZI RULLO E, MARESCA M, BRUNO R, CONDORELLI F, DI ROSA M, MADEDDU G, FOCA E, CALCAGNO A, CELESIA BM, CACOPARDO B, NUNNARI G, PELLICANÒ GF. (2019). Circulating angiopoietin-like protein 2 levels are associated with decreased renal function in HIV+ subjects on cART: a potential marker of kidney disease. *Biomed Rep* 2019; 10: 140-144.
 - 17) CECCARELLI M, VENANZI RULLO E, VACCARO M, FACCIOLÀ A, D'ALEO F, PAOLUCCI IA, CANNAVÒ SP, CACOPARDO B, PINZONE MR, PELLICANÒ GF, CONDORELLI F, NUNNARI G, GUARNERI C. HIV-associated psoriasis: epidemiology, pathogenesis, and management. *Dermatol Ther* 2019; e12806
 - 18) CECCARELLI M, VENANZI RULLO EV, CONDORELLI F, VITALE F, DI MARCO V, NUNNARI G, PELLICANÒ GF. Unusual signs and symptoms in HIV-positive patients coinfecting with leishmania spp: The importance of neglected tropical disease in differential diagnosis. *Open Access Maced J Med Sci* 2018; 6: 843-847
 - 19) VENANZI RULLO E, CECCARELLI M, CONDORELLI F, FACCIOLÀ A, VISALLI G, D'ALEO F, PAOLUCCI I, CACOPARDO B, PINZONE MR, DI ROSA M, NUNNARI G, PELLICANÒ GF. Investigational drugs in HIV: pros and cons of entry and fusion inhibitors (Review). *Mol Med Rep* 2019; 19: 1987-1995.
 - 20) PINZONE MR, CACOPARDO B, CONDORELLI F, ROSA MD, NUNNARI G. Sirtuin-1 and HIV-1: an overview. *Curr Drug Targets* 2013; 14: 648-652.
 - 21) VISALLI G, FACCIOLÀ A, D'ALEO F, PINZONE MR, CONDORELLI F, PICERNO I, NUNNARI G, PELLICANÒ GF, CECCARELLI M, VENANZI RULLO E. HPV and urinary bladder carcinoma: a review of the literature. *World Cancer Res J* 2018; 5: e1038.
 - 22) TROVATO M, RUGGERI RM, SCIACCHITANO S, VICCHIO TM, PICERNO I, PELLICANÒ G, VALENTI A, VISALLI G. Serum interleukin-6 levels are increased in HIV-infected patients that develop autoimmune disease during long-term follow-up. *Immunobiology* 2018; 223: 264-268.
 - 23) SQUILLACE N, RICCI E, QUIRINO T, GORI A, BANDERA A, CARENZI L, DE SOCIO GV, OROFINO G, MARTINELLI C, MADEDDU G, RUSCONI S, MAGGI P, CELESIA BM, CORDIER

- L, VICHI F, CALZA L, FALASCA K, DI BIAGIO A, PELLICANÒ GF, BONFANTI P. Safety and tolerability of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in a real life setting. Data from surveillance cohort long-term toxicity antiretrovirals/antivirals (SCOLTA) project. *PLoS One* 2017; 12: e0179254.
- 24) BELLISSIMO F, PINZONE MR, CACOPARDO B, NUNNARI G. Diagnostic and therapeutic management of hepatocellular carcinoma. *World J Gastroenterol* 2015; 21: 12003-12021.
 - 25) NUNNARI G, SULLIVAN J, XU Y, NYIRJESY P, KULKOSKY J, CAVERT W, FRANK I, POMERANTZ RJ. HIV type 1 cervicovaginal reservoirs in the era of HAART. *AIDS Res Hum Retroviruses* 2005; 21: 714-718.
 - 26) NUNNARI G, LETO D, SULLIVAN J, XU Y, MEHLMAN KE, KULKOSKY J, POMERANTZ RJ. Seminal reservoirs during an HIV type 1 eradication trial. *AIDS Res Hum Retrovirus Res* 2005; 21: 768-775.
