Antiretroviral Therapy: Past, Present, Future

David A Cooper
The University of New South Wales
Sydney, Australia
Antiretroviral Therapy

The eighties
ART development
Transmission
Early treatment
Rollout
Antiretroviral Therapy

The eighties

ART development

Transmission

Early treatment

Rollout
The eighties
Thirty years of antiretroviral therapy

Becky, Kangaroo, Anna, Joep
ACUTE AIDS RETROVIRUS INFECTION

Definition of a Clinical Illness Associated with Seroconversion

David A. Cooper
Prudence Maclean
Robert Finlayson
Harry M. Michelmore

Julian Gold
Basil Donovan
Timothy G. Barnes
Peter Brooke

Ronald Penny
for the Sydney AIDS Study Group*
Thirty years of antiretroviral therapy

The eighties

**Clinical features**: maculopapular rash
### Acute AIDS retrovirus infection: clinical findings in 12 cases

#### Patient's Age (years)

<table>
<thead>
<tr>
<th>Age Range</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-35</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>36-50</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Mean 35.4, range (23-64)

#### Duration of Illness (days)

<table>
<thead>
<tr>
<th>Duration</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>6-10</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>4 (36%)</td>
</tr>
</tbody>
</table>

Mean 8.1 (range 3-14)

#### Selected Signs and Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever/sweats</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Myalgia/arthritis</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Malaise/lethargy</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Anorexia/nausea/vomiting</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>Headaches/photophobia</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (33%)</td>
</tr>
</tbody>
</table>

Cooper et al. Lancet 1985
Antibody response: IFA and ELISA

<table>
<thead>
<tr>
<th>criterion</th>
<th>IgM IFA antibody</th>
<th>IgG IFA antibody</th>
<th>ELISA</th>
<th>P for IgM vs IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>first detection in days</td>
<td>5 ± 3 (5)</td>
<td>11 ± 3 (6)</td>
<td>31 ±14 to 58 ± 32</td>
<td>0.01</td>
</tr>
<tr>
<td>peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>days</td>
<td>24 ± 17 (7)</td>
<td>133 ± 63 (8)</td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td>titer</td>
<td>1:160 (6)</td>
<td>1:10,240 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:40 (1)</td>
<td>1:2,560 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disappearance in days</td>
<td>81 ± 27 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(n) = no of subjects contributing data

Cooper et al JID 1987
Lymphocyte responses: CD4 and CD8

CD4 cell count

CD8 cell count

Cooper et al JID 1988
The eighties

**The Lancet, 26th July 1986**

**EXPRESSION OF HUMAN IMMUNODEFICIENCY VIRUS ANTIGEN (HIV-Ag) IN SERUM AND CEREBROSPINAL FLUID DURING ACUTE AND CHRONIC INFECTION**

Jaap Goudsmit, Deborah A. Paul, Joep M. A. Lange, Hans Speelman, Jan Van Der Noordaa, Hayo J. Van Der Helm, Frank de Wolf, Leon G. Epstein, Willy J. A. Krone, Eric Ch. Wolters, James M. Oleske, Roel A. Coutinho
### HIV-Ag in serum and CSF in PHI and CHI

<table>
<thead>
<tr>
<th>Category</th>
<th>no (%) with HIV-Ab in</th>
<th>Serum</th>
<th>CSF</th>
<th>Serum</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS (n=22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (100)</td>
<td>18 (82)</td>
<td></td>
<td>19 (86)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>symptomless (n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (100)</td>
<td>8 (62)</td>
<td></td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

### PHI patient

<table>
<thead>
<tr>
<th>Date</th>
<th>HIV antibody titre in</th>
<th>HIV antigen (ng/ml) in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>CSF</td>
</tr>
<tr>
<td>Nov 30, 82</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aug 2, 83</td>
<td>140</td>
<td>-</td>
</tr>
<tr>
<td>May 10, 84</td>
<td>211</td>
<td>12</td>
</tr>
<tr>
<td>May 9, 85</td>
<td>280</td>
<td>23</td>
</tr>
</tbody>
</table>
The eighties

