State-of-the-Science: Treatment as Prevention and/or Treatment for Treatment?

IAPAC London 2014

Reuben Granich, MD, MPH
Senior Advisor, Care and Treatment
UNAIDS
State-of-the-Science:
Treatment is prevention (not all of it but a lot of it):

Prevention of:
Illness, death, transmission, costs, loss of social capital, loss of human rights (fill in blank)

IAPAC London 2014

Reuben Granich, MD, MPH
Senior Advisor, Care and Treatment
UNAIDS
To end AIDS we will need to bridge the “innovation to scale” chasm.
UNAIDS treatment targets: getting to scale

- 90% tested
- 90% on treatment
- 90% virally suppressed
Ending AIDS as a major public health problem

Feasible:
“capable of being done or carried out”
--Merriam-Webster’s Dictionary
Bridging the chasm: can we scale innovations to get to 90-90-90?
Treatment works--Lazarus effect

...after 90 days of ARV treatment
Early treatment makes sense and works better

<table>
<thead>
<tr>
<th>Condition</th>
<th>Delayed</th>
<th>Immediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>34 (4%)</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>Serious bacterial infection</td>
<td>13 (1%)</td>
<td>20 (2%)</td>
</tr>
<tr>
<td>WHO Stage 4 event</td>
<td>19 (2%)</td>
<td>9 (1%)</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HIV-related encephalopathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Herpes simplex, chronic</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
<td>1</td>
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<tr>
<td>CNS Lymphoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HIV Wasting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Logrank p = 0.03

Grinsztejn et al (in review)
Unchecked viral replication impacts disease progression independent of CD4 count

Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort

- Cumulative exposure to replicating virus independently associated with mortality.
- Multivariable model (HR 1.44 per log10 copy-year/mL; 95% CI: 1.07–1.94).

Reekie et al. AIDS 2011

EURO SIDA

- Impact of VL on fatal and non-fatal AIDS-related and non-AIDS-related events.
- After adjustment, rates of non-AIDS events were 61% ($P=.001$) and 66% ($P=.004$) higher in those with VLs 500-9,999 and >10,000, respectively, than in those with VLs <500.
Scale matters: access to treatment has a dramatic impact on life expectancy.

World Bank life expectancy data

Slide courtesy D Birx, PEPFAR
Estimated annual AIDS deaths per 1000 people living with HIV
We can deliver services at scale in ways that respect and engage end-users: HIV testing
Scaling high viral suppression is feasible: population based data from Rwanda
HIV treatment reduces viral load and heterosexual transmission (2003)

Scaling treatment has an impact on community HIV transmission

BC Canada

Taiwan

San Francisco

Free ART

Wood et al. BMJ 2009;338b:1649
Fang et al. JAIDS 2004;190:879-85
Das et al. PlosOne 2010
Community scaling of ART coverage reduces individual risk of transmission: KZN South Africa

ART coverage of all HIV-infected individuals 2004-2011

Incidence falls by 1.1% (0.8%-1.4%) for each 1% increase in coverage

Tanser Science 2013; Williams 2013
Projected impact of scaling ART access suggests that it would save lives and costs.

Lives saved by CD4 treatment threshold compared to CD4<200:
- 5.5 million lives
- 3.9 million lives
- 2.0 million lives

Difference in costs by year compared to costs of CD4<200 current scenario:
- US$7.2 billion
- US$17.3 billion
- US$28.7 billion

Tracking 90-90-90 progress

90% tested
90% on treatment
90% virally suppressed
Are we on track to scale?

By end of 2013:

- ~52% of people living with HIV do not know their status
- ~22 million (63%) are not on treatment (76% for children)
- ~1.5 million deaths
- ~2.1 million new infections (5753 per day; 240 per hour)

Bottom line:

- Everyone living with HIV will need ART to survive
- Treatment expansion is part of solution to preventing illness, death, transmission, and costs.
Scaling treatment policy:
ART CD4 initiation criteria for asymptomatic people

94 published policies: 26 countries (27% HIV burden) are at <500 or above

August, 2014
Scaling viral load for ART monitoring (51 countries)

Source: MSF Issue Brief: Getting to Undetectable
Living with HIV

Know HIV status

On ART

Viral suppression

HIV treatment cascade for sub-Saharan Africa, 2012

Notes: No systematic data are available for the proportion of people living with HIV who are linked to care, although this is a vital step to ensuring viral suppression in the community.

Scaling the use of data for transparency, accountability, progress:
UNAIDS Treatment Situation Room

Real-time mapping local epidemiology, interventions and financing to monitor impact
Scale requires break from business as usual: More public domain mashups please

- 3/4 of the countries spend less than 26% of HIV budget on ART
- 1/2 spend less than 12% of HIV budget on ART

Williams, unpublished data, UNAIDS GARPR database 2014
Cities matter—scale requires focus:
Mashup to drive 90-90-90?

