HIV introduction

Dr. Edmund Wilkins
Head of the HIV Clinical Trials Unit
North Manchester General Hospital
“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the Medical Assistance & Medical Education (MAME) Programs
HIV – What do we know so far?

The first 30 years?
Miracles do happen
Why? Because of ARV’s...

How has this happened?
With the price of ART continuing to fall...

Median prices of WHO-preferred first-line regimens per person per year, in US dollars, in low-and middle-income countries, 2004–2013
Gauging recent progress in the global HIV response

<table>
<thead>
<tr>
<th>2013</th>
<th>2009-2013</th>
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<tbody>
<tr>
<td>1.5 million HIV related deaths</td>
<td>▼ 25%</td>
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<td>[1.4 – 1.7 million]</td>
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<tr>
<td>320 000 TB-related deaths in PLWHA*</td>
<td>▼ 36% **</td>
</tr>
<tr>
<td>[300 000 – 340 000]</td>
<td>*2012</td>
</tr>
<tr>
<td>2.1 million HIV infections</td>
<td>▼ 15%</td>
</tr>
<tr>
<td>[1.9 – 2.5 million]</td>
<td></td>
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<tr>
<td>240 000 HIV infections in children</td>
<td>▼ 40%</td>
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<tr>
<td>[210 000 – 280 000]</td>
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With low ART coverage areas starting to catch Africa up

Although the gap between access to ART for children vs. adults continues to widen.

- **Adults**: 9,0 m to 10,9 m, +21%
  - >1 in 3 adults with HIV on ART (37%)

- **Children**: 640 k to 740 k, +15%
  - 1 in 4 children with HIV on ART (23%)

And close to 1 million pregnant women received ARVs, 500,000 still being missed

And in multiple countries laws exist that can hinder service provision for key populations.

- Sex workers: 53%
- MSM: 47%
- PWID: 43%

Source: GARPR 2013 – “Countries reporting existence of laws, regulations or policies that can pose obstacles to effective HIV prevention, treatment, care and support services for key populations”
And global update of 2013 WHO guidelines increasing eligibility for treatment

Percentage of 58 WHO HIV Focal Countries with confirmed adoption of select WHO 2013 ARV recommendations, June 2014

Source: WHO HIV Country Intelligence Database, June 2014
How did the epidemic start?

HIV
New epidemics last millennium

**The Black Death 1347–1350**

- 100,000,000

**Epidemic Influenza (Spanish)**

- 75,000,000

**I Have AIDS Please hug me**

- 35,000,000
The Origin of HIV: a chimp was bitten twice a million years ago…

Red-capped mangabey

Greater Spot – nosed monkey (Cercopithecus nictitans)

Chimpanzee troglodytes
When it began 1900...
Transmission across continents?

- Africa → USA
  → MSM
- ?Haiti
At a time when technology was moving fast
Transmission happened quietly and effectively
Natural History of Untreated HIV Infection

Fauci et al 1996

- Infection
  - Acute HIV syndrome
  - Wide dissemination of virus
  - Seeding of lymphoid organs

SILENT PHASE

- Constitutional Symptoms
- Opportunistic Diseases
- Death

- CD4 Cell Count (cells/mm$^3$)
- HIV/RNA (c/mL)

- Infection
- AIDS
- Weeks
- Years

Fauci et al 1996
1981: The first Recognition of a new Illness...

FIGURE 1. Incidence of Kaposi's Sarcoma (KS), Pneumocystis carinii Pneumonia (PCP), and other opportunistic infections — United States, 1979–1981
Initial Reports

- June 5, 1981: 5 cases of PCP in gay men from UCLA (MMWR)\(^1\)
- July 3, 1981: 26 additional cases\(^2\)
- Dec 10, 1981: 3 NEJM papers describe cases\(^3\)