 - 27) ZANET E, BERRETTA M, MARTELOTTA F, CACOPARDO B, FISICHELLA R, TAVIO M, BERRETTA S, TIRELLI U. Anal cancer: Focus on HIV-positive patients in the HAART-era. *Curr HIV Res* 2011; 9: 70-81.
 - 28) CELESIA BM, CASTRONUOVO D, PINZONE MR, BELLISSIMO F, MUGHINI MT, LUPO G, SCARPINO MR, GUSSIO M, PALERMO F, COSENTINO S, CACOPARDO B, NUNNARI G. Late presentation of HIV infection: predictors of delayed diagnosis and survival in Eastern Sicily. *Eur Rev Med Pharmacol Sci* 2013; 17: 2218-2224.
 - 29) BEARZ A, VACCHER E, MARTELOTTA F, SPINA M, TALAMINI R, LLESHI A, CACOPARDO B, NUNNARI G, BERRETTA M, TIRELLI U. Lung cancer in HIV positive patients: the GICAT experience. *Eur Rev Med Pharmacol Sci* 2014; 18: 500-508.
 - 30) NUVOLI S, CARUANA G, BABUDIEMI S, SOLINAS P, PELLICANO G, PIRAS B, FIORE V, BAGELLA P, CALIA GM, YUE M, SPANU A, MADEDDU G. Body fat changes in HIV patients on highly active antiretroviral therapy (HAART): a longitudinal DEXA study. *Eur Rev Med Pharmacol Sci* 2018; 22: 1852-1859.
 - 31) FACCIOLÀ A, VENANZI RULLO E, CECCARELLI M, D'ALEO F, DI ROSA M, PINZONE MR, CONDORELLI F, VISALLI G, PICERNO I, FISICHELLA R, NUNNARI G, PELLICANÒ GF. Kaposi's sarcoma in HIV-infected patients in the era of new antiretrovirals. *Eur Rev Med Pharmacol Sci* 2017; 21: 5868-5879.
 - 32) D'ALEO F, CECCARELLI M, VENANZI RULLO E, FACCIOLÀ A, DI ROSA M, PINZONE MR, CONDORELLI F, VISALLI G, PICERNO I, BERRETTA M, PELLICANÒ GF, NUNNARI G. Hepatitis C-related hepatocellular carcinoma: diagnostic and therapeutic management in HIV-patients. *Eur Rev Med Pharmacol Sci* 2017; 21: 5859-5867.
 - 33) CECCARELLI M, VENANZI RULLO E, FACCIOLÀ A, MADEDDU G, CACOPARDO B, TAIBI R, D'ALEO F, PINZONE MR, PICERNO I, DI ROSA M, VISALLI G, CONDORELLI F, NUNNARI G, PELLICANÒ GF. Head and neck Squamous cell carcinoma and its correlation with human Papillomavirus in people living with HIV. A systematic review. *Oncotarget* 2018; 9: 17171-17180.
 - 34) D'ALEO F, CAMA BAV, PAOLUCCI IA, VENANZI RULLO E, CONDORELLI F, FACCIOLÀ A, DI FRANCA R, SAVASTA A, PINZONE MR, PICERNO I, VISALLI G, NUNNARI G, PELLICANÒ GF, CECCARELLI M. New and old assumptions on lung cancer in people living with HIV. *World Cancer Res J* 2018; 5: e1036.
 - 35) D'ANDREA F, CECCARELLI M, VENANZI RULLO E, FACCIOLÀ A, D'ALEO F, CACOPARDO B, IACOBELLO C, COSTA A, ALTAVILLA G, PELLICANÒ GF, NUNNARI G. Cancer screening in HIV-infected patients: early diagnosis in a high-risk population. *World Cancer Res J* 2018; 5: e1130.
