Microchip Technology for Global Health Diagnostics

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Global Health

The area of study, research and practice that places a priority on improving health and achieving equity in health for all people

Leading causes of death, high-income countries

Leading causes of death, low-income countries

Top 10 causes of death in low-income countries 2011

- Lower respiratory infections: 98
- HIV/AIDS: 70
- Diarrhoeal diseases: 69
- Stroke: 56
- Ischaemic heart disease: 47
- Prematurity: 43
- Malaria: 38
- Tuberculosis: 32
- Protein energy malnutrition: 32
- Birth asphyxia and related causes: 30

Deaths per 100,000 population

Death Trend by Age

High-income countries:

- 70%
- 29%
- 1%

Low-income countries:

- 22%
- 44%
- 34%

33 million adults living with HIV/AIDS, 2008

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

People With HIV/AIDS, Cumulative Regional Totals

*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

- Botswana
- Zimbabwe
- Zambia
- Uganda
- Malawi

Average life expectancy at birth, in years:
- 65
- 60
- 55
- 50
- 45
- 40
- 35

Years:
- 1955
- 1960
- 1965
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000 projections

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

AIDS’ Toll on Population Structure, Botswana

Population Structure in 2020 (Projected)

Thousands

Age
80+
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

Males
Females

With AIDS
Without AIDS

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/
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
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

Weeks

Years

time→
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
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

- Reverse Transcriptase Inhibitors (11)
- Protease Inhibitors (8)
- Fusion/Entry Inhibitors (1)
- Maturation Inhibitors (~2008)
- Protease Inhibitors (8)
- 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 Graph]

- **CD4 > 200**
- **CD4 50-200**
- **CD4 < 50**

Time from enrolment to death (years)

Survival Probability
Impact of Treatment

Before
Impact of Treatment

After 9 months
Impact of Treatment

Begin ART

CD4

Viral load (HIV RNA level)

Weeks

Years

time→
Impact of Treatment - Society

Source: Centers for Disease Control, 2001

Effective ARVs available

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

Deaths per 100,000 Population

Year

Number of Individuals Receiving ART

Fig. 1. Actual and projected numbers of people receiving antiretroviral therapy in low- and middle-income countries, and by WHO Region, 2003–2015


http://apps.who.int/iris/bitstream/10665/85326/1/9789241505734_eng.pdf
Impact of Treatment - Society

Fig. 2. Annual number of people dying from AIDS-related causes in low- and middle-income countries globally compared with a scenario of no antiretroviral therapy, 1996–2012

http://apps.who.int/iris/bitstream/10665/85326/1/9789241505734_eng.pdf
Basic Water Supply

Clinical Indicators

- 'Viral load': HIV RNA level (copies/mL plasma)
- CD4 cell count (cells/µL blood)

Years
Weeks

CD4 cell count (cells/µL blood)

10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0

1 2 3 4 5 6 7 8

Years

Weeks
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 Fabrication

- 200nm Pores
- 20nm Pores

Viral Concentration (fL)

- Original Sample
- 1mL filtration + 10 µL Wash

Percentage of Virions (%)

- 200nm Pores
- 20nm Pores

Filtrate
- Absorbed on membrane
- Suspended above membrane

Cheng Lab: the Lab of Micro- and Nanotechnology for Medicine
Optically Forced Cytometry for Nanobead Counting