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Aids – Case definition

<table>
<thead>
<tr>
<th>2008 CDC Case Definition for HIV Infection: AIDS-Defining Clinical Conditions</th>
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<tbody>
<tr>
<td>+ Candidiasis (trachea, bronchia, or lung)</td>
</tr>
<tr>
<td>+ Candidiasis (esophageal)</td>
</tr>
<tr>
<td>+ Cervical cancer (invasive)</td>
</tr>
<tr>
<td>+ Coccidioidomycosis (disseminated or extrapulmonary)</td>
</tr>
<tr>
<td>+ Cryptococcosis (extrapulmonary)</td>
</tr>
<tr>
<td>+ Cryptosporidiosis (intestinal, for longer than 1 month)</td>
</tr>
<tr>
<td>+ Cytomegalovirus disease (other than liver, spleen, or nodes)</td>
</tr>
<tr>
<td>+ Cytomegalovirus retinitis (with loss of vision)</td>
</tr>
<tr>
<td>+ Encephalopathy (HIV-related)</td>
</tr>
<tr>
<td>+ Herpes simplex: chronic ulcers (present for longer than 1 month)</td>
</tr>
<tr>
<td>+ Herpes simplex: bronchitis, pneumonitis, or esophagitis</td>
</tr>
<tr>
<td>+ Histoplasmosis (disseminated or extrapulmonary)</td>
</tr>
<tr>
<td>+ Isosporiasis (intestinal, for longer than 1 month)</td>
</tr>
<tr>
<td>+ Kaposi’s sarcoma</td>
</tr>
<tr>
<td>+ Lymphoma, Burkitt’s (or equivalent term)</td>
</tr>
<tr>
<td>+ Lymphoma, immunoblastic (or equivalent term)</td>
</tr>
<tr>
<td>+ Lymphoma, primary of brain</td>
</tr>
<tr>
<td>+ Mycobacterium avium complex, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>+ Mycobacterium kansasii, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>+ Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)</td>
</tr>
<tr>
<td>+ Mycobacterium, other species or unidentified species, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>+ Pneumocystis carinii pneumonia</td>
</tr>
<tr>
<td>+ Recurrent pneumonia (≥ 2 episodes in 1-year period)</td>
</tr>
<tr>
<td>+ Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>+ Salmonella (recurrent septicemia)</td>
</tr>
<tr>
<td>+ Toxoplasmosis (brain)</td>
</tr>
<tr>
<td>+ Wasting syndrome due to HIV: &gt;10% involuntary weight loss plus either chronic diarrhea (≥ 2 stools per day for at least 30 days) or chronic weakness and documented fever (for at least 30 days) in the absence of a concurrent illness or condition other than HIV that could explain this finding.</td>
</tr>
</tbody>
</table>
Physicians getting used to multiple infections...
Inevitably fatal in most...

1981–1987

Proportion surviving

Source: National AIDS case surveillance data, CDC
Early Mistakes – CDC statement 1981

- CDC – “no apparent danger to non-homosexuals from contagion”.

- “The best evidence against contagion is that no cases have been reported to date outside the homosexual community or in women”
This is not a
setting for AIDS.

THE FEAR OF AIDS
Ignorance and Uncertainty Fuel Growing Public Concern
1983: The cause is discovered

Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)

F. Barre-Soussi, J. C. Chermann
F. Rey, M. T. Nugeyre
S. Chamaret, J. Gruest
C. Dauguet, C. Axler-Blin
Institut Pasteur, Département de

‘We tentatively conclude that this virus [...] belong[s] to a family of T-lymphotropic retroviruses that are horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS.’
Treatment for survival....

- 1980’s: finding drugs with *any* antiviral efficacy
The first active drug is found...

US Retrovir Prescribing Information. Revised Nov 2009
Levene PA and Tipson RS. Science 1935;81(2091):623-630
The first active drug is found...

‘AZT administration was associated with a four-to-six-fold reduction in the mortality rates in the study population at nine months.

Brian Gazzard, Personal communication with Margaret Fischl
“We hope to have a vaccine against AIDS ready for testing in two years”

“Yet another terrible disease is about to yield to patience, persistence and outright genius”
Trends in Annual Rates of Death from Leading Causes of Death Among Persons 25-44 Years Old, USA, 1982-1988

*Preliminary 1998 data

National Center for Health Statistics
National Vital Statistics System
1987 AZT Monotherapy

**Drug-Resistant Strains of AIDS Virus Found**

The emergence of AZT-resistant strains of the AIDS virus in patients treated with the drug has serious implications for treating AIDS and preventing its spread.

