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Microchips for Global Health AIDS Diagnostics

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Materials Science and Engineering
Bioengineering
Overview of Presentation

1. Global Health Challenges
2. HIV/AIDS Statistics and Biology
3. HIV/AIDS Diagnostics
4. Microchip Technology for HIV/AIDS Diagnostics
# Leading causes of death, Global

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ischemic heart disease</td>
<td>12.7</td>
</tr>
<tr>
<td>2</td>
<td>Cerebrovascular disease</td>
<td>9.9</td>
</tr>
<tr>
<td>3</td>
<td>Acute lower respiratory infections</td>
<td>7.1</td>
</tr>
<tr>
<td>4</td>
<td>HIV/AIDS</td>
<td>4.8</td>
</tr>
<tr>
<td>5</td>
<td>Chronic obstructive pulmonary disease</td>
<td>4.8</td>
</tr>
<tr>
<td>6</td>
<td>Perinatal conditions</td>
<td>4.2</td>
</tr>
<tr>
<td>7</td>
<td>Diarrheal diseases</td>
<td>4.0</td>
</tr>
<tr>
<td>8</td>
<td>Tuberculosis</td>
<td>3.0</td>
</tr>
<tr>
<td>11</td>
<td>Malaria</td>
<td>1.9</td>
</tr>
</tbody>
</table>

# Leading causes of death, Africa

<table>
<thead>
<tr>
<th>Rank</th>
<th>Disease</th>
<th>% of total</th>
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<tbody>
<tr>
<td>1</td>
<td>HIV/AIDS</td>
<td>20.6</td>
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<tr>
<td>2</td>
<td>Acute lower respiratory infections</td>
<td>10.3</td>
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<tr>
<td>3</td>
<td>Malaria</td>
<td>9.1</td>
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<tr>
<td>4</td>
<td>Diarrheal diseases</td>
<td>7.3</td>
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<td>5</td>
<td>Perinatal conditions</td>
<td>5.9</td>
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<tr>
<td>6</td>
<td>Measles</td>
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<td>7</td>
<td>Tuberculosis</td>
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<td>8</td>
<td>Cerebrovascular disease</td>
<td>3.2</td>
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<tr>
<td>9</td>
<td>Ischemic heart disease</td>
<td>3.0</td>
</tr>
<tr>
<td>10</td>
<td>Maternal conditions</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Cell

Bacteria (TB, Typhoid)

Virus (HIV, hepatitis, SARS, influenza)

HIV emerging from a cell
Global diversity of different HIV-1 strains

Source: Los Alamos Database http://hiv-web.lanl.gov/
33 million adults living with HIV/AIDS, 2008

Source: WHO/UNAIDS, 2008
Growth of the AIDS Epidemic

People With HIV/AIDS, Cumulative Regional Totals

Millions

*Western and Central Europe & North America.
Changes in Life Expectancy, 1950 - 2000

Projected changes in life expectancy in selected African countries with high HIV prevalence, 1995–2000

Average life expectancy at birth, in years

UNAIDS–AIDS–May 1999
## AIDS’ Toll on Population Structure, Botswana

### Population Structure in 2020 (Projected)

<table>
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<tr>
<th>Age</th>
<th>Thousands</th>
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<tbody>
<tr>
<td>80+</td>
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<tr>
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<td>7065</td>
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<td>5</td>
<td>30</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

**With AIDS**

**Without AIDS**

AIDS’ Effect on African Agriculture

Percent of Agricultural Labor Force Lost to HIV/AIDS, 1985-2020 (Projected)

- Namibia: 26%
- Botswana: 23%
- Zimbabwe: 23%
- Mozambique: 20%
- South Africa: 20%
- Kenya: 17%
- Malawi: 14%
- Uganda: 14%
- Tanzania: 13%

HIV Pathophysiology - Life Cycle
HIV Pathophysiology - Life Cycle

CD4 Binding

Co-receptor (CCR5 or CXCR4)
HIV Pathophysiology - Life Cycle

Fusion
HIV Pathophysiology - Life Cycle
HIV Pathophysiology - Life Cycle
HIV Pathophysiology - Life Cycle

