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Small Tools for Big Problems: 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>
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</table>

## Leading causes of death, Africa

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>% of total</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>HIV/AIDS</td>
<td>20.6</td>
</tr>
<tr>
<td>2</td>
<td>Acute lower respiratory infections</td>
<td>10.3</td>
</tr>
<tr>
<td>3</td>
<td>Malaria</td>
<td>9.1</td>
</tr>
<tr>
<td>4</td>
<td>Diarrheal diseases</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>Perinatal conditions</td>
<td>5.9</td>
</tr>
<tr>
<td>6</td>
<td>Measles</td>
<td>4.9</td>
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<tr>
<td>7</td>
<td>Tuberculosis</td>
<td>3.4</td>
</tr>
<tr>
<td>8</td>
<td>Cerebrovascular disease</td>
<td>3.2</td>
</tr>
<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/
39 million adults living with HIV/AIDS, 2006

Source: WHO
Growth of the AIDS Epidemic

People With HIV/AIDS, Cumulative Regional Totals

Millions

*Western and Central Europe & North America.
People With HIV/AIDS, by Region

- Sub-Saharan Africa: 64%
- South and South-East Asia: 18%
- North Africa and Middle East: 1%
- East Asia: 3%
- Latin America: 4%
- Caribbean: 1%
- Oceania: <1%
- North America: 3%
- Eastern Europe and Central Asia: 4%
- Western and Central Europe: 2%

Changes in Life Expectancy, 1950 - 2000

AIDS’ Toll on Population Structure, Botswana

Population Structure in 2020 (Projected)

Thousands

<table>
<thead>
<tr>
<th>Age</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>80+</td>
<td>75</td>
<td>60</td>
</tr>
<tr>
<td>75</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>70</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>65</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>55</td>
<td>15</td>
<td>5</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 destroys immune defenses against TB

Tuberculosis
HIV Pathophysiology - Life Cycle

- HIV
- CD4
- CD4 cell
HIV Pathophysiology - Life Cycle

CD4 Binding

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

Fusion
HIV Pathophysiology - Life Cycle

Virion entry
HIV Pathophysiology - Life Cycle
HIV Pathophysiology - Life Cycle

Reverse transcription

HIV DNA
HIV Pathophysiology - Life Cycle

Translocation to nucleus
HIV Pathophysiology - Life Cycle

Integration
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

Time scale:
- Weeks
- Years
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+

T-cell count: Distance to crash

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

CD4 Count

Time (years)
WHO Stage 1 - Asymptomatic HIV Disease

- Minimal symptoms
- Daily battle between virus and immune system; 10,000,000 new virus copies each day
- CD4 count drops gradually
WHO Stage 2 - Symptomatic HIV Disease

- Early signs of chronic HIV infection:
  - Weight loss (3-5 kg)
  - Skin rashes
  - Respiratory infections
  - Herpes zoster (“shingles”)
  - CD4 count = 350-500

- Normal activity, able to work / attend school
# Opportunistic Infections - Côte d’Ivoire, Thailand

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>29-37%</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>19-38%</td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>8-28%</td>
</tr>
<tr>
<td><em>Pneumocystis</em> pneumonia</td>
<td>5-20%</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>4%</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>3-6%</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>2-3%</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

Sources: Chariyalertsak, 2001; Tansuphasawadikul, 1999; Lorsina, 2004
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

After 9 months
Impact of Treatment

“I was a walking skeleton before I began therapy. I was afraid to go out of my house and no one would buy things from my shop. But now I am fine again… My wife has returned to me and now my children are not ashamed to be seen with me. I can work again.”
Impact of Treatment
Impact of Treatment

Begin ART

CD4

Viral load (HIV RNA level)

Weeks

Years

time→
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, 20
Current Status of Treatment - December 2004

Estimated percentage of people on antiretroviral therapy among those in need, situation as of December 2004

Coverage (%)
- 75 - 100
- 50 - 74.9
- 25 - 49.9
- 10 - 24.9
- Less than 10
- Data not available
Current Status of Treatment - June 2005

Estimated percentage of people on antiretroviral therapy among those in need, situation as of June 2005

Coverage (%)
- 75 - 100
- 50 - 74.9
- 25 - 49.9
- 10 - 24.9
- Less than 10
- Data not available
Number of Individuals Receiving ART

- 1,550,000 on 1/23/2004
- 235,000 on 9/30/2004
- 401,000 on 3/31/2005
- 561,000 on 9/30/2005
- 822,000 on 3/31/2006
- 1,358,500 on 3/31/2007
- 1,641,000 on 3/31/2008

Source: WHO
Community-based Care

Care takes place in the community. Reinforced in the clinic.
Clinical Indicators

- 'Viral load': the number of copies of HIV RNA in the blood.
- CD4 cell count: the number of CD4 cells in the blood.

The graph shows the changes in 'Viral load' and CD4 cell count over time, with 'Viral load' measured in copies/mL plasma and CD4 cell count in cells/μL blood.
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
Microchips for Bioseparation

silane  linker  avidin anti-CD4
Microelectrodes for Biosensing

Due to cell lysis, conductance change is observed.

Captured Cells on Chip by Optical Microscopy
Clinical Validation of the Microchip

N = 49
R² = 0.86

Sensitivity = Test Positive / Total Positive
Specificity = Test Negative / Total Negative

<table>
<thead>
<tr>
<th>CD4 Counts (cells/μL)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>0.86</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt; 350</td>
<td>0.90</td>
<td>0.97</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>0.97</td>
<td>0.94</td>
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</table>
Commercial Development