Adapted from Fischl MA et al. *NEJM* 1987;317:185–91
Issues with early Antiretroviral Therapy

Adherence

Toxicity
Additional NRTI's became available

- NRTI, Nucleoside reverse transcriptase inhibitor
- NNRTI, Non-nucleoside RT inhibitor
- PI, protease inhibitor
- Integrase Inhibitor
- CCR5 Antagonist/Entry Inhibitor
All-cause mortality: DELTA 1 and 2

Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals

Delta Coordinating Committee

Numbers at risk

|AZT| 1055| 1033| 994| 906| 725| 513| 225 |
|AZT + ddC| 1072| 1052| 1019| 937| 776| 554| 242 |
|AZT + ddl| 1080| 1055| 1023| 938| 774| 585| 246 |
Again, expectations dashed

**1987 AZT Monotherapy**

**1994 Two drug therapy**

RNA change (log$_{10}$ copies/mL)

24 week response

Adapted from Fischl MA et al. NEJM 1987;317:185–91c
No halt in epidemic

Trends in Annual Rates of Death from Leading Causes of Death Among Persons 25-44 Years Old, USA, 1982-1988

*Preliminary 1998 data

National Center for Health Statistics
National Vital Statistics System
However, there were successes

Acquired immunodeficiency syndrome and critical care

AIDS has created economic, social, emotional, and medical issues, some of which are reviewed by Layon and D'Amico (1). We would like to emphasize some of the ethical issues that AIDS has caused for practitioners of critical care. Questions have been raised concerning the ethical and economic appropriateness of using expensive life-sustaining treatments that do not alter a patient's underlying disease process or eventual outcome during a period of scarce critical care and medical resources. Accurate medical knowledge is required to answer these questions and to make difficult decisions in a sound ethical manner.

Questions have been raised concerning the ethical and economic appropriateness of using expensive life-sustaining treatments that do not alter a patient's underlying disease process or eventual outcome...
Response rates for PCP

Acute respiratory failure secondary to Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A potential role for systemic corticosteroids.

Improved survival in patients with AIDS, Pneumocystis carinii pneumonia, and severe respiratory failure.

Y Friedman, C Franklin, E C Rackow and M H Well
Chest 1989;96:862-866
DOI 10.1378/chest.96.4.862

The online version of this article, along with updated information and services can be found online on the World Wide Web at: http://chestjournal.chestpubs.org/content/96/4/862

CORTICOSTEROIDS AS ADJUNCTIVE THERAPY FOR SEVERE PNEUMOCYSTIS CARIN PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

A Double-Blind, Placebo-Controlled Trial

Suzanne Gagnon, M.D., Ahmad M. Boota, M.D., Margaret A. Fischl, M.D., Horst Baier, M.D., Otis W. Kirksey, Pharm.D., and Lawrence La Voie, Ph.D.
PCP Survival improved
And there was more testing...
Triple therapy investigated...

- NRTI, Nucleoside reverse transcriptase inhibitor
- NNRTI, Non-nucleoside RT inhibitor
- PI, protease inhibitor
- Integrase Inhibitor
- CCR5 Antagonist/Entry Inhibitor

• Maraviroc
• Raltegravir
• Etravirine
• Tipranavir
• Enfuvirtide
• Atazanavir
• Emtricitabine
• Fosamprenavir
• Tenofovir
• Lopinavir/r
• Amprenavir
• Efavirenz
• Abacavir
• Nelfinavir
• Delavirdine
• Ritonavir
• Indinavir
• Nevirapine
• 3TC
• Saquinavir
• d4T
• ddC
• ddl
• AZT

• NRTI, Nucleoside reverse transcriptase inhibitor
• NNRTI, Non-nucleoside RT inhibitor
• PI, protease inhibitor
• Integrase Inhibitor
• CCR5 Antagonist/Entry Inhibitor
Viral load assays also become available as a surrogate marker 1996

Viral load assays
Combination therapy succeeded where 2NRTI failed – no more clinical endpoint trials

Relative viral load suppression with mono- and combination therapies

- Dual class combination therapy: nucleoside + protease inhibitor (1996)

Adapted from Facui, AS. Nat. Med 2003. 6: 839–843
One drug is not enough in chronic infections
Mortality among persons 25-44 years old, USA 1982-1998 falls...

