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**AETC**  
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# 19<sup>th</sup> Annual HIV CONFERENCE

May 14-15, 2010 • Orlando, FL

## HIV Related Malignancies

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## Why do people with HIV/AIDS have a higher risk of cancer?

- Reduced body's ability to destroy cancer cells and fight infections that may lead to cancer (Angeletti et al. Pharmacology 2008)
- Antigen-driven stimulation, somatic hyper mutations (B-cell lymphomas)
- Opportunistic oncogenic viruses !!!



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## Frequency of malignancies in HIV-infected patients as compared to the general population in the U.S. (from 1996 to 2002)

Tumor	Standardized incidence ratio
All cancer types	1.9
Kaposi sarcoma (AIDS-defining)	790
Primary CNS lymphoma (AIDS-defining)	170
Non-Hodgkin lymphoma (AIDS-defining)	6.5
Cancer of the cervix (AIDS-defining)	2.9
Cancer of the anus	9.1
Hodgkin lymphoma	6.7
Liver cancer	3.1
Cancer of the larynx	2.7
Lung cancer	2.6
Cancer of the oral cavity/pharynx	1.5

From Engels *et al.*, *International Journal of Cancer* 2008



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## Has the introduction of ART changed the cancer risk of people infected with HIV?

- **AIDS Defining Malignancies: Yes**
  - Decreased incidence may be a result of better immune surveillance
  
- **Non-AIDS defining malignancies: No**
  - Despite higher incidence in immune compromised patients, rates in Hodgkin's lymphoma and anal cancer, and possibly melanoma, prostate, liver have increased (Silverberg et al. *Curr Opin HIV AIDS*. 2009)
  
  - Why? : increased screening, tobacco, alcohol, and viral co-infections in aging HIV-population (Silverberg et al. *Curr Opin Oncol* 2007)



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## Oncogenic Viruses

### Human Herpes Virus Type 8 (HHV-8, KSHV)

- Kaposi's Sarcoma
- Multicentric Castleman's Disease
- Primary effusion lymphoma

### Epstein Barr Virus (EBV)

- B and T-Cell Lymphomas
- Nasopharyngeal CA
- Gastric cancer

### Human T Lymphotropic Virus Type I (HTLV-I)

- Adult T-Cell Leukemia

### Human Papilloma Virus (HPV)

- Cervical CA
- Anal carcinoma
- Genital Cancers
- Oropharyngeal CA

### Hepatitis C: Hepatoma



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## Human papilloma virus (HPV)

- **Transmitted by:**
  - Intimate contact, sexual, and fomites
- **Oncogenic types:**
  - 15–20 including: **16, 18**, 31, 33, 35, 39, 45, 51, 52, 58
  - HPV **16** (54%) and HPV **18** (13%) account for majority of worldwide cervical cancer
- **Associated cancers:**
  - cervical and some types of anal, penile, vaginal, vulvar, and oropharyngeal



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### Cancers attributable to high-risk HPV infection United States, 2003

Anatomic site	Total cancers*	% estimated HPV attributable fraction†
Cervix	11,820	100
Anus	4,187	85
Vulva/vagina	4,577	40
Penis	1,059	40
Oral/pharyngeal	29,627	15

\* CDC. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2007;56(No. RR-2):1–24.

† Parkin M. Presented at the International Papillomavirus Conference, Vancouver, Canada, 2005

U.S. Cancer Statistics Working Group  
<http://www.cdc.gov/vaccines/pubs/surv-manual/chpt05-hpv.pdf>



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## HPV oncogenic proteins

- Both HPV E6 and E7 proteins manipulate programmed cell growth and proliferation
- HPV E6:
  - Targets p53 for ubiquitin-mediated degradation thereby abrogating cell cycle control and apoptosis.
- HPV E7:
  - Interacts with retinoblastoma protein (pRb), and other negative cell-cycle regulators involved in the G1/S and G2/M transition.



