ART in the developing world

The way forward

Objective:
an understanding of
the remarkable progress in ART
and its implementation
in the developing world

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ART in the developing world

Standard of care
Treatment as prevention
Access to ART
Clinical and implementation research

Mortality and HAART utilisation

Palella et al, CROI 2002
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**Standard of care**

#### Current drugs and classes

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NtRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>FEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>TFV</td>
<td>NVP</td>
<td>SQV</td>
<td>ENF</td>
</tr>
<tr>
<td>ddi</td>
<td>DLV</td>
<td>RTV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ddc</td>
<td>EFV</td>
<td>IDV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T</td>
<td></td>
<td>NFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td></td>
<td>APV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABV</td>
<td></td>
<td>LPV/r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTC</td>
<td></td>
<td>ATV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fAPV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Targets for anti-HIV drugs

- **Integrase inhibitors**
- **Protease inhibitors**
- **Reverse transcriptase inhibitors**
- **Fusion/entry inhibitors**

*Fauci Nature Medicine 2003*
When to start therapy

Strong evidence base
- symptomatic disease
- CD4+ cell count < 200/µL

Guidelines driven
- 200/µL < CD4+ cell count < 350/µL
- high VL

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Gilead 903: week 144 efficacy

% patients with HIV-1 RNA < 50 c/mL

Gallant et al, 2004
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**Staccato: viral load response during induction period**

- Patients (%)
- 0 weeks
- 8 weeks
- 16 weeks
- 24 weeks

- < 50 copies/ml
- < 400 copies/ml
- 91.0%
- 95.2%

Regimen: 2NRTI + SQV/r

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**Level of adherence determines response**

- HIV RNA below detectable (%) by MEMSCaps
- CD4 cell change (cells/mm³)

- n=84
- p=0.00001

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Ananworanich et al, WAC 2004

Paterson et al, Retroviruses 1999
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Fixed dose combinations

<table>
<thead>
<tr>
<th>advantages</th>
<th>disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>adherence</td>
<td>toxicity management</td>
</tr>
<tr>
<td>pill burden</td>
<td>dose escalation</td>
</tr>
</tbody>
</table>

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Changes in body composition following HAART

Mallon et al, AIDS 2002
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Clinical lipodystrophy

Clinical lipoatrophy in a child
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**Standard of care**

**Choosing first-line regimens**
- Use fixed dose combinations first line
- Implement adherence strategies
- Select NNRTI-based regimens
- Choose HAART regimens on basis of established efficacy, safety, ease of administration, and tolerability
- Suboptimal treatments must not be used
- Track development of ART resistance
- Plan second line regimens for failure
- Integrate TB management

**Failure of first line regimens**
- Design regimens for failure of 2NRTI and NNRTI
- Will require PI-based therapy
- NRTI backbone will be impaired
- Subsequent regimens following PI failure will be problematic
- Substitutions for toxicity will be limited
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Access to ART
Clinical and implementation research

Heterosexual transmission by HIV-1 viral load

Quinn et al, NEJM 2000
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Treatment as prevention

**Infected person**

- treat infected person to reduce transmission

  - examples
    - serodiscordant couple (+ve partner)
    - mother

  - will benefit infected person
  - requires combination ART

**Uninfected person**

- treat uninfected person to prevent transmission

  - examples
    - serodiscordant couple (-ve partner)
    - baby of HIV +ve mother
    - high risk HIV -ve

  - population-based chemoprophylaxis
  - monotherapy may be sufficient
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Adults and children estimated to be living with HIV/AIDS

WHO/UNAIDS 2004

39.4 million estimated to be living with HIV/AIDS in 2004

8,500 deaths every day

3.1 million died in 2004

Total number of people living with HIV: 39.4 million

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Western Europe 610,000

North Africa & Middle East 540,000

Sub-Saharan Africa 25.4 m

Latin America 1.7 million

Caribbean 440,000

Eastern Europe & Central Asia 1.4m

South & SE Asia 7.1 m

North America 1m

East Asia & Pacific 1.1m

Oceania 35,000
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**Projected changes in life expectancy in selected African countries with high HIV prevalence**

![Graph showing life expectancy trends in selected African countries](image)

*United Nations Population Division, 1996*

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**Projected population structure with and without the AIDS epidemic: Botswana 2020**

![Graph showing population structure](image)

*US Census Bureau, 2000*
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*Access to ART*

**What should we do?**

- We cannot afford not to treat those who need to be treated with antiretrovirals (HAART)
- We should avoid the false dichotomy between prevention and treatment

Treat those who need to be treated with antiretrovirals (HAART)

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*Access to ART*

**Reasons to make the fight against HIV, including access to HIV medicines, a global priority**

- Humanitarian
- Economic and social development
- Tuberculosis
- “Security”
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Forces for change

