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ADULTS AND CHILDREN ESTIMATED TO BE LIVING WITH HIV IN 2007
Total: 33.2 (30.6–36.1) million

North America
1.3 million
[0.48–1.9 million]

Caribbean
230 000
[210 000–270 000]

Latin America
1.6 million
[1.4–1.9 million]

Sub-Saharan Africa
22.5 million
[20.9–24.3 million]

Western and Central Europe
760 000
[600 000–1.1 million]

Middle East and North Africa
380 000
[270 000–500 000]

Eastern Europe and Central Asia
1.6 million
[1.2–2.1 million]

East Asia
800 000
[620 000–960 000]

South and South-East Asia
4.0 million
[3.3–5.1 million]

Oceania
75 000
[53 000–120 000]
Estimated Numbers of HIV/AIDS in China in 2007

- The number of estimated HIV/AIDS cases in China has increased to 700,000
- The estimated AIDS patients in China are about 85,000
- The estimated new HIV cases are about 50,000 in 2007
- The estimated deaths from HIV/AIDS are about 20,000 in 2007
- The confirmed cases of HIV/AIDS in China are 223,501 by October 31, 2007
Transmission Routes

- 44.7% of the new cases occurred through heterosexual sex
- 42% occurred from injection drug use
- 12.2% of cases occurred among men who have sex with men
- 1.1% of cases were through mother-to-child transmission
Cancer in China in 2002

- 2,190,623 new cases, 20.2% of the World (World: 10,862,496)

- 1,601,050 Cancer deaths, 23.8% of the world (World: 6,723,887)

- 3,119,947 5-year survival, 12.7% of the world (World: 24,570,115)
# Age Standardized Incidence Rates (/100,000)

<table>
<thead>
<tr>
<th>Site</th>
<th>US Males</th>
<th>US Females</th>
<th>Eastern Asia Males</th>
<th>Eastern Asia Females</th>
<th>World Males</th>
<th>World Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>7.2</td>
<td>3.3</td>
<td>46.1</td>
<td>20.6</td>
<td>22.0</td>
<td>10.3</td>
</tr>
<tr>
<td>Lung</td>
<td>61.9</td>
<td>36.1</td>
<td>42.7</td>
<td>17.7</td>
<td>35.5</td>
<td>12.1</td>
</tr>
<tr>
<td>Liver</td>
<td>5.5</td>
<td>2.0</td>
<td>36.9</td>
<td>13.3</td>
<td>15.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4.9</td>
<td>1.3</td>
<td>24.0</td>
<td>9.7</td>
<td>11.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Colon/Rectum</td>
<td>44.6</td>
<td>33.1</td>
<td>19.6</td>
<td>12.5</td>
<td>20.1</td>
<td>14.6</td>
</tr>
<tr>
<td>Breast</td>
<td>—</td>
<td>101.1</td>
<td>—</td>
<td>20.5</td>
<td>—</td>
<td>37.5</td>
</tr>
<tr>
<td>Leukemia</td>
<td>11.2</td>
<td>7.4</td>
<td>5.8</td>
<td>4.1</td>
<td>5.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8.3</td>
<td>6.3</td>
<td>4.9</td>
<td>3.3</td>
<td>4.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>7.7</td>
<td>0</td>
<td>7.4</td>
<td>0</td>
<td>16.2</td>
</tr>
<tr>
<td>Brain</td>
<td>6.5</td>
<td>4.5</td>
<td>3.7</td>
<td>2.6</td>
<td>3.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Prostate</td>
<td>124.8</td>
<td>0</td>
<td>3.8</td>
<td>0</td>
<td>25.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: GLOBOCAN 2002
Infections and Cancers
<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Agent (group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinomas</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td><em>Schistosoma haematobium</em> (blood fluke)</td>
</tr>
<tr>
<td>Cervical</td>
<td>HPV (papillomavirus)</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>HBV (hepadnavirus)</td>
</tr>
<tr>
<td></td>
<td>HCV (flavivirus)</td>
</tr>
<tr>
<td>Bile duct</td>
<td><em>Opisthorchis viverrini</em> (liver fluke)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>EBV (herpesvirus)</td>
</tr>
<tr>
<td>Stomach</td>
<td><em>Helicobacter pylori</em> (bacterium)</td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell</td>
<td>HTLV-I (retrovirus)</td>
</tr>
<tr>
<td>Burkitt</td>
<td>EBV (herpesvirus)</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>EBV (herpesvirus)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
</tr>
<tr>
<td>Kaposi</td>
<td>HHV8 (herpesvirus)</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein-Bar virus; HTLV-I, human T-cell lymphotropic virus type I; and HHV8: human herpesvirus 8.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Cancer</th>
<th>Number of cases</th>
<th>% of all cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori</td>
<td>Stomach</td>
<td>592,000</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>11,500</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>Cervix</td>
<td>492,800</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Ano-genital</td>
<td>53,880</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mouth, pharynx</td>
<td>14,500</td>
<td></td>
</tr>
<tr>
<td>HBV and HCV</td>
<td>Liver</td>
<td>535,000</td>
<td>4.9</td>
</tr>
<tr>
<td>EBV</td>
<td>Nasopharynx</td>
<td>78,100</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Hodgkin lymphoma</td>
<td>28,600</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma</td>
<td>6,700</td>
<td></td>
</tr>
<tr>
<td>HIV/HHV-8</td>
<td>Kaposi sarcoma</td>
<td>66,200</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>36,100</td>
<td></td>
</tr>
<tr>
<td>Schistosomes</td>
<td>Bladder</td>
<td>10,600</td>
<td>0.1</td>
</tr>
<tr>
<td>HTLV-I</td>
<td>ATL</td>
<td>3,300</td>
<td>0.03</td>
</tr>
<tr>
<td>Liver flukes</td>
<td>Liver</td>
<td>2,500</td>
<td>0.02</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,932,800</td>
<td>17.8</td>
</tr>
</tbody>
</table>
Numbers of Cancer Cases Associated with Infection in China