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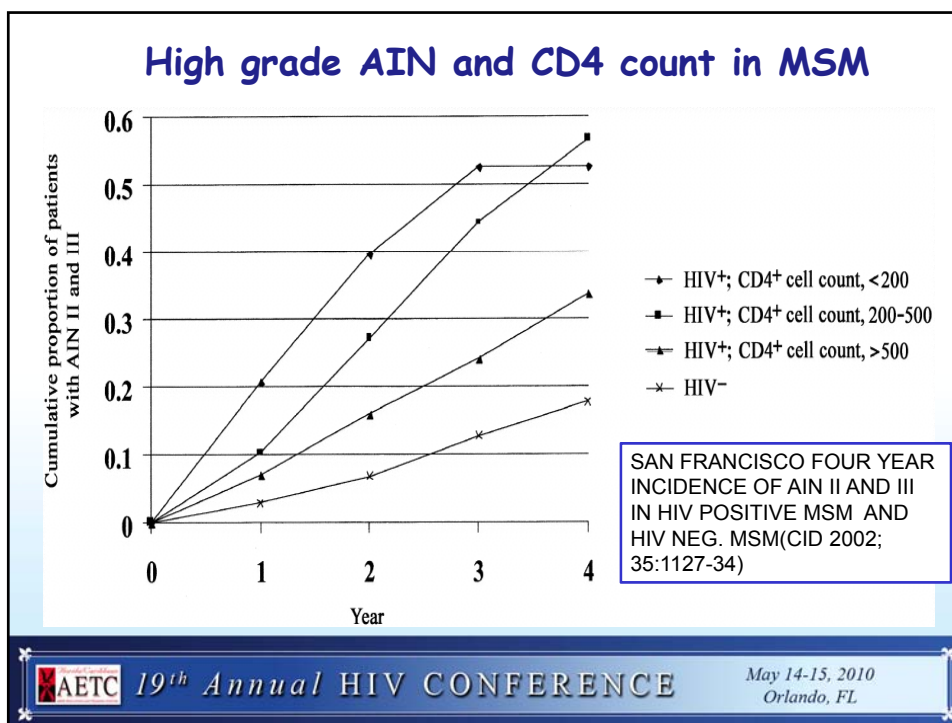
## HIV and HPV in North America

- HIV+ men and women are at an increased risk for developing HPV infection, anogenital intraepithelial neoplasia (AIN) and invasive cancer
- While the incidence of cervical cancer has remained stable since HAART, HIV + women have a 10-fold incidence, and the risk increases with decreasing CD4 count (D'Souza et al. 2010 abstract)
- Anal cancer initially increased among HIV-infected individuals after HAART but rates have recently stabilized (Silverberg et al. 2010 abstract)



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### Anal cancer prevention in HIV patients

- **Quadrivalent HPV vaccine (HPV 6/11/16/18):**
  - Can prevent persistent genital HPV infection, genital condylomas, and high-grade AIN lesions in HIV (-) MSM (Merck 020 trial)
  - AMC 052 trial: qHPV vaccine is safe in HIV+ MSM. Further studies are in progress, including men women. (Palefsky)
- **Visual inspection of anogenital regions, and digital rectal exam**
- **Anal cytology with HPV testing, and high-resolution anoscopy with biopsy of any lesion** should be considered in high-risk patients:
  - men who have sex with men (MSM)
  - any patient with a history of anogenital condylomas
  - women with abnormal cervical and/or vulvar histology
- **Laser or infra-red coagulation, or surgical ablation excision of high grade AIN lesions**
- **Topical treatment of high grade AIN lesions:** Imiquimod, Cidofovir

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## Cervical Cancer Prevention in HIV

- **Yearly PAP smear** in all HIV + women
- **Quadrivalent HPV vaccine**
  - Approved by the FDA for use in females 9 to 26 years old
  - Ongoing clinical trials in HIV + women
    - ACTG 5240
    - AMC-054 (India)



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## Gamma Herpes Viruses: EBV and HHV-8

- Induce both lymphoid and epithelial cancers
- Encode latent and lytic proteins that contribute to oncogenesis
- LMP-1 (EBV) activates NF- $\kappa$ B, similar to constitutive CD40 signaling
- K-1 (KSHV) also activates survival factors
- EBV upregulates cellular cyclins while KSHV encodes its own cyclin



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## Human Herpesvirus-8 (HHV-8)

- **Associated neoplastic diseases:**
  - Kaposi's Sarcoma (KS) (100% association HIV +/-)
  - Primary Effusion Lymphoma (PEL) (~100% association in the setting of HIV); a rare disease
  - Multicentric Castleman's Disease (MCD) (~100% association in the setting of HIV)
- **Seroprevalence between 0-20% in the general population, higher in central Africa and homosexual men**
- **Seroconversion or seropositivity predicts risk for developing KS**
- **Encodes multiple potential oncogenes:**
  - Homologues of cellular genes: vIL-6, vBcl-2, vFLIP, vCyclin, and vGPCR