- global treatments activism
- generic competition
- funding mechanisms
- technical programs

<table>
<thead>
<tr>
<th>HAART</th>
<th>WAC Durban</th>
<th>AAI</th>
<th>MAP</th>
<th>UNGASS</th>
<th>GFHTM</th>
<th>WHO Rx</th>
<th>PEPFAR 3 by 5 program</th>
</tr>
</thead>
</table>

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Access to ART

The reality

- in quite a few countries there is currently (some) government commitment to facilitate access to ART
- a number of NGOs and CBOs are providing HIV treatment and care
- there is also an increase in employer schemes including comprehensive HIV-care, including HAART
- however, out of the millions of people that need to be treated TODAY in the developing world, only 5% of the population in immediate need are receiving it
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Challenges of ART in resource poor settings

1. insufficient political commitment
2. cost of care (including antiretrovirals)
3. lack of infrastructure
4. lack of expertise
5. lack of a common agenda and leadership in implementation
6. planning for the future

Access to ART

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Challenges of ART in resource poor settings

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**Challenges of ART: 2. cost of care**

- Predominance of cheapest fixed dose HAART regimens in developing country ART scale up (d4T/3TC/NVP)
- The long-term costs of this choice should not be ignored.
- While the choice for d4T/3TC/NVP is understandable in the light of emergency, we need to move to less toxic regimens as soon as possible, even if the cost is higher.

Lipodystrophy associated with d4T/3TC/NVP FDC
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Challenges of ART: 2. cost of care

- health care budgets of most countries are limited; in poor developing countries per capita spending is often less than $10 per year
- so HAART scale up is dependent on the international donor community
- but… governments also make choices…

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Challenges of ART: 4. lack of expertise

There simply are not enough expert doctors to cope with the scale up; the situation is most extreme in sub-Saharan Africa, but Asia also has a problem (Treat Asia Report).

- massive training effort needed
- involvement in delivery of care by non-physicians may be necessary (DOT?)
- retention of health care workers is a priority
Like people in developed countries, people in developing countries need to be able to make a decent living out of their activities even if they involve laudable goals like providing HIV therapy to the millions.

Challenges of ART: bridging the leadership gap?

Rischard, High Noon: 20 global issues, 20 years to solve them
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**Access to ART**

**Challenges of ART:** 5. lack of a common agenda and leadership in implementation

- a sense of urgency and funding may be there with regard to the antiretroviral scale up, but there is still no undisputed global leadership and common agenda with a clear division of tasks
- majority of funding delivered through the public sector
- in countries, donors and technical assistance agencies are often in clear competition with each other

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**Access to ART**

**Challenges:** 6. planning from thousands to millions?

- robust drugs
- drug distribution
- cheap & simple monitoring
- simple regimens
- expertise and manpower
- financing health care
- operational research
- prevention
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Challenges: **planning** for independence

- technology transfer to manufacture generic antiretrovirals
- models of free comprehensive ART, using manufacture of generics followed by pressure on pharma to cut price
- national generic manufacturing programs
- regional agreements with pharma on price cuts
- cheap, robust assays for CD4 and viral load

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Access to ART

**Challenges: summary**

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
  - academia
- with clear divisions of tasks and accountability
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Cambodia meeting the challenge in 2005

- PLWHA: 123,000
- eligible for treatment: 20,000
- currently on treatment: 6,100 at 15 sites
- end 2005 on treatment: 10,000 at 26 sites

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Treatment as prevention

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the use of combination antiretroviral therapy has led to reduced morbidity and mortality caused by HIV infection in western countries.

- relatively little is known regarding HIV disease natural history and response to antiretroviral treatments among Asian people infected with HIV.

- information from observational studies is important for developing treatment and care guidelines, and planning resources for health services.

**Treat Asia: what is it?**

A cooperative network of clinicians throughout Asia and the Pacific that aims to expand capacity for the broader introduction of HIV/AIDS treatments in the region.
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TAHOD: what is it?

- first collaborative study by the TREAT Asia network
- a multi-centre, observational study of patients with HIV

TAHOD: primary objectives

- develop capacity in HIV clinical data collection in countries of the Asia-Pacific region
- assist in evaluation of new HIV treatments for the Asia-Pacific region
- monitor anti-retroviral and prophylactic treatment as related to demographics and markers of HIV disease stage
- monitor toxicity to anti-retroviral therapy
- examine HIV natural history, including relationship between access to antiretroviral therapy and disease progression
Current participating sites:
1. Beijing Ditan Hospital, Beijing
2. Queen Elizabeth Hospital, Hong Kong, Special Administrative Region of the People’s Republic of China
3. Taipei Veterans General Hospital and AIDS Prevention and Research Centre, Taipei
4. HIV Project, Ruby Hall Clinic, Pune
5. YRG Centre for AIDS Research and Education, Chennai
6. HIVNET/The Thai Red Cross AIDS Research Centre, Bangkok
7. Ramathibodi Hospital, Bangkok
8. Research Institute for Tropical Medicine, Manila
9. Hospital Kuala Lumpur, Kuala Lumpur
10. University of Malaya, Kuala Lumpur
11. Tan Tock Seng Hospital, Singapore
12. Udayana Medical School, Bali