- NPC: 36,863
- Liver Cancer: 278,200
- Stomach Cancer: 248,640
- Cervical Cancer: 45,338
- NHL: 2,996
- Total: 1,224,087 (China all Cancer cases: 2,190,623), 55.9% associated with infection
Cancer-causing Infectious Agents

- Most important agents that lead to cancer are viruses:
  - hepatitis B (HBV) and hepatitis C (HCV)
  - Epstein-Barr virus (EBV)
  - Human herpes virus 8/KS (HHV8)

- 15% of all cancer incidences worldwide are attributed to infections.
  - 23% of all malignancies in economically developed countries, 7% in developed countries
Infections and Cancers

- Evaluation for cause of the infectious agents as human carcinogens is difficult due to:
  - Ubiquitous nature
  - Substantial length of time between infection and cancer occurrence
  - Nature of cofactors
  - Rarity of malignancy among those infected
Characteristics of Cancer-causing Infectious Agents

- The agents share common biological characteristics:
  - **Capacity to become persistent**
    - Carrier state- periodic/continuing transmission of agent to new hosts occurs.
    - Conditionally persistent or chronic infection (HBV can become chronic infection if not initially cleared by effective immune response).
  - **Dynamic host-agent interaction**
    - Factors that influence interaction include: age, gender, route of infection, and presence of co-infections.
Age-Specific Incidence Rates for Major Virus-Associated Malignancies

- ATL
- Burkitt
- Hodgkin lymphoma

- Liver
- Cervix
- Nasopharynx
Mechanisms of Infection-Induced Malignancy

Chronic Inflammation and Carcinogenesis
- Chronic host-pathogen interaction
  Immune suppression, lack of immune surveillance
- Chronic inflammation
  Oxidative Stress
  DNA damage and mutations
  Cell injury
  Cell division
- Infection inducing Cell proliferation

Production of Oncogenic Proteins

Genomic Instability from Viral Genomic Integration
Mechanisms of Infection-induced Malignancies