Clinical course of SI versus NSI isolates

<table>
<thead>
<tr>
<th>group</th>
<th>type of isolate</th>
<th>CD4 cells</th>
<th>HIV-Ag</th>
<th>clinical outcome</th>
<th>median F/U until AIDS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SI</td>
<td>5 0 5 1 4</td>
<td>- +</td>
<td>AS 0 5</td>
<td>15</td>
</tr>
<tr>
<td>B</td>
<td>fast NSI</td>
<td>7 0 7 2 5</td>
<td>- +</td>
<td>AS 1 6</td>
<td>25</td>
</tr>
<tr>
<td>C</td>
<td>slow NSI</td>
<td>22 13 9 16 6</td>
<td>- +</td>
<td>AS 18 4</td>
<td>&gt; 42</td>
</tr>
</tbody>
</table>

Tersmette et al; Lancet 1989
Antiretroviral Therapy

The eighties

ART development

Transmission

Early treatment

Rollout
### EACG017: progression of disease

AZT monotherapy 500mg bd n=335 for 60 weeks deferral

<table>
<thead>
<tr>
<th></th>
<th>AIDS/severe ARC</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1990</td>
<td>PBO</td>
<td>AZT</td>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>0.89</td>
<td>0.97</td>
<td>(0.02, 0.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>0.86</td>
<td>0.92</td>
<td>(-0.02, 0.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>0.86</td>
<td>0.86</td>
<td>(-0.10, 0.10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Probabilities of remaining free of disease progression [95% CI for difference]

Mulder et al AIDS 1994
Thirty years of antiretroviral therapy

ART development

**ACTG 076: MTCT**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Zidovudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (95% CI)</td>
<td>25.5 (18.4-32.5)</td>
<td>8.3 (3.9-12.8)</td>
</tr>
</tbody>
</table>

Connor et al; NEJM 1994
Thirty years of antiretroviral therapy

ART development

**CAESAR**: progression to AIDS and death

<table>
<thead>
<tr>
<th>final analysis</th>
<th>current treatment plus placebo</th>
<th>current treatment plus 3TC</th>
<th>current treatment plus 3TC and loviride</th>
<th>( p )</th>
<th>relative hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>471</td>
<td>907</td>
<td>462</td>
<td></td>
<td></td>
</tr>
<tr>
<td>protocol-defined new AIDS or death</td>
<td>95 (20%)</td>
<td>86 (9%)</td>
<td>42 (9%)</td>
<td>&lt;0.0001</td>
<td>0.43 (0.32-0.57)</td>
</tr>
<tr>
<td>new AIDS or death</td>
<td>103 (22%)</td>
<td>91 (10%)</td>
<td>46 (10%)</td>
<td>&lt;0.0001</td>
<td>0.41 (0.31-0.55)</td>
</tr>
<tr>
<td>death</td>
<td>28 (6%)</td>
<td>23 (3%)</td>
<td>14 (3%)</td>
<td>0.0007</td>
<td>0.40 (0.23-0.69)</td>
</tr>
</tbody>
</table>

CAESAR trial, Lancet, 1997
PETRA: early efficacy of AZT/3TC

<table>
<thead>
<tr>
<th>HIV-1 infection or death</th>
<th>n (%)</th>
<th>early efficacy at wk 6 (RR [95% CI])</th>
<th>p</th>
<th>HIV-1 infection rates at 18mo % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>regimen A</td>
<td>20 (7.0%)</td>
<td>0.39 (0.24-0.64)</td>
<td>0.001</td>
<td>15% (9-23)</td>
</tr>
<tr>
<td>regimen B</td>
<td>32 (11.6%)</td>
<td>0.64 (0.42-0.97)</td>
<td>0.003</td>
<td>18% (12-26)</td>
</tr>
<tr>
<td>regimen C</td>
<td>51 (17.5%)</td>
<td>0.97 (0.68-1.38)</td>
<td>0.85</td>
<td>20% (13-30)</td>
</tr>
<tr>
<td>placebo</td>
<td>49 (18.1%)</td>
<td>1.00</td>
<td>-</td>
<td>22% (16-30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>pregnancy from 36 wks</th>
<th>intrapartum</th>
<th>postpartum (7d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>regimen A</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>regimen B</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>regimen C</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>placebo</td>
<td>no</td>
<td>no</td>
<td>no</td>
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</table>

