HIV: We’ve Come a Long Way

HPV: It’s Not Only Ugly, It’s Deadly

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Medicine Institute
Cleveland Clinic Foundation
The Gathering Storm…

FIGURE. MMWR report on Pneumocystis pneumonia in five previously healthy young men in Los Angeles — June 5, 1981

In the period October 1980–May 1981, 5 young men, all active homosexual persons treated for anogenital herpes, Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had lab tests for HIV, and all were positive.

Patient 1: A previously healthy 33-year-old man developed P. carinii pneumonia in March 1981 after 2 months of symptoms including fever, cough, and dyspnea. The patient was treated with trimethoprim-sulfamethoxazole and responded well. However, he died in May 1981 with P. carinii pneumonia and no evidence of neoplastic disease.
AIDS unfolding

• MMWR July 4, 1981
  – Report of 26 cases of Kaposi’s sarcoma in homosexual men –
    New York and California (Los Angeles and San Francisco)
  – Most patients had concomitant illnesses

  – An additional 10 cases of Pneumocystis pneumonia were reported
    from California

• MMWR Aug 28, 1981 additional 108 cases

An epidemic was unfolding

Spread

• France
• South America
• Canada
• United Kingdom
• Africa
Origin of HIV-1

- SIVcpz → HIV-1
- At least 3 transmissions for groups M, N, O
- Group M: 1930

Pan troglodytes troglodytes

Why now?

1980s:
- Likely several transmission events
- Social disruption, enslavement, urbanization, prostitution, etc.
- Bushmeat trade - commercial enterprise no longer subsistence
Cross-species transmission: The first evidence

- Sooty Mangabee
- SIV<sub>sm</sub> HIV-2
- Transmission to non-host species can result in a variety of clinical outcomes
- Hunted for food, orphans kept for pets
- At least 4 transmission events

*Cercopithecus atys*

Brief History

- **1926-1946** HIV spread monkeys → humans in Africa
- **1959** First AIDS death - Congo
- **1981** Kaposi's Sarcoma (KS) gay men USA
- **1982** AIDS (Acquired Immunodeficiency Syndrome)
- **1983** HIV virus isolated France/U.S.A
- **1985** FDA approves first antibody test
- **1987** FDA approves first HIV treatment: AZT
- **1996** HAART becomes standard of care

Transmission

Modes of Transmission

1. Sexual
2. Blood and blood products/ organ transplantation
3. Mother-to-child transmission (pregnancy and breastfeeding)

Sexual transmission

<table>
<thead>
<tr>
<th>Per contact risk of HIV transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertive anal intercourse</td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
</tr>
<tr>
<td>Vaginal intercourse</td>
</tr>
</tbody>
</table>

Factors which increase risk of sexual transmission:

- Ulcerative STD
- Increased viral load of the infected partner
- Receptive Intercourse
- Stage of Infection (low CD4, high viral load), acute seroconversion
- Concomitant STD

**Blood and body fluids**

- **Needle stick injury**
  - Overall risk estimate for occupational exposure - 0.3%
  - Risk increases if hollow bore needle, visibly contaminated with blood, in vein or artery, deep injury, end-stage AIDS
    
    [N Engl J Med 2003;348:826-33]
  - Sharing needles – 0.67%
    

- **Blood transfusion** – not completely safe
  - Risk of transmission after transfusion of blood products with HIV >90%
  - Rarely through organ transplantation

- **Factors which increase risk of blood transmission:**
  - IV drug use
  - Transfusion
  - Occupational Exposure

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**Mother-to-child transmission**

- 35-40% in developing countries
- 15-25% in US
- ↓ to 8% with Rx
- 25-30% without intervention
- Can occur at any time —
  - Pregnancy
  - During labor
  - Breast feeding

