

# Non-AIDS Defining Cancers

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- HIV pandemics began during the early 1980s, seemingly appearing from nowhere.
- After more than ten years of the HIV epidemics, the introduction of the Highly Active Anti-Retroviral Therapy (HAART) led to a real revolution for PLWH.
- HIV infection was no longer a death sentence, with the possibility of living an almost normal life.

- However, such good news was soon followed by its downside: the increasing incidence of chronic pathologies and especially non-AIDS defining cancers (NADCs).

## **Non-AIDS defining cancers: a comprehensive update on diagnosis and management**

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G. LA ROCCA<sup>7</sup>, M. DI ROSA<sup>8</sup>, F. CONDORELLI<sup>9</sup>, M. BERRETTA<sup>10</sup>, G. NUNNARI<sup>1</sup>

- Increased cancer risk in PLWH is related to different factors:
  - ❑ First and foremost, HIV causes a **dysregulation of the immune system**.
    - ✓ Chronic upregulation of pro-inflammatory cytokines, such as IL-6, IL-8, IL-12 and TNF, even when the viral load is undetectable.
    - ✓ Chronic inflammatory stimulus has been related to cancer in several studies.

### ❑ **Oncogenic Viruses**

- ✓ HBV
- ✓ HCV
- ✓ HPV
- ✓ EBV

*The Journal of Infectious Diseases*

MAJOR ARTICLE

2018

 IDSA  
Infectious Diseases Society of America

 hivma  
hiv medicine association

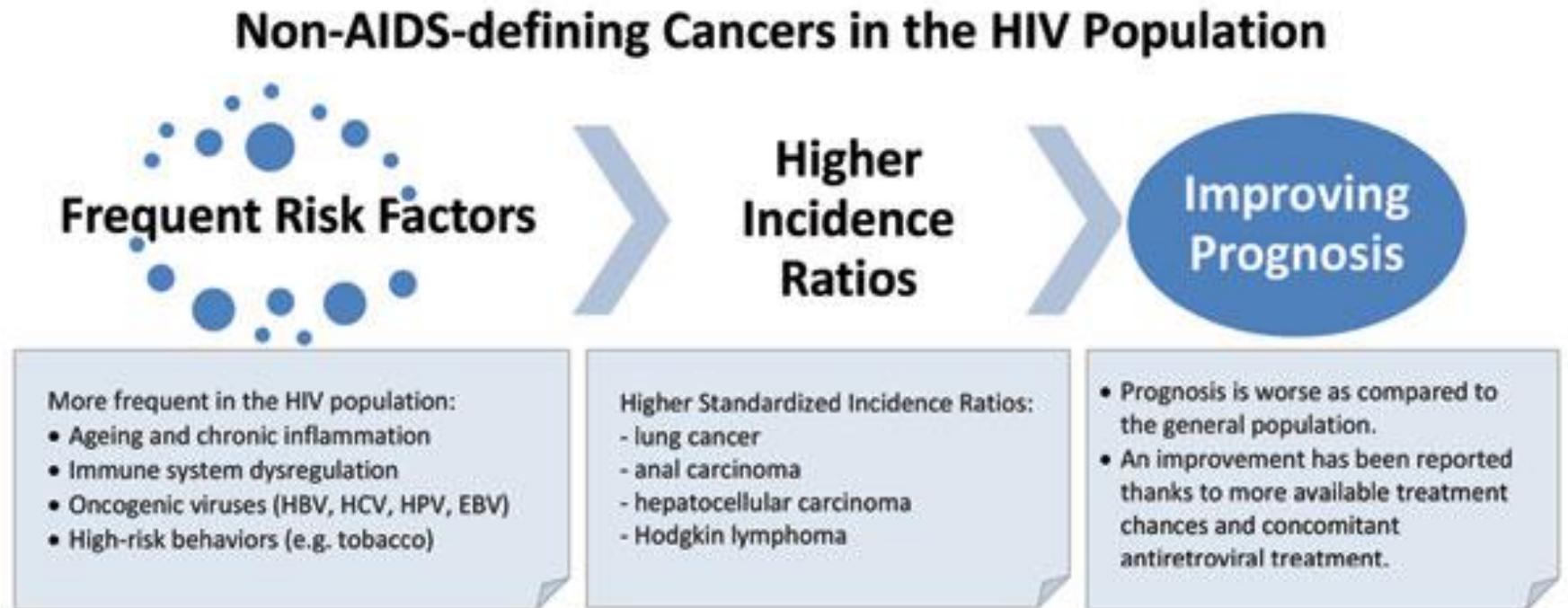
 OXFORD

Changes in Inflammation but Not in T-Cell Activation Precede Non-AIDS-Defining Events in a Case-Control Study of Patients on Long-term Antiretroviral Therapy