Petra study team; Lancet 2002
Thirty years of antiretroviral therapy

ART development

**BI 1010:** alternating NVP and AZT monotherapy

<table>
<thead>
<tr>
<th></th>
<th>NVP</th>
<th>AZT</th>
<th>NVP</th>
<th>AZT</th>
<th>NVP</th>
<th>AZT</th>
<th>NVP</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>5</td>
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<td>6</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
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<tr>
<td>9</td>
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<td>10</td>
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<td>11</td>
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<td>12</td>
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<tr>
<td>13</td>
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</tr>
</tbody>
</table>

median % change from baseline in HIV p24 antigen

weeks

de Jong et al, JID 1994
Thirty years of antiretroviral therapy

ART development

**INCAS:** efficacy with NNRTI (NVP)

% patients with no detectable HIV-1 RNA (<20 copies/mL)

duration of treatment, week

Montaner et al, JAMA 1998
### Thirty years of antiretroviral therapy

**ACTG 320**: disease progression with protease inhibitors

<table>
<thead>
<tr>
<th></th>
<th>IDV, ZDV/d4T 3TC</th>
<th>ZDV/d4T 3TC</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no of patients (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>all patients</strong></td>
<td>577</td>
<td>579</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS or death</td>
<td>33 (6)</td>
<td>63 (11)</td>
<td>0.50 (0.33-0.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>death</td>
<td>8 (1)</td>
<td>18 (3)</td>
<td>0.43 (0.19-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>≤ 50 CD4 cells/µL</td>
<td>219</td>
<td>220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS or death</td>
<td>23 (11)</td>
<td>44 (20)</td>
<td>0.49 (0.30-0.82)</td>
<td>0.005</td>
</tr>
<tr>
<td>death</td>
<td>5 (2)</td>
<td>13 (6)</td>
<td>0.37 (0.13-1.04)</td>
<td>0.05</td>
</tr>
<tr>
<td>51-200 CD4 cells/µL</td>
<td>358</td>
<td>359</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS or death</td>
<td>10 (3)</td>
<td>19 (5)</td>
<td>0.51 (0.24-1.10)</td>
<td>0.08</td>
</tr>
<tr>
<td>death</td>
<td>3 (1)</td>
<td>5 (1)</td>
<td>0.59 (0.14-2.46)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Hammer et al, NEJM 1997
ART development

**ART:** viral load response

- **Monotherapy**
- **Dual therapy**
- **Triple therapy**

Decrease in plasma HIV RNA $\log_{10}$ copies/mL

Month of therapy

De Clercq et al, Antiviral Research 1998
ART development
Thirty years of antiretroviral therapy
HIVNAT 1990’s
Bangkok, Thailand
Thirty years of antiretroviral therapy

**HIVNAT: mission and objectives**

- conduct multi-centre HIV-related clinical studies according to good clinical practice (GCP) and good laboratory practice (GLP) guidelines in Thailand and the region
- provide access to antiretroviral therapy for HIV-infected people in Thailand
- educate healthcare workers in Thailand and the region on GCP, GLP and HIV medicine
Thirty years of antiretroviral therapy

ART development

1996: 1 room, 1 nurse, 1 doc, 1 secretary

Current situation: dedicated offices, 112 staff
Thirty years of antiretroviral therapy

ART development

HIVNAT studies

- new drug development
- therapeutic strategies
- co-infection studies
- HIV vaccine development
- pharmacokinetic studies
- HIVNAT long-term observational cohort

HIVNAT 006
1900 adults
Thirty years of antiretroviral therapy

ART development

**What HIV-NAT has achieved over 18 years?**

- sustainability
- ~2,000 adults and children on ART for as long as 10 years
- exceptional adherence to ART
- HIV clinical trials to GCP standards
- international recognition as a model for clinical research in the developing world
- annual Bangkok symposium attracting up to 600 delegates each January
- now an ACTG site (2013)
Thirty years of antiretroviral therapy
### Thirty years of antiretroviral therapy