- With proper care, transmission is now < 2%

**Adults and children estimated to be living with HIV**

- **Western & Central Europe**: 850,000 (710,000 – 870,000)
- **Eastern Europe & Central Asia**: 1.5 million (1.4 – 1.7 million)
- **Middle East & North Africa**: 310,000 (250,000 – 380,000)
- **Sub-Saharan Africa**: 22.4 million (20.0 – 24.1 million)
- **South & South-East Asia**: 5.8 million (5.4 – 6.3 million)
- **North America**: 1.4 million (1.2 – 1.6 million)
- **Latin America**: 2.0 million (1.8 – 2.2 million)
- **Caribbean**: 240,000 (220,000 – 260,000)
- **South & South-East Asia**: 3.8 million (3.4 – 4.3 million)
- **Oceania**: 59,000 (51,000 – 68,000)
- **Caribbean**: 240,000 (220,000 – 260,000)

**Total**: 33.4 million (31.1 – 35.8 million)

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**Estimated number of adults and children newly infected with HIV**

- **North America**: 55,000 (36,000 – 61,000)
- **Caribbean**: 20,000 (16,000 – 24,000)
- **Latin America**: 170,000 (150,000 – 200,000)
- **Western & Central Europe & Central Asia**: 30,000 (23,000 – 35,000)
- **Middle East & North Africa**: 35,000 (24,000 – 46,000)
- **Sub-Saharan Africa**: 1.9 million (1.8 – 2.2 million)
- **East Asia**: 110,000 (100,000 – 130,000)
- **South & South-East Asia**: 280,000 (240,000 – 320,000)
- **East Asia**: 75,000 (58,000 – 88,000)

**Total**: 2.7 million (2.4 – 3.0 million)
Global estimates for adults and children, 2008

- People living with HIV: 33.4 million (31.1 - 35.8 million)
- New HIV infections: 2.7 million (2.4 - 3.0 million)
- Deaths due to AIDS: 2.0 million (1.7 - 2.4 million)

Over 7400 new HIV infections a day in 2008

- More than 97% are in low- and middle-income countries
- About 1200 are in children under 15 years of age
- About 6200 are in adults aged 15 years and older, of whom:
  - almost 48% are among women
  - about 40% are among young people (15–24)
Gender of persons living with HIV, USA

- Females: 26%
- Males: 74%

HIV Life Cycle

- RTI
- NNRTI
- PI
- CCR5
- Fu-Inh
- In Inh
- CD4
Question

• The acute retroviral syndrome is associated with:
  • a. Lymphadenopathy in ~ 75% of patients
  • b. Pharyngitis in less than half of the patients
  • c. Rash &/or mucocutaneous ulceration in 70%
  • d. Fever in 1/3 of patients
  • e. a & c only
Question

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  - c. Rash &/or mucocutaneous ulceration in 70%
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Primary HIV Infection

- 50-90% are symptomatic seroconverters
- Illness begins 1 to 4 wks after exposure
- Clinical features similar to acute EBV
- High viral burden at seroconversion predicts rapid clinical progression

Clinical Presentation

- Fever >80-90%
- Fatigue >70-90%
- Rash >40-80%
- HA 32-70%
- LAN 40-70%
- Pharyngitis 50-70%
- Myalgias/Arthralgias 50-70%
- N/V/D 50-60%
- Night sweats 50%
- Aseptic meningitis 24%
- Oral Ulcers 10-20%
- GU ulcers 5-15%
- Thrombocytopenia 45%
- Leukopenia 40%
- Transaminitis 21%

Labs
Early Manifestations of HIV Infection

• Mucocutaneous signs
  – Seborrheic dermatitis, psoriasis, folliculitis
  – Thrush, vaginal candidiasis, severe tinea

• Lymphadenopathy

• Laboratory abnormalities
  – Thrombocytopenia, anemia, leukopenia
  – Elevated total protein levels
  – Proteinuria

HIV Testing

• Screening: ELISA

• Confirmatory: Western Blot

• Other:
  – Qualitative vs. quantitative PCR
  – p24 antigen detection
  – Viral culture
**Who should be tested?**

Recommendations:

- Everyone between the ages of 13 and 64
- Everyone beginning a sexual relationship with a new partner
- All pregnant women as early on in 1st trimester as possible and again in the 3rd trimester
- All patients seeking treatment for sexually transmitted disease
- All patients who have been diagnosed with Tb