- **Interleukins:**
  - Production of cytokines in response to infection may contribute to development of lymphomas, especially in HIV-infected hosts.
  - Major cellular sources of cytokines: T cells, monocytes, and bone marrow cells.
  - Interleukin-6 (IL-6), a cytokine, is especially relevant to polyclonal B-cell expansion and to malignant transformation in lymphomas.
  - IL-6 may augment HIV replication and infection progression.
Table 5.1 Selected potential factors involved in the pathogenesis of malignancies arising in immunologically disturbed states

<table>
<thead>
<tr>
<th>Host factors: disruption of genomic integrity, orderly proliferation, and differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncogene activation or dysregulation (e.g., c-myc, cyclin D1/bcl-1, bcl-2, bcl-6 ras)</td>
</tr>
<tr>
<td>Tumor suppressor inactivation (e.g., p53, Rb, cyclin-dependent kinase inhibitors)</td>
</tr>
<tr>
<td>Cytokine dysregulation (e.g., IL-2, IL-6, IL-10, IL-12, fibroblast growth factors)</td>
</tr>
<tr>
<td>Defective repair of DNA Damage (including insertional mutagenesis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infectious pathogens: transformation and chronic antigenic stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA viruses (e.g., EBV, KSHV, HPV)</td>
</tr>
<tr>
<td>Retroviruses (e.g., HTLV-1, HIV)</td>
</tr>
<tr>
<td>Bacteria (e.g., Helicobacter)</td>
</tr>
<tr>
<td>Parasitic (e.g., Strongyloides in HTLV-1)</td>
</tr>
</tbody>
</table>
HIV/AIDS & Malignancies
Malignancies among HIV/AIDS Patients

- **AIDS-defining malignancies:**
  - Kaposi Sarcoma (KS)
  - Non-hodgkin Lymphoma (NHL)
  - Cervical Cancer

- **Non-AIDS defining malignancies:**
  - Liver, Lung, oral, rectal, anal cancer, penile, nasopharyngeal, etc.
“Epidemic” or AIDS-associated KS

- Occurs in HIV-positive people, primarily in homosexual men.
- Most prevalent type of KS in many countries.
- Can be most clinically aggressive and disseminated type of KS.
- Affects lymph nodes and visceral mucosal tissues as well as skin.
- Immune dysfunction is primary factor in pathogenesis of KS.
AIDS Lymphomas

- HIV infection characterized by defects such as immune regulation, loss of specific immune-cell subsets, changes in lymphoid tissues, and abnormal immune surveillance
  - Dysregulation may lead to increase in rate of transformed lymphocytes and ability to escape surveillance and as result, cause disease

- HIV infection can lead to T-cell destruction and impairment in B-cell maturation
  - Non-hodgkin Lymphoma (NHL)
  - Hodgkin Lymphoma (HL)
  - Burkitt Lymphoma (BL)
Hodgkin Lymphoma (HL)

- HL is relatively common malignancy among young adults in Westernized populations
- Risk associated with higher social class and small family size
- Occurs later in young adult life
- 25-50% of HL cases are EBV-positive
Burkitt Lymphoma (BL)

- Malignancy that occurs endemically primarily among young children, boys, in central Africa and New Guinea.
- Occurs sporadically among all ages in other parts of world as well.
- Risk of BL results from enhanced proliferation of B-lymphocytes by early EBV infection.
- Jaw and abdominal organs are frequent sites of malignancy.
- In other areas, BL is a rare tumor.
Cervical Cancer

- Invasive

- Main risk factors include:
  - ----HPV infection
  - ----sexual behaviors, multiple sex partners
  - ----living with HIV/AIDS
Associates for Increased Incidence of Malignancies among HIV/AIDS Patients

- Traditional risk factors for cancers:
  - Age, sex, smoking, drinking, dietary, ethnic and geographical factors, etc.