Konstantia Angelidou,<sup>1</sup> Peter W. Hunt,<sup>2</sup> Alan L. Landay,<sup>3</sup> Cara C. Wilson,<sup>4</sup> Benigno Rodriguez,<sup>5</sup> Steven G. Deeks,<sup>2</sup> Ronald J. Bosch,<sup>1</sup> and Michael M. Lederman<sup>5</sup>

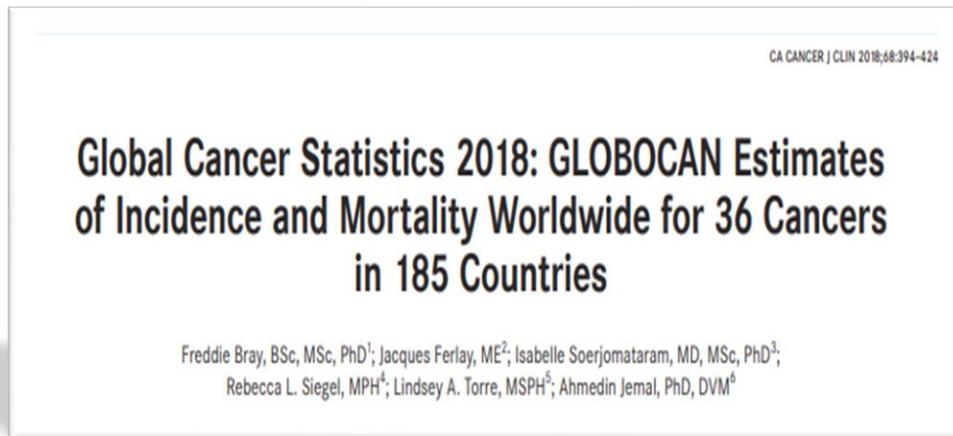
- ❑ Moreover, at **risk behaviors**, such as smoking and alcohol use have been found to be more frequent in PLWH than in the general population.

- In addition to its increased frequency, in PLWH cancer is also more aggressive and tends to progress faster.
- Therefore, for an infectious diseases (ID) specialist, and for every clinician, it is important to know the dangers linked to the infection.



# Lung Cancer

- Lung cancer is the most frequent cancer in the world, representing the 11.6% of all cancers newly diagnosed in 2018.
- This high rate is also found in PLWH, for whom lung cancer is the most common NADC and the most frequent cause of cancer-related death.



CHEST

Commentary

**Epidemic of Lung Cancer in Patients With HIV Infection**

*Tiffany A. Winstone, MD; S. F. Paul Man, MD, FCCP; Mark Hull, MD; Julio S. Montaner, MD, FCCP; and Don D. Sin, MD, FCCP*

**2013**

## Lung Cancer *(Cont'd)*

- PLWH are burdened by a risk 3-fold higher of developing lung cancer than the general population, probably because of the higher rate of smoking in this population.
- Moreover, PLWH seem to develop lung cancer at a younger age than the general population, with an increased mortality as the cancer exhibits a more aggressive behavior and faster progression.