Reverse transcription

HIV DNA
HIV Pathophysiology - Life Cycle

Translocation to nucleus
HIV Pathophysiology - Life Cycle
HIV Pathophysiology - Life Cycle

Transcription / Translation of HIV mRNA / polyprotein
HIV Pathophysiology - Life Cycle

Protease processing and viral assembly
**HIV infection**

HIV attacks CD4 cells, the generals of the immune system’s army. HIV inserts itself into our genes. HIV creates many different strains.
HIV infection

- **Viral load**
- **CD4**

![Graph showing the progression of HIV infection over time with viral load and CD4 counts.](image-url)
Relationship Between CD4 count and Viral Load

Figure 1. T-cell count = distance to crash, HIV RNA = speed of train

HIV RNA (viral load) = speed of train

Slow: <5,000, Fast: 50,000+

Source: John Coffin, PhD, Tufts University.
WHO Stage 1:
Asymptomatic HIV infection
CD4 >500

WHO Stage 2 and 3:
Symptomatic HIV infection
CD4 200 - 500
Mild infections
Weight loss, fatigue
TB, Thrush

WHO Stage 4
AIDS
CD4 < 200
TB, infections
Death ~18 months

Time (years)
CD4 Count

1000
200
6
Goals of HIV Treatment

- Improve quality of life
- Prevent opportunistic infections
- Prevent progression to AIDS
- Prevent death
- Reduce the likelihood of transmission to others ("Secondary prevention")
HIV Treatment - Antiretrovirals

- Fusion/Entry Inhibitors (1)
- Maturation Inhibitors (~2008)
- Protease Inhibitors (8)
- Reverse Transcriptase Inhibitors (11)
- Integration Inhibitors (~2008)
HIV Treatment - Timing of HIV Treatment

• Therapy is delayed until patients develop WHO Stage 3 or Stage 4 disease
  – Delaying therapy until Stage 3 or 4, if done carefully, does not decrease the likelihood of successful treatment

  – Treatment is lifelong and expensive, do not want to start unnecessarily early

  – Delayed therapy minimizes opportunity for side effects

  – Delayed therapy minimizes opportunity for drug resistance
CD4 and Mortality - Zimbabwe

Survival Probability

Time from enrolment to death (years)

CD4 > 200

CD4 50-200

CD4 < 50
Impact of Treatment

Before
Impact of Treatment

After 9 months
Impact of Treatment

Begin ART

CD4

Viral load (HIV RNA level)

time

Weeks

Years
Impact of Treatment - Society

Effective ARVs available

- Unintentional injury
- Cancer
- Heart disease
- Suicide
- HIV infection
- Homicide
- Chronic liver disease
- Stroke
- Diabetes

Deaths per 100,000 Population

Year

Source: Centers for Disease Control, 2001
Number of Individuals Receiving ART

Number of people receiving antiretroviral therapy (end of year, lower- and middle-income countries)

Source: AVERT.org
Community-based Care

Care takes place in the community. Reinforced in the clinic.
State of the Art Technologies

CD4-count
start treatment < 200 cells/ul

Viral load count
measure resistance to treatment
Lab Diagnostics in Resource Poor Settings
What is Needed

- Low cost
- Easy to use
- Rapid and Robust
- Portable
- Sensitive and specific
Microchip Technology for Medicine
CD4 counting microchip
Mechanism of the CD4 Counter
Nanoporous Membrane for Viral Processing and Sensing

- Controllable pore size
- High porosity
- Bio-functionality
- Tight pore size distribution
- Thin membranes
Embedded Nanoporous Membranes for Viral Processing

- **200nm Pores**
  - Filtrate
  - Absorbed on membrane
  - Suspended above membrane

- **20nm Pores**
  - Filtrate
  - Absorbed on membrane
  - Suspended above membrane

**Viral Concentration (mL)**

- Original Sample
- 1mL filtration + 10μL Wash

**% of Virions Captured on Membranes**

- Bare
- PEG

**AntiCD44**

**Filtration Efficiency (%)**

- 80
- 100
- 120

**Pore Sizes**

- 200nm
- 20nm