**ART development**

#### 2NN: treatment failure

<table>
<thead>
<tr>
<th></th>
<th>NVP qd (n=220)</th>
<th>NVP bid (n=387)</th>
<th>EFV (n=400)</th>
<th>NVP + EFV (n=209)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment failure on or before week 48 (%)</td>
<td>96 (43.6%)</td>
<td>169 (43.7%)</td>
<td>151 (37.8%)</td>
<td>111 (53.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>components of failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>virological</td>
<td>25 (11.4%)</td>
<td>73 (18.9%)</td>
<td>61 (15.3%)</td>
<td>34 (16.3%)</td>
<td>0.108</td>
</tr>
<tr>
<td>progression</td>
<td>7 (3.2%)</td>
<td>11 (2.8%)</td>
<td>10 (2.5%)</td>
<td>5 (2.4%)</td>
<td>0.949</td>
</tr>
<tr>
<td>change of treatment</td>
<td>64 (29.1%)</td>
<td>85 (22.0%)</td>
<td>80 (20.0%)</td>
<td>72 (34.4%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>plasma [HIV-1 RNA] &lt;50 copies/mL at 48 weeks (%)</td>
<td>154 (70.0%)</td>
<td>253 (65.4%)</td>
<td>280 (70.0%)</td>
<td>131 (62.7%)</td>
<td>0.193</td>
</tr>
</tbody>
</table>

NVP bid vs EFV comparisons NS

van Leth et al, Lancet 2004
Thirty years of antiretroviral therapy

**ART development**

**Triple-class failure clinical trials: improved outcomes**

<table>
<thead>
<tr>
<th>study</th>
<th>drug regimen</th>
<th>HIV-1 RNA &lt;50 copies/mL,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TORO</td>
<td>ENF + OBR</td>
<td>18.3</td>
</tr>
<tr>
<td></td>
<td>OBR alone</td>
<td>7.8</td>
</tr>
<tr>
<td>RESIST</td>
<td>TPV/r + OBR</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>PI/r + OBR</td>
<td>10.2</td>
</tr>
<tr>
<td>POWER</td>
<td>DRV + OBR</td>
<td>45.0</td>
</tr>
<tr>
<td></td>
<td>PI/r + OBR</td>
<td>10.0</td>
</tr>
<tr>
<td>DUET</td>
<td>ETV + DRV/r containing OBR</td>
<td>60.0</td>
</tr>
<tr>
<td></td>
<td>placebo + DRV/r containing OBR</td>
<td>40.0</td>
</tr>
<tr>
<td>MOTIVATE</td>
<td>MVC qd+ OBR</td>
<td>41.8</td>
</tr>
<tr>
<td></td>
<td>MVC bid+ OBR</td>
<td>46.8</td>
</tr>
<tr>
<td></td>
<td>placebo + OBR</td>
<td>16.1</td>
</tr>
<tr>
<td>BENCHMRK</td>
<td>RAL + OBR</td>
<td>63.0</td>
</tr>
<tr>
<td></td>
<td>placebo + OBR</td>
<td>33.0</td>
</tr>
</tbody>
</table>
Thirty years of antiretroviral therapy

ART development

**Cabotegravir**: monthly LA injections protect macaques against repeated vaginal SHIV exposures

---

**Drug/virus challenge phase**  **Drug washout/infection follow-up**

![Graph showing survival rates](garcia Lerma et al. CROI 2014; Boston, MA. Slides)

- **CAB (n=6)**
- **Placebo controls (n=6)**

$p=0.0005$
Antiretroviral Therapy

The eighties

ART development

Transmission

Early Treatment

Rollout
HPTN 052: HIV-1 transmission

Total HIV-1 transmission events: 39

- Linked transmissions: 28
  - Immediate arm: 1
  - Delayed arm: 27
- Unlinked or TBD transmissions: 11

- 18/28 (64%) transmissions from infected participants with CD4 >350 cells/µL
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

Cohen et al NEJM 2011
## Africa Centre cohort: ART coverage and HIV acquisition

<table>
<thead>
<tr>
<th>Community-level ART (versus &lt;10%)</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20%</td>
<td>aHR (95% CI)</td>
</tr>
<tr>
<td>0.93 (0.8 - 1.08)</td>
<td>0.325</td>
</tr>
<tr>
<td>20-30%</td>
<td>0.79 (0.67 - 0.92)</td>
</tr>
<tr>
<td>30-40%</td>
<td>0.62 (0.50 - 0.76)</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>0.63 (0.44 - 0.91)</td>
</tr>
</tbody>
</table>

Tanser et al, Science 2013
HIV treatment cascade: Australia 2014

- Living with HIV: 27,000
- Diagnosed: 23,000
- Linked to care: 20,000
- Retained in care: 19,000
- Receiving ART: 17,000
- Suppressed virus: 15,000