# Lung Cancer *(Cont'd)*

- HIV is an independent risk factor for lung cancer:
  - HIV-infected individuals who did not recover a CD4+ T-cell count to at least 500 cells/ $\mu$ L had an increased risk of developing lung cancer ([Hleyhel et al 2014](#)).
  - Other studies also highlighted the role of HIV-related chronic inflammation as an independent risk factor for lung cancer. The effects of a persistent increase of plasmatic IL-6, CRP, and D-dimer on the incidence of lung cancer ([Borges et al 2013](#)).
  - HIV has been found to infect lung macrophages, a reservoir in which its activity is not suppressed by antiretroviral therapy (ART), even in non-smokers affected by lung cancer ([Cribbs et al 2015](#)).

## Lung Cancer *(Cont'd)*

- There are no conclusive reports about a direct oncogenic activity of HIV on lung.
- Given its high incidence in PLWH and its burden in mortality, it is important to prevent this cancer or diagnose it at an early stage, when it is still not symptomatic.
- Primary prophylaxis is represented by smoking cessation.
- A survival rate of 50-80% at 5 years is granted by early diagnosis.

# Lung Cancer *(Cont'd)*

- A once-a-year low-dose (LD) chest computerized tomography (CT) scan is recommended especially for people considered at high-risk of developing lung cancer.
- **Italian guidelines** for the diagnosis and management of HIV-1 infection recommend screening to all PLWH who are older than 40 years, with an active smoking history of more than 30 pack/year or who have ceased smoking for less than 15 years.



## Lung Cancer *(Cont'd)*

- The **US Preventive Task Force** have already established in 2004 that a screening program for asymptomatic people was not cost-effective, especially in PLWH, who are affected by a high prevalence of non-cancerous pulmonary nodules.
- The same opinion seems to be shared by the **EACS 2017** did not include lung cancer screening in their guidelines.
- Further studies are needed to establish the real risk-benefit ratio for lung cancer screening in PLWH.

## Lung Cancer *(Cont'd)*

- Erlotinib and Afatinib, which are **inhibitors of the epithelial growth factor receptor**, decrease the production of activated and memory CD4+ T-lymphocytes and are therefore not indicated in PLWH.
- **Inhibitors of the immune-checkpoints** (Pembrolizumab, nivolumab and atezolizumab)
  - They are directed towards molecules mediating the regulation of the immune system, such as PD-1 and PD-L1.
  - They seem to be effective even against the most difficult type of cancers and have a role in modulating T-cell activation in peripheric tissues.

# Lung Cancer *(Cont'd)*



2016

RESEARCH ARTICLE

## CD4<sup>+</sup> T Cells Expressing PD-1, TIGIT and LAG-3 Contribute to HIV Persistence during ART

Rémi Fromentin<sup>1</sup>, Wendy Bakeman<sup>2</sup>, Mariam B. Lawani<sup>2</sup>, Gabriela Khoury<sup>3,4</sup>, Wendy Hartogensis<sup>5</sup>, Sandrina DaFonseca<sup>2</sup>, Marisela Killian<sup>6</sup>, Lorrie Epling<sup>6</sup>, Rebecca Hoh<sup>6</sup>, Elizabeth Sinclair<sup>6</sup>, Frederick M. Hecht<sup>6</sup>, Peter Bacchetti<sup>5</sup>, Steven G. Deeks<sup>6</sup>, Sharon R. Lewin<sup>3,4</sup>, Rafick-Pierre Sékaly<sup>7</sup>, Nicolas Chomont<sup>1,2,8\*</sup>

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## Lung Cancer *(Cont'd)*

- Currently, there are no reports showing an increased risk for metastatic cancers or AIDS in PLWH treated with immune-checkpoints inhibitors.
- On the contrary, **Fromentin et al 2016** showed that CD4+ T-cells highly expressing PD-1 and TIGIT have an increased probability to be infected by HIV compared to cells not expressing them.
- Therefore, the use of immune checkpoints inhibitors directed against PD-1 could also help eradicate the infection by activating latently infected cells and mediating a “shock and kill” approach.