- Change of policy 9/2006
- Opt out testing

**Who should seek additional HIV Testing?**

- Those at high risk:
  - Injection drug users and their partners
  - People who exchange sex for money and their partners
  - Individuals who have had more than one sexual partner since their last HIV test
Ask the Tough Questions

- How many sexual partners
- Sex of partners
- What type of sexual activity engaged in
- Drug use
- History of sexual transmitted diseases
- Travel
- Condoms
  - Ask about them and support the use of condoms for ALL types of sexual activity

Missed opportunities

Tested Positive:

- 50 year old male in good health until he developed lymphadenopathy in axillae and groin
- Claims exposure probably came after being raped by his cousin who died of unknown causes
  - No one talks about cousin in family
- New diagnosis of AIDS with CD4: 29 and VL: 284,000
- Only patient’s wife knows about his status
  - Doesn’t want to tell his parents or family members
**Missed Opportunities**

- 1 year prior to this presentation he was seen by his private physician for genital warts and referred to a urologist for treatment
- Six months ago saw an ENT for thrush
- 18 mos ago was treated for GC through a local Emergency Room.
- Was placed on a broad spectrum antibiotic for the enlarged lymph nodes and was not checked for HIV for 2 months

- HIV is a serious health disorder that can be detected before symptoms occur
- Persons living with HIV/AIDS (PLHA) who are unaware of their status may account for 54-70% of new infections
  - Estimated that 25% of PLHA were unaware of their infection
  - Increasing awareness from the current 75 to 100% could reduce sexual transmission by 40%
Awareness of Serostatus Among People with HIV and Estimates of Transmission

- ~25% Unaware of Infection
- ~75% Aware of Infection

Accounting for:
- ~54% of New Infections
- ~46% of New Infections

People Living with HIV/AIDS: 1,039,000 - 1,185,000

New Sexual Infections Each Year: ~32,000

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Clinical Course

- Primary infection
- Possible acute HIV syndrome
- Wide dissemination of virus
- Seeding of lymphoid organs

Clinical latency

Constitutional symptoms

Opportunistic diseases

Death

Plasma Viral Titer

CD4+ T Cells/mm³

0 3 6 9 12 1 2 3 4 5 6 7 8 9 10 11

0 100 200 300 400 500 600 700 800 900 1000 1100 1200

Weeks

Years

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### CDC - AIDS defining conditions

- Bacterial infections, multiple and recurrent
- Candidiasis of bronchi, trachea or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcus, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus disease (other than liver, spleen or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex, chronic ulcers (> 1 month duration); or bronchitis, pneumonitis or esophagitis

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### CDC - AIDS defining conditions

- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month duration)
- Kaposi’s sarcoma
- Lymphoid interstitial pneumonia
- Lymphoma, Burkitt’s (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- MAI or *M. kansasi* disseminated or extrapulmonary
- *M. tuberculosis* (pulmonary or extrapulmonary)
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of the brain
- Wasting syndrome of HIV
Case #1
Fever, Cough, Dyspnea

- 31 year old caucasian male, MSM, HIV for 4 years – no therapy
- >2 weeks progressive pulmonary symptoms – early summer
- Nonproductive cough, DOE, fatigue, fever
- Lives locally, no travel, no exposure
- CD4 111, viral load 473,167
The most likely diagnosis

A. Influenza
B. Congestive heart failure
C. Bacterial pneumonia
D. Pneumocystis pneumonia
E. Hypersensitivity pneumonitis
Pulmonary Manifestations in HIV-Infected Patients

• Infection
  – Bacterial: community pathogens, TB, Nocardia
  – Fungal: histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis (geography)
  – Viral
  – Protozoal (?): *Pneumocystis jiroveci*