% of people living with HIV: 100%
Kirby Institute: newly diagnosed HIV infection in Australia

Transmission

![Graph showing the number of newly diagnosed HIV infections in Australia from 1984 to 2012. The number of infections peaked in 1985 and has since declined, with a small increase in recent years.]
Transmission

**Test and Treat in Australia: modelling**

30% \(\uparrow\) in testing and \(~55\%\) to 80% \(\uparrow\) ART  
\(~50\%\) \(\downarrow\) in new infections

Jansson et al Sexual Health 2014
Transmission

**Treatment Cascade Indonesia: HIV care 2011-2012**

- **PLHIV enrolled in care**: 421,000
- **Eligible for ART**: 118,343
- **Ever received ART**: 80,039
- **Still on ART**: 58,328
- **Still on ART**: 31,002

(AIDS data hub, UNAIDS)
Antiretroviral Therapy

The 80s

ART development

Transmission

Early Treatment

Rollout
## SMART: event rates

<table>
<thead>
<tr>
<th>event</th>
<th>DC group</th>
<th>VS group</th>
<th>HR (DC/VS) [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>rate</td>
<td>n</td>
<td>rate</td>
</tr>
<tr>
<td>primary endpoint: OD or death</td>
<td>120</td>
<td>3.3</td>
<td>47</td>
<td>1.3</td>
</tr>
<tr>
<td>death</td>
<td>55</td>
<td>1.5</td>
<td>30</td>
<td>0.8</td>
</tr>
<tr>
<td>serious OD</td>
<td>13</td>
<td>0.4</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>non-serious OD</td>
<td>63</td>
<td>1.7</td>
<td>18</td>
<td>0.5</td>
</tr>
<tr>
<td>major CVD, renal and hepatic events</td>
<td>65</td>
<td>1.8</td>
<td>39</td>
<td>1.1</td>
</tr>
<tr>
<td>grade 4 events</td>
<td>173</td>
<td>5.0</td>
<td>148</td>
<td>4.2</td>
</tr>
<tr>
<td>grade 4 event or death</td>
<td>205</td>
<td>5.9</td>
<td>164</td>
<td>4.7</td>
</tr>
</tbody>
</table>

El-Sadr et al, NEJM 2007
Early treatment

**Impact of HIV on inflammation, coagulation, and health**

**Microbial Translocation**
- Loss of CD4+ T cells
- Loss of epithelial cells
- Altered bowel flora
- Loss of Th17 cells
- Local inflammation (IFN-α, IDO)

**Initiators of Inflammation**
- HIV replication/production
- Co-pathogen excess (CMV, HCV)
- Microbial translocation
- Loss of regulatory responses
- Obesity
- Lipodystrophy
- Metabolic syndrome
- Substance abuse

**Innate Immunity**
- Activated monocytes and macrophages

**Cardiovascular Disease**
- Atherosclerosis
- Plaque Rupture
- Vascular dysfunction

**Liver Fibrosis or Dysfunction**
- Microbial translocation
- HIV infection of liver cells
- Inflammation
- ARV toxicity
- HCV
- HBV
- Alcohol

**Other Risk Factors**
- Antiretroviral/HIV toxicity
  - Mitochondrial toxicity
  - Telomerase/telomere dysfunction
  - Metabolic abnormalities
  - Kidney dysfunction
  - Neuropathy
  - Sarcopenia
  - Osteopenia
  - Immunosenescence
- Substance abuse
- Social isolation
- Polypharmacy

**Hypercoagulation**
- Microclotting
- VTE, MI, CVA

**Age-Associated Diseases**

Deeks et al; Immunity 2013
Antiretroviral Therapy

Early treatment

Why are we treating earlier?