# Breast Cancer

- Little is known about the epidemiology of breast cancer in PLWH.
- Different studies had different conclusions, but all of them agree on the fact that breast cancer incidence in PLWH is similar or even slightly lower than in general population.
- Despite the fact that the incidence of breast cancer is not increased in PLWH, several studies showed how the virus play a role in accelerating the evolution of the cancer, especially acting on immune signaling, angiogenesis upregulation and metastatic spread, leading to a **worse** prognosis.

# Breast Cancer *(Cont'd)*

- Therefore, it is imperative to try and diagnose breast cancer in PLWH as soon as possible.
- In PLWH, genetic factors (BCRA1 and 2 genes, Li Fraumeni syndrome), familiarity, iatrogenic factors (chest irradiation at a young age, hormonal therapy) and individual factors (atypical hyperplasia, pregnancy in old age, premature menarche and late menopause) contribute to define the level of risk for breast cancer.

European Review for Medical and Pharmacological Sciences

2019; 23: 1158-1164

## Breast cancer in women living with HIV

F. D'ANDREA<sup>1</sup>, M. CECCARELLI<sup>1,2</sup>, A. FACCIOLÀ<sup>1</sup>, G. NUNNARI<sup>1</sup>,  
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<sup>3</sup>Department of Human Pathology of the Adult and the Developmental Age "G. Barresi", University of Messina, Messina, Italy

## Breast Cancer Screening for High-Risk Patients of Different Ages and Risk - Which Modality Is Most Effective?

Cureus 2016

Elizabeth Wellings<sup>1</sup>, Lauren Vassiliades<sup>2</sup>, Reem Abdalla<sup>1</sup>

1. Medical Student, University of Central Florida College of Medicine 2. Medical Student III, University of Central Florida College of Medicine

## Breast Cancer *(Cont'd)*

- Therapy is not different in PLWH, despite the need to avoid drug-drug interactions.
- A study demonstrated an upregulation of TAR binding protein 2 (TARBP2) in the case of tamoxifen-resistant breast cancers. It is possible to hypothesize that an upregulation of TARBP2 can happen in presence of HIV-1, thus conferring to it tamoxifen resistance. Further studies are needed to confirm this possibility.



2019



Article

### TARBP2-Enhanced Resistance during Tamoxifen Treatment in Breast Cancer

Ming-Yang Wang <sup>1,\*</sup>, Hsin-Yi Huang <sup>2</sup>, Yao-Lung Kuo <sup>3</sup>, Chiao Lo <sup>1</sup>, Hung-Yu Sun <sup>4,5</sup>, Yu-Jhen Lyu <sup>1,6</sup>, Bo-Rong Chen <sup>1</sup>, Jie-Ning Li <sup>5,6</sup> and Pai-Sheng Chen <sup>5,6,\*</sup>

## Breast Cancer *(Cont'd)*

- HER-2 positive cancers can be targeted with **monoclonal antibodies against HER-2** (trastuzumab, pertuzumab).
- Trastuzumab and Pertuzumab increase the number of CD4+, especially those infiltrating the tumor, leading to a better rate of complete response.
- According to this effect, it is reasonable to think that the use of these molecules is immunologically safe in PLWH with breast cancer.

### **Non-AIDS defining cancers: a comprehensive update on diagnosis and management**

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# Colorectal Cancer

- Colorectal Cancer (CRC) is the third cancer per mortality rate in the general population.
- Reports are discordant about whether PLWH have an increased risk for CRC than HIV-negative individuals.
- However, most PLWH are diagnosed for CRC in a more advanced stage, at a younger age and with more aggressive forms of cancer, leading to a poorer prognosis.
- Most of the drugs used for CRC cause a deep decrease in CD4+ T-cell count.