 - 36) FACCIOLÀ A, CECCARELLI M, VENANZI RULLO E, D'ALEO F, CONDORELLI F, VISALLI G, CACOPARDO B, PINZONE MR, DI ROSA M, NUNNARI G, PELLICANÒ GF. Prostate cancer in HIV-positive patients: a review of the literature. *World Cancer Res J* 2018; 5: e1136.
 - 37) CECCARELLI M, CONDORELLI F, VENANZI RULLO E, PELLICANÒ GF. Editorial - Improving access and adherence to screening tests for cancers: a new, though old, challenge in the HIV epidemics. *World Cancer Res J* 2018; 5: e1030.
 - 38) SPINA M, BERRETTA M, TIRELLI U. Hodgkin's disease in HIV. *Hematol Oncol Clin North Am* 2003; 17:843-858.
 - 39) PINZONE MR, GUSSIO M, BELLISSIMO F, COCO C, BISICCHIA F, PELLICANÒ G, PALERMO F, MUGHINI MT, CACOPARDO B, NUNNARI G, CELESIA BM. Self-reported sexual dysfunction in HIV-positive subjects: a cross-sectional study. *Infect Dis Trop Med* 2015; 1: e104.
 - 40) CASTRONUOVO D, PINZONE MR, MORENO S, CACOPARDO B, NUNNARI G. HIV infection and bone disease: a review of the literature. *Infect Dis Trop Med* 2015; 1: e116.
 - 41) WORM SW, BOWER M, REISS P, BONNET F, LAW M, FÄTKENHEUER G, D'ARMINIO-MONFORTE A, ABRAMS DI, GRULICH A, FONTAS E, KIRK O, FURRER H, DE WIT S, PHILLIPS A, LUNDGREN JD, SABIN CA, D:A:D Study Group. Non-AIDS defining cancers in the D:A:D Study-time trends and predictor of survival: a cohort study. *BMC Infect Dis* 2013; 13: 471.
 - 42) NUNNARI G, COCO C, PINZONE MR, PAVONE P, BERRETTA M, DI ROSA M, SCHNELL M, CALABRESE G, CACOPARDO B. The role of micronutrients in the diet of HIV-1-infected individuals. *Front Biosci (Elite Ed)* 2012; 4: 2442-2456.
 - 43) BERRETTA M, LLESHI A, CAPPELLANI A, BEARZ A, SPINA M, TALAMINI R, CACOPARDO B, NUNNARI G, MONTESARCHIO V, IZZI I, LANZAFAME M, NASTI G, BASILE F, BERRETTA S, FISICHELLA R, SCHIANTARELLI C C, GARLASSI E, RIDOLFO A, GUELLA L, TIRELLI U. Oxaliplatin based chemotherapy and concomitant highly active antiretroviral therapy in the treatment of 24 patients with colorectal cancer and HIV infection. *Curr HIV Res* 2010; 8: 218-222.
 - 44) RUBINSTEIN PG, ABOLAFIA DM, ZLOZA A. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. *AIDS* 2014; 28: 453-465.
 - 45) MITSUYASU RT. Non-AIDS defining cancers. *Top Antivir Med* 2014; 22: 660-665.
 - 46) VISALLI G, PAIARDINI M, CHIRICO C, CERVASI B, CURRÒ M, FERLAZZO N, BERTUCCIO MP, FAVALORO A, PELLICANÒ G, STURNIOLO G, SPATARO P, IENTILE R, PICERNO I, PIEDIMONTE G. Intracellular accumulation of cell cycle regulatory proteins and nucleolin re-localization are associated with pre-lethal ultrastructural lesions in circulating T lymphocytes: the HIV-induced cell

- cycle dysregulation revisited. *Cell Cycle* 2010; 9: 2130-2140.