- biology of continuous viral replication and immune deficiency
- simpler regimens with higher efficacy, less adverse events and less resistance
- large cohorts of early treatment with improved outcomes
- treatment reduces non-AIDS complications which increase with aging
- CD4 gradient of serious OI’s (TB and HPV) and serious non-AIDS complications
- prevention of transmission with public health benefit
- guidelines
- aspirational goals
Early treatment

**Why then the push-back?**

- RCT data are not compelling
- event-rates are low at high CD4 counts
- life-expectancy in rich countries with current guidelines is essentially normal
- HIV may not be the only culprit in determining serious non-AIDS events
- guidelines depend on expert opinion which is occasionally incorrect
- prevention of transmission while critical for discordant couples may not be achievable at the population level
Antiretroviral Therapy

Early treatment

**Australian HIV Observational Database:**
10 year survival by age and time updated CD4+ cell count

---

10 year survival probability

---

**AUS males 08 - 09**

- **< 350**
- **350 – 500**
- **> 500**

---

age
Early treatment

**Antiretroviral Therapy**

**START**: design

- **HIV-infected adults, ART naive with CD4+ >500 cells/µL**
  - randomise

- **early ART group**
  - start immediately following randomisation
  - n=2,326

- **deferred ART group**
  - when CD4+ declines to 350 cells/µL or AIDS develops
  - n=2,359

- 5 years average follow-up
- primary end-point; time to AIDS, non-AIDS or death from any cause (n=213)

Current status: enrolment completed end 2013
Substudies assessing various organ dysfunction incl. arteries, neuro-system, lungs, bone
Early treatment

**START: impact of scenarios**

- Superiority will lead to change of guidelines such that treatment will be recommended for all HIV-infected persons.
- Inferiority or harm will lead to guidelines recommending the status quo of a CD4 ceiling of 500/µL to start ART.
- Equivalence will lead to a moderated approach whereby prevention of transmission will become paramount in recommending ART.
Antiretroviral Therapy

The eighties

ART development

Transmission

Early Treatment

2000 and beyond
A reminder

Of all the ills that kill the poor, none is as lethal as bad government

Economist, August 14, 1999
Bridging the leadership gap?

- First we should recognize the facts:
  - We are facing a problem of immense complexity, that is getting out of hand in an exponential way.
  - The traditional way of working of human institutions - along a linear time scale - will not be able to cope with this.
  - Clash between “dog years” and “bureaucratic years”

*J.F. Rischard, High Noon: 20 Global Issues, 20 Years to Solve Them*
J.F. Rischard, High Noon: 20 Global Issues, 20 Years to Solve Them
The case beyond compassion: the economy, etc.

- HIV/AIDS seriously hampers economic development of many developing nations, particularly in sub-Saharan Africa:

  “It is hard to imagine robust economic growth where so many adults are dying in their productive prime, leaving the very young and the very old to cope alone” (Economist August 14, 1999)
Moving beyond the lack of a common agenda and leadership in implementation

- The wide-scale introduction of adequate antiretroviral therapy in developing countries, requires:
  - a concerted global effort
  - of a broad coalition of the public sector, the private sector, civil society and academia
  - with clear divisions of tasks and accountability
Planning for a future without donor money and donor dependence

- The antiretroviral scale-up will only succeed and prevail if the issue of sustainable financing of health care for the masses has been solved:
  - Establishment of robust insurance schemes (by reliable institutions, thus not necessarily the state) is a prerequisite and priority
Planning for success

“The sight of the affluent young of the west wishing to protect the poor of the world from the processes that delivered their own remarkable prosperity is unutterably depressing.”

Martin Wolf “Why Globalization Works”, Yale University Press 2004
Planning for success

Principle of “what works” should prevail over the (questionable!) notion of what constitutes an “ideal society”
**Antiretroviral Therapy**

**Rollout**

**ART eligibility: 5 policy scenarios**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Estimated Millions of People Eligible</th>
<th>CD4 Cut-off</th>
<th>Eligibility Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>CD4 ≤ 200</td>
<td>recommended since 2002</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>CD4 ≤ 350</td>
<td>recommended since 2010</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>CD4 ≤ 350 + TasP</td>
<td>incremental approach 2012</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>CD4 ≤ 500</td>
<td>recommended since 2013</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>all HIV+</td>
<td>“test and treat”</td>
</tr>
</tbody>
</table>
WHO: persons receiving ART 2003-2015

Actual and projected numbers of people receiving ART in LMIC

- African region
- Region of the Americas
- SE Asia region
- European region
- Eastern Mediterranean region
- Western Pacific region

2013 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS)
### What can we do to improve the situation?