• Neoplasm

• Idiopathic
  – Lymphocytic interstitial pneumonitis

Sputum Sampling - PCP

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectorated</td>
<td>10-30%</td>
</tr>
<tr>
<td>Induced</td>
<td>10-97%</td>
</tr>
<tr>
<td>MiniBAL (“snake 'em”)</td>
<td>Variable</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td></td>
</tr>
<tr>
<td>Washing</td>
<td>30-70%</td>
</tr>
<tr>
<td>Brushing</td>
<td>30-70%</td>
</tr>
<tr>
<td><strong>Lavage</strong></td>
<td><strong>95-99%</strong></td>
</tr>
<tr>
<td>Biopsy</td>
<td>70-90%</td>
</tr>
<tr>
<td>Open Biopsy</td>
<td>99%</td>
</tr>
</tbody>
</table>
Incidence of PCP among HIV+ men as related to baseline CD4

(Simonds et al, CID 1995)
Therapy of PCP

• TMP/SMX 5 mg/kg q 8 hours x 21 days
• If pO2 < 70, prednisone taper over 21 days
• Alternative therapies
  Clindamycin/primaquine
  Pentamidine IV
  Atovaquone (mild disease)
  Trimetrexate/leukovorin

Case #2
Headache, Fever, Confusion

• 43 year old caucasian male, MSM
• Above noted over 2-3 weeks by partner
• Progressed insidiously. Convulses in ED
• Live near park – pigeons; pet cats at home
• CD4 78, viral load 224,871
The most likely diagnosis

A. CNS lymphoma
B. Tuberculoma
C. Bacterial abscess
D. Metastatic lung cancer
E. Toxoplasmosis
The most likely diagnosis

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Differential Diagnosis of Ring Enhancing Lesions of CNS

- Toxoplasmosis *
- CNS lymphoma
- Histoplasmosoma
- Cryptococcoma
- Bacterial abscess
- Tuberculoma
- Metastatic carcinoma
Response to treatment

- Generally rapid
- 80% show improvement by day 7
- If no improvement, biopsy/further testing
- Repeat imaging at one month

HIV dementia

- HIV crosses BBB on monocytes/lymphocytes
- HIV is found in microglial cells/astrocytes
- Chemokines, cytokines; possibly viral proteins responsible for neuronal injury
Case #3  
Fever, Night Sweats, Weight Loss

- 49 year old A.A. female, married IDU  
- HCV  
- HIV 9 years, failed several regimens  
- CD4 33, viral load 48,941  
- WBC 1.8, Hgb 7.9 Plt 84  
- AST 57 ALT 61 Alk Phos 378 Bili 1.9

Fever, Night Sweats, Weight Loss

- 38.7° C, BP 102/54, HR 98  
- Wasted  
- Scattered 1-2 cm nodes  
- Hepatosplenomegaly  
- No obvious murmur  
- Mmmmmmm?! Differential Diagnosis?
Workup

• Routine blood cultures negative
• TTE negative
• CT of chest and abdomen: HSM, diffuse 2-4 cm central adenopathy
• Empiric zosyn and vancomycin – fevers persist

Your next diagnostic test

A. AFB blood cultures
B. Bone marrow biopsy and culture
C. Lymph node biopsy and culture
D. Liver biopsy
E. Any of the above
Your next diagnostic test

A. AFB blood cultures
B. Bone marrow biopsy and culture
C. Lymph node biopsy and culture
D. Liver biopsy
E. Any of the above

Diagnosis of MAI

• Suspicion
• CD4 usually < 50 (increased risk with high viral load and previous OI)
• Wasting disease: fatigue, weight loss, fevers, night sweats, diarrhea
• Pancytopenia, elevated alkaline phosphatase
• Central adenopathy
**Treatment of MAI**

- Clarithromycin 500 mg bid or azithromycin 600 mg daily
  - + Ethambutol 25 mg/kg/day
  - or Rifabutin, ciprofloxacin, amikacin, clofazimine

  Duration – 12 months then suppression

**Treatment Caveats**

- Clarithromycin more active than azithromycin, but more GI intolerance
- More rapid clearance with clarithromycin
- Usually treat with two drugs
- No response 4-8 weeks, consider third drug, resistance testing (controversial)
- HAART
HIV Therapy