- 47) LA FERLA L, PINZONE MR, PELLICANÒ GF, NUNNARI G. Kaposi's sarcoma in HIV-infected patients: a review of the literature. *Infect Dis Trop Med* 2016; 2: e239
 - 48) VISALLI G, BERTUCCIO MP, CURRÒ M, PELLICANÒ G, STURNIOLO G, CARNEVALI A, SPATARO P, IENTILE R, PICERNO I, CAVALLARI V, PIEDIMONTE G. Bioenergetics of T cell activation and death in HIV type 1 infection. *AIDS Res Hum Retroviruses* 2012; 28: 1110-1118.
 - 49) CHAO C, LEYDEN WA, XU L, HORBERG MA, KLEIN D, TOWNER WJ, QUESENBERRY CP JR, ABRAMS DI, SILVERBERG MJ. exposure to antiretroviral therapy and risk of cancer in hiv-infected persons. *AIDS* 2012; 26: 2223-2231.
 - 50) SILVERBERG MJ, CHAO C, LEYDEN WA, XU L, HORBERG MA, KLEIN D, TOWNER WJ, DUBROW R, QUESENBERRY CP JR, NEUGEBAUER RS, ABRAMS DI. HIV Infections, Immunodeficiency, viral replication and the risk of cancer. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 2551-2559.
 - 51) JEMAL A, BRAY F, CENTER MM, FERLAY J, WARD E, FORMAN D. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90.
 - 52) GOEDERT JJ, SCHAIRER C, MCNEEL TS, HESSOL NA, RABKIN CS, ENGELS EA, HIV/AIDS cancer match study. Risk of breast, ovary, and uterine corpus cancers among 85,268 women with AIDS. *Br J Cancer* 2006; 95: 642-648.
 - 53) PARAMESWARAN L, TAUR Y, SHAH MK, TRAINA TA, SEO SK. Tolerability of chemotherapy in HIV-infected women with breast cancer: are there prognostic implications? *AIDS Patient Care STDS* 2014; 28: 358-364.
 - 54) MONI MA, LIO P. Network-based analysis of comorbidities risk during an infection: SARS and HIV case studies. *BMC Bioinformatics* 2014; 15: 333.
 - 55) HUANG PL, SUN Y, CHEN HC, KUNG HF, LEE-HUANG S. Proteolytic fragments of anti-HIV and anti-tumor proteins MAP30 and GAP31 are biologically active. *Biochem Biophys Res Commun* 1999; 262: 615-623.
 - 56) ROBINSON SC, SCOTT KA, WILSON JL, THOMPSON RG, PROUDFOOT AE, BALKWILL FR. A chemokine receptor antagonist inhibits experimental breast tumor growth. *Cancer Res* 2003; 63: 8360-8365.
 - 57) RAZMKHAH M, TALEI AR, DOROUDCHI M, KHALILI-AZAD T, GHADERI A. Stromal cell-derived factor-1 (SDF-1) alleles and susceptibility to breast carcinoma. *Cancer Lett* 2005; 225: 261-266.
 - 58) HURLEY J, FRANCO S, GOMEZ-FERNANDEZ C, REIS I, VELEZ P, DOLINY P, HARRINGTON W JR, WILKINSON J, KANHOSH R, LEE Y. Breast cancer and human immunodeficiency virus: A report of 20 cases. *Clin Breast Cancer* 2001; 2: 215-220.
 - 59) BEN-BARUCH A. Host microenvironment in breast cancer development: Inflammatory cells, cytokines and chemokines in breast cancer progression: Reciprocal tumor-microenvironment interactions. *Breast Cancer Res* 2003; 5: 31-36.
 - 60) MAÑES S, MIRA E, COLOMER R, MONTERO S, REAL LM, GÓMEZ-MOUTÓN C, JIMÉNEZ-BARANDA S, GARZÓN A, LACALLE RA, HARSHMAN K, RUIZ A, MARTINEZ-A C. CCR5 expression influences the progression of human breast cancer in a p53-dependent manner. *J Exp Med* 2003; 198: 1381-1389.