# Hepatocellular Carcinoma

- Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the sixth most common cancer in the world.
- The majority of the cases are related to Hepatitis C Virus (HCV) or Hepatitis B Virus (HBV) infections.
- Due to the comparable geographical spread of HCV and HBV infections and HIV infection, HCC has become a burden for PLWH ever since the introduction of ART.

# Hepatocellular Carcinoma (Cont'd)

- HCC is the best studied NADC, with its six-fold higher risk of developing the cancer in PLWH than the general population.
- Guidelines for the diagnosis and management of HIV-1 infection suggest to screen PLWH every 6-12 months if co-infected with HCV or HBV and suffering from liver cirrhosis.
- Screening is performed through a hepatic US and a-fetoprotein (AFP) dosage,

European Review for Medical and Pharmacological Sciences

2012; 16: 1257-1270

## Hepatocellular carcinoma in HIV positive patients

G. NUNNARI<sup>1,2</sup>, M. BERRETTA<sup>3</sup>, M.R. PINZONE<sup>1</sup>, M. DI ROSA<sup>1</sup>,  
S. BERRETTA<sup>4</sup>, G. CUNSOLO<sup>4</sup>, M. MALAGUARNERA<sup>5</sup>, S. COSENTINO<sup>1</sup>,  
P. DE PAOLI<sup>6</sup>, J.M. SCHNELL<sup>2</sup>, B. CACOPARDO<sup>1</sup>

## Hepatocellular Carcinoma (Cont'd)

- Prevention of HBV-related and HCV-related HCC can be achieved by treating the hepatotropic infections.
- According to the EASL guidelines, PLWH co-infected with HCV and/or HBV should be treated accordingly to their conditions.
- Since 2017, treatment for HCV is available to all the people who are infected, independently from the stage of the disease.

## Hepatocellular Carcinoma (Cont'd)

- For HIV/HCV co-infection, similar to general population, the suggestion is to treat the infection as soon as possible, paying attention to drug-drug interactions with ART.
- EASL guidelines for the treatment of HBV infection suggest that PLWH co-infected with HBV should be treated with a tenofovir disoproxil fumarate (TDF)-based or tenofovir alafenamide fumarate (TAF)-based regimen.

# Hepatocellular Carcinoma (Cont'd)

- Similar to what happens for other cancers, PLWH are often diagnosed with HCC in an advanced stage.
- Liver transplantation offer the best survival rates for HCC. Milan's criteria for eligibility for transplantation in PLWH do not differ from those applied to the general population.