### FDA-Approved Antiretroviral Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| NRTI     | Zidovudine  
           | Didanosine  
           | Zalcitabine  
           | Stavudine  
           | Lamivudine  
           | Abacavir  
           | Tenofovir  
           | Emtricitabine |
| NNRTI    | Nevirapine  
           | Delavirdine  
           | Efavirenz  
           | Etravirine |
| PI       | Saquinavir  
           | Ritonavir  
           | Indinavir  
           | Nelfinavir  
           | Amprenavir  
           | Lopinavir  
           | Atazanavir  
           | Fosamprenavir  
           | Tipranavir  
           | Darunavir |
| Entry Inhibitor | Maraviroc |
| Integrase Inhibitor | Raltegravir |
| Combinations | 6 available, combining 2 or 3 drugs |
| Fusion Inhibitor | Enfuvirtide (T-20) |
Side Effects

• Most common nausea, vomiting, headache, diarrhea, fatigue

• Generally improve over length of administration

• Recognize serious events

Serious Side Effects

• Steven-Johnson-nevirapine, efavirenz, etravirine, all PIs and many NRTIs

• Hepatic Necrosis-nevirapine

• Hep B flares due to discontinuation of agents: tenofovir, lamivudine, emtricitabine

• Neuromuscular weakness-stavudine

• Lactic acidosis with weight loss-nucleoside analogs: zidovudine, didanosine, stavudine

• Tetragenicity- efavirenz
What is HAART?

Highly Active Anti-Retroviral Therapy is a potent combination of 3 or more anti-HIV drugs

- For the treatment-naïve patient, HAART is typically composed of 2 NRTIs plus either 1 NNRTI or 1-2 PIs
- The drugs work together to interrupt the HIV replication cycle at various steps

Toxicities associated with HAART: Metabolic disorders

- Hyperglycemia
- Lipid Abnormalities
  - hypertriglyceridemia
  - hypercholesterolemia
- Osteonecrosis/osteoporosis
- Lipodystrophy
Lipodystrophy
### Who Should Start Antiretroviral Therapy? One View

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4+</th>
<th>My View</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe symptoms</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;200/µL</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200-500/µL</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;500/µL</td>
<td>Treat if patient is ready!</td>
</tr>
</tbody>
</table>


### Vaccine
HIV

- AIDS Vaccine 2010 (Emory)
- Date: September 28 - October 1, 2010
- Location: Atlanta, GA
- The Center for AIDS Research at Emory University and the Global HIV Vaccine Enterprise invite you to Atlanta, Georgia for the AIDS Vaccine 2010 Conference. The AIDS Vaccine conference has become one of the most important annual events for the exchange of scientific information relating to HIV vaccine research and development. This year we are pleased to mark its tenth anniversary, and to celebrate a decade of collaboration, education, and the spirited exchange of scientific ideas, all with the purpose of advancing the science of HIV vaccines.

Lower CD4 Counts are associated with:

- Cancer: Kaposi’s, non-Hodgekins lymphoma, cervical cancer, Hodgekins, anal, respiratory and oral cancers
  » Actual incidence of Kaposi’s non-Hodgekins, cervical cancer have decreased with screening. Non AIDS defining cancers are up
- Cardiovascular: Protease inhibitors raise trig, LDL and TChol and risk for MI.
- HIV regardless of therapy is an independent risk factor for coronary disease.
- Neurocognitive disorders
- Osteoporosis and osteonecrosis
Surveillance

- CBC
- CD4
- HIV viral load
- Testing for resistance

Health Maintenance

- Age appropriate guidelines
- Focus CVD, cancer and bone health
- Heightened awareness of prevention
- Vaccine updates
Vaccines in HIV infected persons

• Yearly influenza (inactivated)
• Pneumococcal polysaccharide vaccine
• Hepatitis B
• Hepatitis A vaccine (MSM, IVDU)
• If a vaccine is given with CD4+ count of <200, to be repeated when CD4+ count rises to >200 with HAART