 - 61) ENDO M, INATSU A, HASHIMOTO K, TAKAMUNE N, SHOJI S, MISUMI S. Human immunodeficiency virus-induced apoptosis of human breast cancer cells via CXCR4 is mediated by the viral envelope protein but does not require CD4. *Curr HIV Res* 2008; 6: 34-42.
 - 62) NIX LM, TIEN PC. Metabolic syndrome, diabetes, and cardiovascular risk in HIV. *Curr HIV/AIDS Rep* 2014; 11: 271-278.
 - 63) PORTO-MASCARENHAS EC, ASSAD DX, CHARDIN H, GOZAL D, DE LUCA CANTO G, ACEVEDO AC, GUERRA EN. Salivary biomarkers in the diagnosis of breast cancer: A review. *Crit Rev Oncol Hematol* 2017; 110: 62-73.
 - 64) SU M, WHEELER TK, PICKEN S, NEGUS S, MILNER AJ. P53 autoantibodies in 1006 patients followed up for breast cancer. *Breast Cancer Res* 2000; 2: 438-443.
 - 65) JIN HJ, PARK HY, LEE YH. Clinical value of CEA, CEA15-3 and TPS in breast cancer. *J Korean Breast Cancer Soc* 2001; 4: 136-143.
 - 66) DUFFY MJ. CA 15-3 and related mucins as circulating markers in breast cancer. *Ann Clin Biochem* 1999; 36: 579-586.
 - 67) LEE JS, PARK S, JI MP, CHO JH, KIM SI, PARK BW. Elevated levels of serum tumor markers CA 15-3 and CEA are prognostic factors for diagnosis of metastatic breast cancers. *Breast Cancer Res Treat* 2013; 141: 477-484.
 - 68) MATTOS-ARRUDA LD, CORTES J, SANTARPIA L, VIVANCOS A, TABERNERO J, REIS-FILHO JS, SEOANE J. Circulating tumour cells and cell-free DNA as tools for managing breast cancer. *Nat Rev Clin Oncol* 2013; 10: 377-389.
 - 69) KONISHI H, MOHSENI M, TAMAKI A, GARY JP, CROESSMANN S, KARNAN S, OTA A, WONG HY, KONISHI Y, KARAKAS B, TAHIR K, ABUKHDEIR AM, GUSTIN JP, CIDADO J, WANG GM, COSGROVE D, COCHRAN R, JELOVAC D, HIGGINS MJ, ARENA S, HAWKINS L, LAURING J, GROSS AL, HEAPHY CM, HOSOKAWA Y, GABRIELSON E, MEEKER AK, VISVANATHAN K, ARGANI P, BACHMAN KE, PARK BH. Mutation of a single allele of the cancer susceptibility gene *brca1* leads to genomic instability in human breast epithelial cells. *Proc Natl Acad Sci U S A* 2011; 108: 17773-17778.
 - 70) MATAMALA N, VARGAS MT, GONZÁLEZ-CÁMPORA R, MIÑAMBRES R, ARIAS JI, MENÉNDEZ P, ANDRÉS-LEÓN E, GÓMEZ-LÓPEZ G, YANOWSKY K, CALVETE-CANDENAS J. Tumor microrna expression profiling identifies circulating micrornas for early breast cancer detection. *Clin Chem* 2015; 61: 1098-1106.
 - 71) BORGES AH, DUBROW R, SILVERBERG MJ. Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier combination antiretroviral therapy will alter this risk. *Curr Opin HIV AIDS* 2014; 9: 34-40.
 - 72) FULLER MS, LEE CI, ELMORE JG. (2015). Breast cancer screening: an evidence-based update. *Med Clin North Am* 2015; 99: 451-468.
 - 73) GOEDERT JJ, HOSGOOD HD, BIGGAR RJ, STRICKLER H, RABKIN CS. Screening for cancer in persons liv-

- ing with HIV infection. *Trends Cancer* 2016; 2: 416-428.
- 74) ELMORE JG, ARMSTRONG K, LEHMAN CD, FLETCHER SW. Screening for breast cancer. *JAMA* 2005; 293: 1245-1256.