European Review for Medical and Pharmacological Sciences

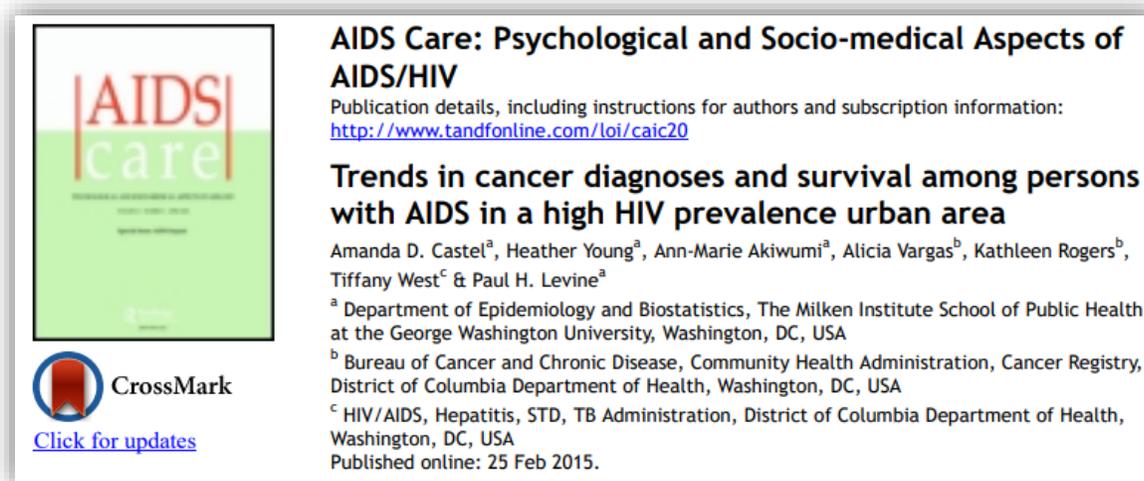
2017; 21: 3421-3435

## **Multimodal oncological approach in patients affected by recurrent hepatocellular carcinoma after liver transplantation**

G.P. GUERRINI<sup>1</sup>, M. BERRETTA<sup>2</sup>, G. TARANTINO<sup>1</sup>, P. MAGISTRI<sup>1,3</sup>,  
A. PECCHI<sup>4</sup>, R. BALLARIN<sup>1</sup>, F. DI BENEDETTO<sup>1</sup>

# Hodgkin's Lymphoma

- HL has a very low incidence rate in general population (0.01%).
- However, PLWH have an increased risk for all B-cell lymphoproliferative disorders, and HL in particular.
- It has been demonstrated that HL has a 13-fold higher incidence in PLWH than in general population.



# Hodgkin's Lymphoma (Cont'd)

- Median age at diagnosis is around 30 years, and the highest incidence is around 7 years and a half after the patients are diagnosed with HIV infection.
- HL affects PLWH when their CD4+ T-lymphocyte counts are higher
  - The increasing number of CD4+ T-lymphocytes stimulates the activation of all B-lymphocytes, and tumoral B-lymphocytes (Hodgkin's Reed-Sternberg cells, HRS) in particular.
  - The presence of HRS stimulates the activation of CD4+ T-lymphocytes with inflammatory signals. Therefore, the increase in CD4+ T-lymphocytes is caused by the presence of the cancer.
  - There is a higher risk for other AIDS-related diseases in PLWH with a low CD4+ T-cell count, thus creating a "competition" with HL.

## Hodgkin's Lymphoma (Cont'd)

- HL is associated with EBV infection and this association is especially important in PLWH.
- Despite decreasing mortality, PLWH are affected by less favorable histological types: mixed cellularity (MC) and lymphocyte depleted (LD) HL. Both of them are rich in HRS.
- Moreover, PLWH are affected by a higher prevalence of B-symptoms, than the general population.

## Hodgkin's Lymphoma (Cont'd)

- **Standard chemotherapy** with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) allows complete remission (CR) in 87% of HL in PLWH, with a relapse rate of 11% after 6-8 cycles of therapy.
- The introduction of cART and G-CSF allowed PLWH to reach similar overall survival to the general population.
- **Immune checkpoint inhibitors** have not been studied in PLWH with CHL. Therefore, their use in this setting should be evaluated on a case-by case basis.

# Conclusion

- Cancer has always been an important cause of death in PLWH, becoming the first one after the introduction of ART.
- NADCs are especially frequent in PLWH in a good immune-virologic status, with high CD4+ T-lymphocytes and undetectable viremia. Therefore, it is particularly important for cancer screening schedules to be followed attentively.
- Cancer onset happens around 10 years earlier in PLWH compared to general population.

## Conclusion *(Cont,d)*

- As a matter of fact, too often PLWH are still diagnosed to be affected by late-stage cancers, leading to a worse prognosis even in patients who are well controlled for the HIV infection.
- Due to the fact that NADCs represent the most frequent cause of death in PLWH, that their onset is in younger patients who are in a good viroimmunologic status, and that the prognosis in these patients is worse than that of the general population, it seems that **clinical trials should include PLWH.**



Thank You