CDC. Recommended Adult Immunization Schedule -- United States, 2009. MMWR 2008;57(53).
Per-Person Survival Gains (months)

- Cancer chemotherapy
- CABG
- BMT for lymphoma
- HAART for HIV

Walensky et al, CROI 2005, Abs T43

Every Life Deserves World Class Care
• If it starts with H and it ends with V it is most likely a sexually transmitted disease
  
  – HIV
  – HBV
  – HCV
  – HSV

  – And HPV

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**HPV Epidemiology**

• Approximately 20 million people currently infected with HPV in the US
• At least 50% of sexually active men and women acquire genital HPV at some point in their lives
• By age 50, at least 80% of women will have acquired genital HPV infection
• Approximately 6.2 million Americans get a new HPV infection each year
• Most are transient and are gone within 2 years
HPV

- Over 100 types of HPV, with over 35 infecting the human skin and genital tract
- Types 6 and 11 cause an estimated 90% of cases of genital warts
- Types 16 and 18 are responsible for approx 70% of cases of cervical and genital cancers. Types 31, 33, 45, 52, 58 cause 20%.

Condyloma

- 500,000 new cases of anogenital warts per year in the US with approx 600,000 health care visits
- Approximately 1% of sexually active adults have visible warts at any given time
- “individual episodes of care for genital warts involved 3.1 physician visits and incurred costs of $436.” Insinga et al, Clinical Infection 2004
Treatment

- **Patient-Applied:**
  - **Podofilox 0.5% solution or gel.** Patients should apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm², and the total volume of podofilox should be limited to 0.5 mL per day. If possible, the health-care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. The safety of podofilox during pregnancy has not been established.
  - OR
  - **Imiquimod 5% cream.** Patients should apply imiquimod cream once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6–10 hours after the application. The safety of imiquimod during pregnancy is Class C recommendation.

- **Provider-Administered:**
  - **Cryotherapy** with liquid nitrogen or cryoprobe. Repeat applications every 1–2 weeks.
  - OR
  - **Podophyllin resin 10%–25%** in a compound tincture of benzoin. A small amount should be applied to each wart and allowed to air dry. The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, some specialists recommend that application be limited to <0.5 mL of podophyllin or an area of <10 cm² of warts per session. Some specialists suggest that the preparation should be thoroughly washed off 1–4 hours after application to reduce local irritation. The safety of podophyllin during pregnancy has not been established.
  - OR
  - **Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90%**. A small amount should be applied only to warts and allowed to dry, at which time a white “frosting” develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate (i.e., baking soda), or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.
  - OR
  - **Surgical removal** either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery.
### Cost of Genital Wart Therapy


<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost</th>
<th>Clearance</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryo</td>
<td>$268</td>
<td>60-90%</td>
<td>20-40%</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>$607</td>
<td>30-50%</td>
<td>15%</td>
</tr>
<tr>
<td>Interferon</td>
<td>$2744</td>
<td>20-60%</td>
<td>?</td>
</tr>
<tr>
<td>Laser</td>
<td>$197</td>
<td>25-50%</td>
<td>5-50%</td>
</tr>
<tr>
<td>Podofilox</td>
<td>$200</td>
<td>45-80%</td>
<td>5-30%</td>
</tr>
<tr>
<td>Podophyllin</td>
<td>$385</td>
<td>30-80%</td>
<td>20-65%</td>
</tr>
<tr>
<td>Surg exc</td>
<td>$210</td>
<td>35-70%</td>
<td>20%</td>
</tr>
<tr>
<td>TCA</td>
<td>$513</td>
<td>50-80%</td>
<td>35%</td>
</tr>
</tbody>
</table>

### HPV
Perianal HPV
HPV leads to cervical cancer

- Persistence of infection
- Presence of a “high-risk” HPV type.
- Other factors: smoking, long-term contraceptive use, high parity (> 5 full term pregnancies), other STIs, or immunosuppressive conditions.