<table>
<thead>
<tr>
<th>step</th>
<th>targeting</th>
<th>intervention examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing</td>
<td>HIV testing capacity; demand for HIV testing; completion of staging and linkage to ART care</td>
<td>decentralisation of testing; self-testing; targeted testing in high risk groups</td>
</tr>
<tr>
<td>pre-ART care</td>
<td>retention in pre-ART care prior to ART eligibility</td>
<td>task shifting; transport allowance; earlier initiation</td>
</tr>
<tr>
<td>ART care</td>
<td>increase retention; increase reinitiation for treatment interrupters</td>
<td>support tools; home-delivered ART; health information systems for tracking LTFU</td>
</tr>
</tbody>
</table>

*ongoing implementation research is essential*

Kranzer et al; JIAS 2012
Rollout

**WHO 2013:** consolidated guidelines for ART

- Adult ART
- Maternal and child health
- Operational and service delivery
- Programmatic guidelines
We have tantalising preliminary indications that we may be able to reduce incidence by an effective roll-out.

We have no vaccine or cure right now so ART is our major intervention which could reduce incidence.

It would be a tragedy if we could not try to get enough people on treatment to reduce incidence.

We need to persuade civil society that flat lining of funds is just plain unacceptable.

We MUST finish the job.
Rollout

Joep’s legacy: the next generation

Clinical Implications of Immune Recovery during Antiretroviral Treatment for HIV Infection
Anouk Kessels

Outcomes of Antiretroviral Therapy in Thai Adults
Christopher J. Duncombe

THE EPIDEMIOLOGY OF HIV AND HIV IN KIGALI, RWANDA | NENKE | VELDUIJZEN

PHARMACOLOGICAL STUDIES
SASKIA AUTAR

Optimizing Protease Inhibitor-Based Antiretroviral Therapy for HIV-1-Infected Thai Adults and Children
Joep van der Lugt

Antiretroviral Therapy in Thai Adults and Children with HIV-1 Infection
Jintanat Ananworanich

FEDDE GROOT / DE DERTIGE CELL-MEDIATED HIV TRANSMISSION

Metabolic complications of antiretroviral therapy
Marc van der Valk

HBV RNA as a new marker of virus replication
Maarten Penning

The use of non-nucleoside reverse transcriptase inhibitors in the treatment of HIV-1 infection
FRANK VAN LEHT

E.W.N.M. Wit

Studies on the efficacy and toxicity of highly active antiretroviral therapy

T cell turnover and thymic function in HIV-1 infection
Mette D. Hazenberg

Michel P. de Bree

The impact of HIV-1 subtypes on molecular diagnostics

HIV-1 SUBTYPE C IN ETHIOPIA
Altma Abybo

HIV and the Immune System during Highly Active Antiretroviral Therapy
James Cohen Stuart

Viral dynamics and immune reconstitution in HIV-1 infection during potent antiretroviral therapy
Deaan Notterman

Bionanysis and Clinical Pharmacology of Antiretroviral Drugs
Rolf P.G. van Heeswijk

Human herpesvirus 8 and Kaposi’s sarcoma in the Amsterdam Cohort Studies
Neil Renwick

Measuring treatment response in HIV-1 infection
Gerrit Jan Weverling

Tangible effects of antiretroviral therapy in HIV-1 infected patients
N.A. Koudraïne 1999

T-cell dynamics in HIV-1 infection: the effect of therapy
Nadine Pakker 1998

The role of HIV-1 syncytium inducing variants in AIDS pathogenesis
Maarten Koot

HIV-1 phenotype variation in the natural course of infection: a longitudinal study under treatment
A.B. van ‘t Wout

Studies on the treatment of HIV-1 infection
Jan Veenstra

Evaluation of the efficacy of zidovudine treatment in HIV-1-infected subjects
J.W. Mulder

Studies on clinical aspects of and interventions in HIV-1 infection
Jan Veenstra

Restoration of HIV-1-specific CD4+ T cell responses with potent antiretroviral therapy
Jan Veenstra

HIV-1 reversion and its aftermath among homosexual men
RENÉ KEET

Drug-failure in HIV-1 infection
Menno D. de Jong

Characterisation of human immunodeficiency viruses during clade B treatment
Charles A.B. Boucher

PETER REISS — HEMORRHAGIC IMMUNE RESPONSE TO VIRAL ACCESSORY GENE PRODUCTS IN HIV-1 INFECTION

Kirby Institute