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## Kaposi's Sarcoma

- **Association with HHV-8 made in 1994 (Chang and Moore)**
- **Seen in immune compromised patients:**
  - HIV
  - post transplant
  - Induced by immunosuppressive drugs
- **Classic KS:**
  - Mediterranean populations
  - Endemic Central African variant



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## Treatment of KS

- **Stage T0 (Limited KS)**- Confined to skin and/or lymph nodes and/or minimal oral disease
  - May respond completely to reversal of immunosuppression (HAART)
  - Local treatment may include: intralesional chemotherapy, cryotherapy, radiation, and retinoids
- **Stage T1 (Advanced, Systemic KS)**- Tumor-associated edema or ulceration, extensive oral disease, and disease in other non-nodal viscera
  - Usually requires systemic treatment
  - Partially to responsive to liposomal doxorubicin, paclitaxel, vinca alkaloids, interferon



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## Multicentric Castleman's Disease

- **B-cell lymphoproliferative disorder:** lambda chain restriction
- **Symptoms:** fever, lymphadenopathy, and less common splenomegaly, hepatomegaly, fluid retention (ascites/effusions)
- **Can give rise to Multicentric Castleman's disease-associated plasmablastic lymphomas**
- **Patients can also develop KS and PEL**
- **Pathogenesis:** Infection of immunoblasts by HHV-8 and production of viral interleukin-6 (IL-6)



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## HIV-Castleman's Disease

- Nearly all HIV cases are associated with HHV-8
- Affects mainly men
- Can develop while on HAART
- Median survival ~ 12 months (improved after HAART era)
- A better immune status (ie. high CD4 count, or undetectable HIV viral load) does not seem to affect survival (Mylona *et al. AIDS Rev. 2008*)
- Treatment (as in HIV negative): chemotherapy, interferon, rituximab



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## HHV-8 Associated Primary Effusion Lymphoma (PEL)

- Usually occur in advanced AIDS
- Characterized by effusions in the absence of tumor masses spreading along serous membranes without infiltrative growth patterns ( Carbone *et al. Br J Haematol. 2008*)
- Solid variant can occur (nodal and extranodal sites)

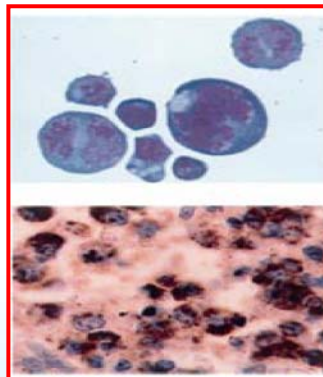


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## Characteristics of PEL

- Large polypoid and lobated cell, prominent nucleoli, and abundant plasmocytoid cytoplasm”
- B-cell at late stage of differentiation
  - Usually express a plasma cell-related phenotypic profile [(CD138+, MUM1+, EMA+/-), CD30+/-, CD45+/-] (weak)]
  - Downregulate mature B cell markers: CD19, CD20, and CD79A/B



Carbone, *Blood* March 1998



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## Treatment of PEL

- Most patients are poor responders to conventional chemo and have a dismal prognosis
  - Median survival is approximately 6 months (Boulanger et al, 2005)
- Investigational agents
  - Bortezomib (NF- $\kappa$ B inhibitor) + chemotherapy
  - HDAC inhibitors
  - Antiviral nucleosides (AZT, GCV)



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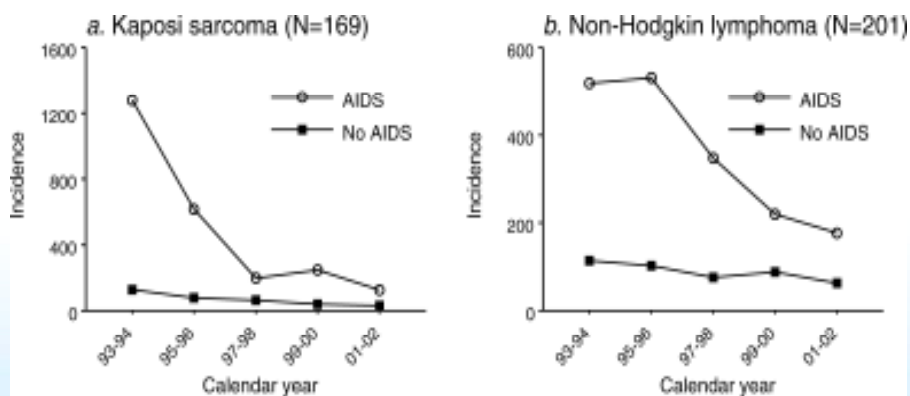
## AZT + IFN- $\alpha$ can induce remission in AIDS related PEL

Gosh et al, Blood 2003



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## Impact of HAART Therapy on AIDS NHL in the U.S.