Cervical Cancer

- Second most common malignant neoplasm affecting women worldwide
- Approx 273,000 deaths from cervical cancer worldwide
- CDC estimated 10,520 new cases of cervical cancer in US in 2004
Normal Ectocervix

PAP

• Need to collect vaginal wall, exocervical, and endocervical samples

• Pap, GC/chlamydia, and HPV testing can be performed on this specimen
Normal Pap smear

Pap with ASCUS
Invasive squamous cell carcinoma

[Images of histological sections]
**High Risk HPV DNA testing**

- FDA approved
- Detects presence of any high risk HPV types 16, 18, 33, 35, 39, 45, 51, 52, 56, 58, 59, 69
- Appropriate for use in patients of any age with ASCUS to determine further therapy.
- Routine adjunct screening along with Pap test in women aged 30 or older
- Not for use in patients with genital warts or other STIs
- Not approved for men

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**Other cancers**

- Vulva
- Vaginal
- Penis
- Anal
Anal Cancer Symptoms

• Symptoms according to the American Cancer Society website:
  • rectal bleeding (more than half of patients)
  • rectal itching
  • pain in the anal area
  • change in the diameter of stool
  • abnormal discharge from the anus
  • swollen lymph nodes in the anal or groin areas

Vaccines

• There are 2 vaccine available for prevention of HPV

  • Cervarix-Bivalent for protection against HPV types 16 and 18

  • Gardasil-Quadrivalent protecting against types 6, 11, 16, 18
Vaccine

• Indication
  – GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of cervical, vulvar, and vaginal cancers; precancerous or dysplastic lesions; and genital warts caused by human papillomavirus (HPV) Types 6, 11, 16, and 18.

Vaccine

• GARDASIL
  – is indicated in boys and men 9 through 26 years of age for the prevention of genital warts caused by HPV Types 6 and 11.
Vaccine

• GARDASIL has not been demonstrated to provide protection against diseases from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.

• GARDASIL is not intended to be used for treatment of active external genital lesions; cervical, vulvar, and vaginal cancers; cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), or vaginal intraepithelial neoplasia (VaIN).

HPV

— GARDASIL does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening.
### Vaccine

- **Dosage and Administration**

  - **GARDASIL** should be administered in 3 separate intramuscular injections in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

<table>
<thead>
<tr>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• first dose at an elected date</td>
</tr>
<tr>
<td>• second dose 2 months after the first dose</td>
</tr>
<tr>
<td>• third dose 6 months after the first dose.</td>
</tr>
</tbody>
</table>
Vaccine

- Each dose is 0.5mL
  - Comes in single dose pre filled syringes

Adverse Experiences

<table>
<thead>
<tr>
<th>Injection site (1 to 5 days postvaccination)</th>
<th>GARDASIL® (N=5,088)</th>
<th>Placebo (Aluminum) (N=3,470)</th>
<th>Placebo (Saline) (N=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>83.9%</td>
<td>75.4%</td>
<td>48.6%</td>
</tr>
<tr>
<td>Swelling</td>
<td>25.4%</td>
<td>15.8%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Erythema</td>
<td>24.6%</td>
<td>18.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.1%</td>
<td>2.8%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Systemic Adverse Event (1 to 15 days postvaccination)

<table>
<thead>
<tr>
<th></th>
<th>GARDASIL (N=5,088)</th>
<th>Placebo (N=3,790)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.2%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

- Few subjects (0.1%) discontinued due to AEs.

1. Data on file, MSD.
**Vaccine Challenges**

- 3 doses, difficult to get adolescents scheduled for this
- Cannot make part of infant immunization-unclear on interactions with other vaccines and unclear on durability of response
- Some Parents and groups against vaccinating for STIs- large education campaign needed
- Does not eliminate need for pap smears as not all oncogenic types present in vaccines
- Cost- series of 3 total cost is approx $350
- Huge need in developing countries where pap smears are unavailable and death rates are high

**Resources**

**Human Papillomavirus: HPV Information for Clinicians**

Center for Disease Control and Prevention

November 2001
Resources

• merckservices@merck.com

» Thank you for your attention-ivansen@ccf.org