- 75) HUMPHREY LL, HELFAND M, CHAN BK, WOOLF SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; 137: 347-360.
- 76) NUNNARI G, MALAGUARNERA L, LAZZARA F, CAMBRIA G, DISTEFANO A, LONGO A, PALUMBO M, FAGONE P, DI ROSA M. Th17 common genes in CD4 T-cells of HIV-1-infected naïve patients and elite controllers. *Infect Dis Trop Med* 2015; 1: e121.
- 77) PINZONE MR, NUNNARI G. Prevalence of comorbidities in a cohort of women living with HIV. *Infect Dis Trop Med* 2015; 1: e165.
- 78) DI ROSA M, FAGONE P, PINZONE MR, NUNNARI G. Cathepsin A levels in CD4+ T cells from HIV-positive patients. *Infect Dis Trop Med* 2016; 2: e245.
- 79) POSTORINO MC, LUCIANI F, PELLICANÒ G, MANGANO C, CARPENTIERI MS, SCERBO P, PRIAMO A, BERARDELLI G, MARINO R, VALLONE A, CARIOTI J, SERRAO N, PISANI V, COSTA C, CESARIO F, TERREMOT A, FOTI G, COSCO L, CORIGLIANO D, MAZZITELLI M, STRAZZULLA A, NUNNARI G, TORTI C. Number and characteristics of new HIV diagnoses in the Calabria Region and in one nearby centre in Messina: a resurgent or still hidden epidemic in Southern Italy? *Infect Dis Trop Med* 2016; 2: e297.
- 80) FONTANA DEL VECCHIO R, PINZONE MR, CELESIA BM, PALERMO F, CACOPARDO B, NUNNARI G. ZDV/3TC to ABC/3TC switch and bone marrow toxicity in the post-HAART era. *Infect Dis Trop Med* 2015; 4: e39.
- 81) LE MT, MOTHERSILL CE, SEYMOUR CB, McNEILL FE. Is the false-positive rate in mammography in North America too high? *Br J Radiol* 2016; 89: 20160045.
- 82) NELSON HD, TYNE K, NAIK A, BOUGATSOS C, CHAN BK, HUMPHREY L, U.S. Preventive Services Task Force. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; 151: 727-737, W237-W242.
- 83) ELMORE JG, JACKSON SL, ABRAHAM L, MIGLIORETTI DL, CARNEY PA, GELLER BM, YANKASKAS B C, KERLIKOWSKA K, ONEGA T, ROSENBERG RD, SICKLES EA, BUIST DS. Variability in interpretive performance at screening mammography and radiologists' characteristics associated with accuracy. *Radiology* 2009; 253: 641-651.
- 84) MANDELSON MT, OESTREICHER N, PORTER PL, WHITE D, FINDER CA, TAPLIN SH, WHITE E. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 2000; 92: 1081-1087.
- 85) HOOLEY RJ, SCOUTT LM, PHILPOTTS LE. Breast ultrasonography: state of the art. *Radiology* 2013; 268: 642-659.
- 86) SCHENBERG T, MITCHELL G, TAYLOR D, SAUNDERS C. MRI screening for breast cancer in women at high risk; is the Australian breast MRI screening access program addressing the needs of women at high risk of breast cancer? *J Med Radiat Sci* 2015; 62: 212-225.
- 87) SOCIETÀ ITALIANA DI MALATTIE INFETTIVE E TROPICALI. Linee Guida Italiane sull'utilizzo della Terapia Antiretrovirale e la gestione diagnostico-clinica delle persone con infezione da HIV-1. Edn 2017; http://www.salute.gov.it/imgs/C_17_pubblicazioni_2696_allegato.pdf Accessed 31 May 2018.
- 88) WELLINGS E, VASSILIADES L, ABDALLA R. Breast cancer screening for high-risk patients of different ages and risk - which modality is most effective? *Cureus* 2016; 8: e945.