Introduction of HAART

* Preliminary 1998 data

Hopes...
Combination therapy succeeded where 2NRTI failed

Pre-HAART Era 1987-1996

Concorde

CD4 Count

PCP prophylaxis
AZT monotherapy

Hit Hard Era 1997-2000

David Ho

DHHS

350

BHIVA

Time to Hit HIV, Early and Hard

D Ho NEJM 1995; 333:450-451
Treatment for success...

- 1980’s: finding drugs with *any* antiviral efficacy
- 1990’s: attempting to get *durable* antiviral efficacy
Eradicating impossible
With standard HAART – The Reservoir of latently infected Cells decays slowly

Decay of Latent Reservoir in Patients with full HAART suppression for 3-7 years

- HIV Integrates into cells with extremely long biological half-life
- Integrated HIV persists in patients on HAART
- Latent reservoir makes HIV infection incurable
- Potential for clonal expansion of latently infected cells and proliferation

Siliciano JD et al., Nature Medicine 2003;9:727

\( \leq 70y \) before cure
Resistance test became widely used – Mistakes made...

- ZDV/DDI/SAQ
- D4T/DDI/LOP/r
- D4T/3TC/IND
- ZDV/3TC/SAQ/LOP/R
- ZDV/3TC/SAQ/EFV
- ZDV/DDI
- NFV/NVP/DDI
- ZDV/3TC/RIT
- Virological failure
- Peripheral neuropathy
Further drugs lead to the advent of ART

- **NRTI**, Nucleoside reverse transcriptase inhibitor;
- **NNRTI**, Non-nucleoside RT inhibitor;
- **PI**, Protease inhibitor
- **Integrase Inhibitor**
- **CCR5 Antagonist/Entry Inhibitor**
Where are we now with treatment?

• 1980’s: finding drugs with *any* antiviral efficacy
• 1990’s: getting *durable* antiviral efficacy
• 2000’s: making treatments easier and less toxic
• 2010’s: aiming for normal life expectancy
We live in the resourced nations where...
Prevalence of HIV-infected individuals is increasing, but mortality rate is decreasing.

Diagnosed HIV infected individuals in the WHO European region:

- Numbers may rise, for recent years, as further reports are received.

AIDS deaths per year in the WHO European region:

Treatment is easy...

HIV

Type 1 Diabetes
If patients take their tablets they don’t fail
UK cohort, ART uptake, and virological failure

<table>
<thead>
<tr>
<th>Year</th>
<th>Cohort</th>
<th>ART</th>
<th>VF</th>
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<tbody>
<tr>
<td>2000</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>3%</td>
<td></td>
<td></td>
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<tr>
<td>2005</td>
<td>2%</td>
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<td>2006</td>
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<td>2007</td>
<td>2%</td>
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<tr>
<td>2008</td>
<td>2%</td>
<td></td>
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<tr>
<td>2009</td>
<td>1%</td>
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</table>
A growing number of people with HIV are reaching older age

Number of people living with diagnosed HIV infection and accessing HIV-related care, by age group, UK: 2000-2009

Life-expectancy approached that of HIV-individuals

HIV cohort
Prediction life expectancy
From age 24y
Taking HAART

Shaded areas represent the interquartile range and dashed lines represent the general population.

The only one?

Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation

Kristina Allers, Gero Hütter, Jörg Hoffmann, Christoph Loddenkemper, Kathrin Rieger, Eckhard Thiel and Thomas Schneider
Attacking the reservoir...

- Intensification?
- New drugs in current classes?
- Purging the reservoir?
- Novel agents?
Until then - Prevention
Ending the AIDS epidemic by 2030

Source: UNAIDS estimates (2014), Gap report
Thank you

For further information please contact:

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