- HIV risk-taking behaviors:
  - Vaginal, oral and anal sexual behaviors: HPV, HHV8
  - Needle sharing among Injection Drug Users (IDUs): HBV, HCV
  - Blood/plasma donors: HBV, HCV
Associates for Increased Incidence of Malignancies among HIV/AIDS Patients

- Long-term immunodeficiency
  - Absence of protective immune surveillance for recognition and elimination of abnormal clones
  - Disruption of normal balance between cell proliferation and differentiation
  - Chronic antigenic stimulation (sometimes accompanied by infection)
  - Inability of cell to recognize, respond, to and repair DNA damage
- Longer life expectancy of HIV/AIDS patients due to HAART (Highly Active Anti-Retroviral Therapy)
  - Increased number of existing older AIDS patients
Changing Epidemiology of AIDS-related Cancer during HAART Era

- AIDS-defining malignancies especially Kaposi Sarcoma and Non-hodgkin Lymphoma are decreasing

- No significant decreasing for cervical cancer

- But non-AIDS defining malignancies has been increasing dramatically
Prevention/Intervention/Therapy for AIDS-related Malignancies

- Intervention early in course of HIV infection that interfere with factors promoting hyperproliferation and clonal expansion (IL-6, EBV, HHV-8) may decrease occurrence or prolong development of AIDS-related malignancies

- Key strategy is to maintain cellular immunity at level to prevent development and perpetuation of transformed clones
Prevention/Intervention/Therapy for AIDS-related Malignancies

- Vaccinations and preventions against infection
- Dietary Antioxidants
- Omega-3 fatty acids (anti-inflammatory agents)
- Anti-inflammatory Drugs, nonsteroidal anti-inflammatory drugs (NSAIDS) such as aspirin
Table 5.2 Exploiting molecular pathogenesis for therapy and prevention of lymphoproliferative malignancies

<table>
<thead>
<tr>
<th>Category</th>
<th>Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic therapies</td>
<td>New mechanisms (e.g., paclitaxel and other tubulin-directed agents, camptothecins)</td>
</tr>
<tr>
<td></td>
<td>Mechanisms to overcome drug resistance</td>
</tr>
<tr>
<td>Cytokine-based (biomodulatory) therapies</td>
<td>IL-2, IL-12, interferon</td>
</tr>
<tr>
<td></td>
<td>Anti-IL-6, anti-IL-10, anti-tumor necrosis factor</td>
</tr>
<tr>
<td>Immune-based therapies</td>
<td>Monoclonal antibodies, including immunotoxins and radioimmunoconjugates</td>
</tr>
<tr>
<td></td>
<td>Vaccines (anti-idiotype, antiviral)</td>
</tr>
<tr>
<td>Immunorestorative approaches</td>
<td>Bone marrow transplantation</td>
</tr>
<tr>
<td></td>
<td>Stem cell reconstitution (gene-altered)</td>
</tr>
<tr>
<td></td>
<td>Adoptive immunotherapy (HIV, EBV, CMV)</td>
</tr>
<tr>
<td></td>
<td>Immunopotentiating hormones</td>
</tr>
<tr>
<td>Gene-targeted approaches</td>
<td>Antisense (host and viral genomes)</td>
</tr>
<tr>
<td></td>
<td>Ribozymes</td>
</tr>
<tr>
<td>Antiviral strategies</td>
<td>New virocidal agents (including anti-KSHV)</td>
</tr>
<tr>
<td></td>
<td>Antiviral immunity</td>
</tr>
<tr>
<td></td>
<td>Adoptive immunotherapy, immunomodulation, vaccines</td>
</tr>
<tr>
<td></td>
<td>Modulation of EBNA gene expression (alteration of gene methylation)</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral targets</td>
</tr>
<tr>
<td></td>
<td>Reverse transcriptase, protease, nucleocapsid protein, integrase</td>
</tr>
</tbody>
</table>
Future Research

- Epidemiology of HHV8 in Chinese populations, especially Uygurs

- HIV/AIDS patient cohorts to understand the epidemiology of AIDS-related malignancies in HIV/AIDS patients in China, especially HCC among former plasma donors or injection drug users, KS among Uygurs, and cervical cancer and other non-AIDS defining cancers