Engels et al. Int J Cancer. 2008

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## Overall Impact: HAART era (1996-2006)

- Overall NHL rates are decreasing
- Increased risks:
  - CD4 risk < 250 cells/mm
  - Viral load > 5.00 log<sub>10</sub> copies/mL

Engels EA et al. J Acquir Immune Defic Syndr 2010



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## Prognosis of HIV Lymphomas

- **Poor risk features:**
  - CD4 < 100 cell/mm<sup>3</sup>
  - CNS involvement
  - High-Intermediate IPI score or above:
    - > 2 factors: stage III or IV, elevated LDH, ≥ 2 extranodal sites, performance status ≥ 2, age ≥ 60 years
  - Histologies:
    - Activated B-cell type DLBCL (express NF-κB)
    - Burkitt lymphoma
    - Plasmablastic lymphoma
    - Primary effusion (PEL)
    - Primary CNS lymphoma



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## EBV Association in HIV-Related Lymphomas

- Diffuse Large B-cell lymphoma (DLBCL): 30-60%
- Burkitt Lymphoma: 20-40 %
- Hodgkin's lymphoma: 80-100%
- Primary CNS lymphoma: ~100%
- Oral plasmablastic lymphoma: 80%



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## Epstein Barr Virus (EBV)

- In adults  $1-50 \times 10^6$  cells are latently infected with EBV
- EBV is a linear virus that becomes a circular episome upon infection of B cells
- EBV-Latent Membrane Protein (LMP) acts as an oncogene, mimics CD-40, upregulates NF- $\kappa$ B and Bcl-2
- Different forms of latency programs(I,II, and III)



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## Standard Treatment of HIV Related Lymphomas

- **Chemotherapy:**
  - non-Hodgkin's lymphoma: CHOP, EPOCH or CDE +/- rituximab
  - Hodgkin's lymphoma: ABVD, BEACOPP
  - Burkitt lymphoma: Hyper cVAD, CODOX-m/IVAC
- **Radiation Therapy:** primary CNS lymphoma



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## Novel Investigational Therapies for HIV Related Lymphomas

- **Autologous Stem cell Transplant** in relapse disease
- **Antiviral therapies:**
  - i. **EBV specific cytotoxic T-cells**
  - ii. **EBV/HHV-8 lytic-inducing agents:**
    - **Arginine butyrate:** in combination with antiviral nucleoside analogs (GCV)
    - **Zidovudine (AZT):** in combination with chemotherapy or interferon (ie. PEL)
    - **NF-κB inhibitors:** bortezomib (Velcade)
    - **Histone deacetylase (HDAC) inhibitors:** vorinostat

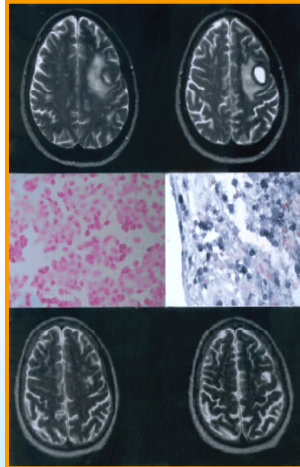


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## Promiscuous expression of EBV-TK (lytic) in PCNSL responsive to AZT-GCV treatment