Potential participating sites:
13. Hospital for Tropical Medicine, Ho Chi Minh City

TAHOD: patient recruitment

<table>
<thead>
<tr>
<th></th>
<th>n=</th>
<th>with follow-up</th>
<th>follow-up rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov 2003</td>
<td>1,282</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mar 2004</td>
<td>1,887</td>
<td>1,174</td>
<td>92%</td>
</tr>
<tr>
<td>Sep 2004</td>
<td>2,089</td>
<td>1,710</td>
<td>91%</td>
</tr>
</tbody>
</table>
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TAHOD: patient characteristics

<table>
<thead>
<tr>
<th>n= 2089</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender</td>
</tr>
<tr>
<td>median age (IQR)</td>
</tr>
<tr>
<td>ethnicity</td>
</tr>
<tr>
<td>Chinese</td>
</tr>
<tr>
<td>Indian</td>
</tr>
<tr>
<td>Thai</td>
</tr>
<tr>
<td>exposure</td>
</tr>
<tr>
<td>heterosexual contact</td>
</tr>
<tr>
<td>homosexual contact</td>
</tr>
<tr>
<td>injecting drug use only</td>
</tr>
</tbody>
</table>

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TAHOD: patient characteristics

<table>
<thead>
<tr>
<th>at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>median baseline CD4 count (IQR)</td>
</tr>
<tr>
<td>baseline HIV viral load</td>
</tr>
<tr>
<td>median (IQR)</td>
</tr>
<tr>
<td>ARV at entry to TAHOD</td>
</tr>
<tr>
<td>no ARV</td>
</tr>
<tr>
<td>mono/ dual ARV</td>
</tr>
<tr>
<td>HAART</td>
</tr>
</tbody>
</table>
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## Clinical and Implementation Research

### TAHOD: prior AIDS at entry (42%)

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Prior AIDS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>37.1</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>21.5</td>
</tr>
<tr>
<td>oesophageal candidiasis</td>
<td>7.3</td>
</tr>
<tr>
<td>cryptococcus/ extrapulmonary</td>
<td>4.5</td>
</tr>
<tr>
<td>toxoplasmosis</td>
<td>4.5</td>
</tr>
<tr>
<td>herpes simplex</td>
<td>4.2</td>
</tr>
<tr>
<td>cytomegalovirus retinitis</td>
<td>4.2</td>
</tr>
<tr>
<td>Salmonella septicemia</td>
<td>3.0</td>
</tr>
<tr>
<td>non-TB mycobacterial diseases</td>
<td>2.9</td>
</tr>
<tr>
<td>candidiasis/ bronchi, trachea, lung</td>
<td>2.6</td>
</tr>
<tr>
<td>HIV wasting syndrome</td>
<td>2.4</td>
</tr>
<tr>
<td>penicilliosis</td>
<td>1.5</td>
</tr>
<tr>
<td>cryptosporidiosis</td>
<td>1.0</td>
</tr>
<tr>
<td>cytomegalovirus</td>
<td>0.9</td>
</tr>
<tr>
<td>recurrent pneumonia</td>
<td>0.9</td>
</tr>
<tr>
<td>histoplasmosis</td>
<td>0.4</td>
</tr>
<tr>
<td>lymphoma/ Burkitt</td>
<td>0.2</td>
</tr>
<tr>
<td>lymphoma/ brain</td>
<td>0.2</td>
</tr>
<tr>
<td>isosporiasis</td>
<td>0.1</td>
</tr>
<tr>
<td>lymphoma/ immunoblastic</td>
<td>0.1</td>
</tr>
<tr>
<td>toxoplasmosis</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### TAHOD: rates of AIDS or death

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1710</td>
</tr>
<tr>
<td>Number with AIDS or death</td>
<td>91</td>
</tr>
<tr>
<td>Years of follow-up</td>
<td>1199</td>
</tr>
<tr>
<td>Event rates</td>
<td>7.6 per 100 person-years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>5.6</td>
</tr>
<tr>
<td>no</td>
<td>17.0</td>
</tr>
</tbody>
</table>
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TAHOD: summary

- overall response to HAART in terms of CD4 and HIV viral load in Asian patient populations is similar to that seen in western countries
- higher rates of clinical progression (new AIDS and/or death) among TAHOD patients compared to that seen in western countries
- similar predictors related to clinical progression
  - baseline CD4 count the most important predictor
  - other markers (e.g. hemoglobin) provide useful prognostic models when CD4 count unavailable

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