- Basic research for understanding the relationship between viral infection, immunodeficiency and carcinogenesis
Human Herpes Virus 8 (HHV8)
Human Herpes Virus 8 (HHV8)

- HHV8 or also known as Kaposi sarcoma (KS)- associated herpes virus, is a human herpes virus with restricted geographic distribution.
- Most infections with HHV8 remain asymptomatic, similar to EBV.
- However, HHV8 has oncogenic potential since it is associated with all types of KS with primary effusion or body cavity-based lymphomas.
HHV8 Structure

- Outer lipid envelope
- Protein-rich tegument
- Core of linear double-stranded DNA surrounded by capsid
- Approximately 165kb in size and encodes more than 85 viral proteins.
Natural History of HHV8 Infection

- HHV8 establishes lifelong persistent infection in host, like other herpes viruses.
- Cell types most frequently infected with HHV8 are B-lymphocytes and monocytes.

- No severe clinical illness has been described in association with primary HHV8 infection.
  - Some symptoms shown are:
    - Transient/nonspecific symptoms such as localized skin rash, lymphadenopathy, and fatigue.
    - Low grade fever also common in children.
Epidemiology of HHV8

- Unlike EBV, HHV8 is not an ubiquitous infection
- Geographic distribution closely parallels that of KS
- Risk factors that influence epidemiology of HHV8 in given population include:
  - Older age, Mediterranean or Eastern European origin, HIV infection, and homosexual or other high-risk sexual behaviors.
- Seroprevalence range 2-9% in U.S. and 14-30% in Mediterranean populations.
Major HHV8-Associated Malignancies

- Kaposi Sarcoma (KS)
- Primary Effusion Lymphoma
- Multicentric Castleman Disease
Epstein-Barr Virus (EBV)
Epstein-Barr Virus (EBV)

- A herpes virus that infects great majority of world’s population

- Latent infection in B-lymphocytes and can induce proliferation of infected cells

- Most EBV infections are benign but there is potential to lead to cancer

- Identified in 1964 in culture from a BL tumor
Structure of EBV

- Like all herpes viruses, EBV consists of:
  - Outer envelope with external, glycoprotein spikes
  - Viral capsid
  - DNA core

- 2 Major EBV strains
  - 1 & 2: They differ somewhat in geographic distribution
Natural History of EBV Infection

- Majority of EBV infections are transmitted by oral contact
- EBV enters and multiplies in B-lymphocytes
- Can multiply in epithelial cells of oropharynx, parotid gland, and uterine cervix
- Infection with EBV persists for life
Host Response to EBV infection

- Carriers produce antibodies to lytic and latent antigens but these antibodies appear to provided little or no protection in control of established EBV infection.

- Varies with age at the time of infection
  - It is usually subclinical when infection occurs early in life.
    - Common in most underdeveloped countries and among populations with poorer socioeconomic living conditions.
  - When infection occurs in older childhood or young adult life, IM (infectious mononucleosis) occurs in almost half of primary infections.
Epidemiology of EBV Infection

- Most infections occur in childhood.
  - Factors influencing probability of EBV infection in childhood:
    - exposure to other children within household, neighborhood, or in group care settings
    - Level of hygiene
    - Sharing and prechewing of food

- Infections can also occur during adolescence.
  - Incidence of EBV infection is associated with intimate kissing because the virus is largely transmitted through oral contact, the virus being in the saliva
Epidemiology of EBV Infection

- Prevalent throughout the world even in remote areas

- Prevalence of infection varies with socioeconomic conditions:
  - In economically developing populations, infection generally occurs early in life
  - Infection usually occurs later in life in economically developed populations because there is not as high probability to transmit to children due to better conditions
Major EBV-Associated Malignancies

- Burkitt Lymphoma (BL)
- Nasopharyngeal Carcinoma (NPC)
- Hodgkin Lymphoma (HL)
Thank YOU