Roychowdhury et al. Cancer Research 2003



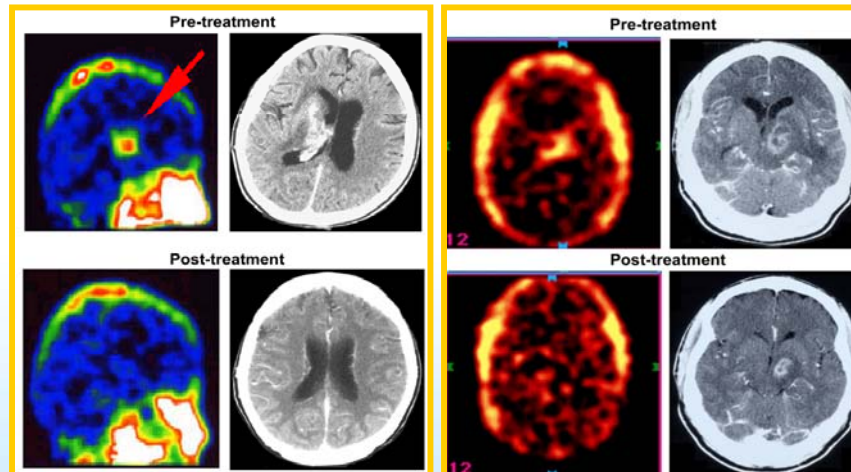
**Top panels:** MRI brain images of a patient with post-transplant primary central nervous system lymphoproliferative disorder associated with the Epstein-Barr Virus (EBV). **Middle panels:** Non-reactive control tissue (*left*), and stereotactic core brain biopsy of this patient's tumor demonstrating evidence of constitutive EBV thymidine kinase gene expression by *in situ* RT-PCR (*right*). **Bottom panels:** MRI brain images of the patient one year after initiating treatment with high dose anti-viral therapy (ganciclovir and zidovudine) show only residual scar tissue. The patient has now been disease-free for three years.



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## AZT/Hydroxyurea is Active in AIDS PCNSL (University of Miami)

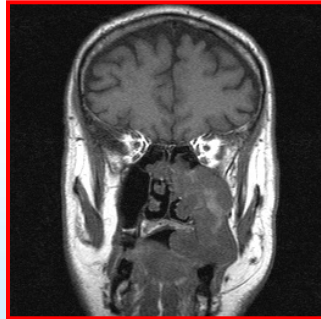


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**Regression of EBV+  
Plasmablastic Lymphoma  
After High-dose  
Methotrexate/AZT  
(University of Miami)**

7/24/08



7/24/08



8/4/08



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**Clinical Response to AZT/Hydroxyurea in  
Combination with Doxorubicin,  
Methotrexate (UM trial)**

52 y/o HIV+ male with relapsed EBV+ and HHV-8+  
solid primary effusion variant



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## Ongoing AMC Clinical Trial

**AMC 053: Pilot Trial of the Anti-viral and Anti-tumor Activity of Velcade Combined with (R)ICE in EBV and/or HHV-8 Positive Relapsed/Refractory AIDS Associated Non-Hodgkin's Lymphomas**



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## New AMC lymphoma trial

**AMC 075: A SEQUENTIAL PHASE I/RANDOMIZED PHASE II TRIAL OF VORINOSTAT AND RISK-ADAPTED CHEMOTHERAPY WITH RITUXIMAB IN HIV-RELATED B-CELL NON-HODGKIN'S LYMPHOMA**



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  - Ronald Mitsuyasu
  - Joseph Sparano

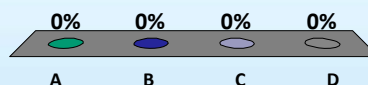


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### Which of the following statements is true regarding the trends of cancer incidence in the HIV population since the introduction of HAART?

- A. The incidence of non-Hodgkin lymphoma continues to increase
- B. The incidence of HPV related diseases (cervical and anal cancer) is decreasing
- C. The incidence of Kaposi's Sarcoma continues to increase
- D. The incidence of high grade anal intra epithelial neoplasia is higher in patients with low CD4 count

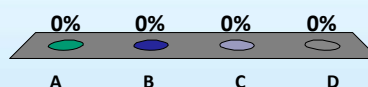


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**Which of the following characteristics is the worst predictor of survival in HIV-related non-Hodgkin lymphoma?**

- A. Advanced stage
- B. Involvement of > 1 extranodal site
- C. Lactose dehydrogenase (LDH) level
- D. Low CD4 count

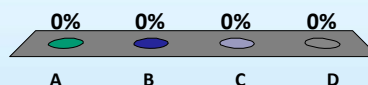


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**Which of the following is the causative agent of HIV-related primary CNS lymphoma?**

- A. Human Herpes Virus-8
- B. Human papilloma virus
- C. Epstein Barr virus
- D. HIV



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