Spatial distribution of total community viral load by San Francisco Neighborhood, 2005-2008

Grant Colfax, HIV Prevention and Mapping Community Vital Load
Scaling innovations to end AIDS is feasible:

- Think big—set ambitious targets to realize potential
- We have the tools—scaling testing and treatment is fundamental to our response
- Scale by working with community to reach everyone living with HIV to prevent illness, death, transmission, costs…
- Global solidarity to finance scale up—focus resources to ensure efficiency and impact
- Scale data sharing and encourage wisdom of crowds—liberate the data and “just say no” to hoarding behavior
- Mind the Innovation Chasm—we will need to understand the behavioral economics to ensure that innovations can go to scale
Thank You

Views expressed in this presentation are those of the author and do not necessarily represent the views of the Joint United Nations Programme on HIV/AIDS (UNAIDS).
“Tear down that data wall”

- Findable
- Standardized
- Trustworthy
- Narrative (why was the data collected and why it matters)
Get the right people in the room with the right data...
ART for asymptomatic people living with HIV

- **≤200 cells/mm³**: Afghanistan, Bangladesh, Botswana, Burundi, Cambodia, Cameroon, Colombia, Costa Rica, El Salvador, Ethiopia, Ghana, Guinea, Haiti, India, Indonesia, Ireland, Kenya, Korea, Lesotho, Lithuania, Malawi, Malaysia, Mongolia, Morocco, Mozambique, Myanmar, Nepal, Nicaragua, Nigeria, Norway, Pakistan, Panama, Paraguay, Peru, Philippines, Portugal, Romania, Russia, Rwanda, South Africa, Switzerland, Thailand, Tunisia, Ukraine, United Kingdom, United States, Vietnam, Zambia, Zimbabwe.

- **≤350 cells/mm³**: Afghanistan, Bangladesh, Botswana, Burundi, Cambodia, Cameroon, Costa Rica, El Salvador, Ethiopia, Ghana, Guinea, Haiti, India, Indonesia, Ireland, Kenya, Korea, Lesotho, Lithuania, Malawi, Malaysia, Mongolia, Morocco, Mozambique, Myanmar, Nepal, Nicaragua, Nigeria, Norway, Pakistan, Panama, Paraguay, Peru, Philippines, Portugal, Romania, Russia, Rwanda, South Africa, Switzerland, Thailand, Tunisia, Ukraine, United Kingdom, United States, Vietnam, Zambia, Zimbabwe.

- **≤500 cells/mm³**: Afghanistan, Bangladesh, Botswana, Burundi, Cambodia, Cameroon, Costa Rica, El Salvador, Ethiopia, Ghana, Guinea, Haiti, India, Indonesia, Ireland, Kenya, Korea, Lesotho, Lithuania, Malawi, Malaysia, Mongolia, Morocco, Mozambique, Myanmar, Nepal, Nicaragua, Nigeria, Norway, Pakistan, Panama, Paraguay, Peru, Philippines, Portugal, Romania, Russia, Rwanda, South Africa, Switzerland, Thailand, Tunisia, Ukraine, United Kingdom, United States, Vietnam, Zambia, Zimbabwe.

**Source**: published policy
Time to CD4 cell count: South African women infected with sub-type C

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Mlisana CID 2014
Global solidarity has resulted in remarkable progress

- By end of 2013
  - New HIV infections are down by 38% since 2001
  - Over 12.9 million persons are on treatment for HIV
  - HIV deaths are down by 35% since 2005
  - We are on a trajectory to eliminate new HIV infections in children globally
Community based delivery can lead to high uptake of ART (83%)
Re-think delivery: SEARCH Uganda community trial of test and treat

**Approach: Multidisease “Community Health Campaign” HIV + other diseases**

**Principles:**
- community led
- high throughput
- health services for children/adults

**Findings:**
- Adults with HIV 8%
- Hypertension 12%
- Diabetes 3.5%

[Bar chart with CD4+ Count: 0-200 (80%), 201-350 (20%), >350 (80%)]

Chamie, PLOS Med, 2012
Treatment has a positive economic impact: healthy people go back to work
Shorten OODA loop

- **Observe**
  - Implicit Guidance & Control
  - Cultural Traditions
  - Genetic Heritage
  - Analyses & Synthesis
  - New Information
  - Previous Experience

- **Orient**
  - Implicit Guidance & Control
  - Unfolding Interaction With Environment
  - Feedback

- **Decide**
  - Implicit Guidance & Control
  - Decision (Hypothesis)
  - Feedback

- **Act**
  - Feed Forward
  - Action (Test)
  - Unfolding Interaction With Environment

increase anti-fragility
“Kahneman Gamble”

We cannot predict your viral load or how long before you become ill from HIV. We do know that there are some downsides of waiting and for starting ART. At what level of cumulative risk of adverse outcomes of AIDS, serious non-AIDS or death would you want to start ART? At what point would adverse drug risks outweigh the risk of illness from HIV?

- 1% risk of AIDS, serious non-AIDS or death;
- 5% risk of AIDS, serious non-AIDS or death
- 10% risk of AIDS, serious non-AIDS or death
- Over 10% risk of AIDS, serious non-AIDS or death
Significant cumulative risk?

Risk of AIDS, serious non-AIDS or death (Anglaret 2012)

Fitted risk of event to CD4 data

Adverse events:

- <200 38%
- <350 21%
- <500 15%
- <950 2%

Anglaret, et al, CID 2012; Williams, Archives 2013
Mash-up to drive implementation and health outcomes: 90-90-90

Rates of people living with HIV or AIDS diagnosis by zip code, New York City 2011

WHO 2013 Guidelines
Using new science to optimize TasP

• Earlier Initiation of ART (CD4 ≤ 500):
  – Strategic use to maximize treatment & prevention benefits
  – Symptomatic and CD4 ≤ 350 as a priority
  – CD4-independent situations for ART initiation:
    • TB-HIV and HBV-HIV
    • pregnant women (*Option B+*)
    • sero-discordant couples
    • children < 5 years of age
• No specific recommendations for key populations
Conceptual diagram of CD4+ response on ART: starting later translates in lower CD4 levels (and higher risk)

5-7 YEARS

Le Moing et al. HIV Med 2007;8:156.


Countries with studies on TasP for PWID

Dark blue represents countries where 15-25% of IDUs are living with HIV (2011); pink represents countries where >25% of IDUs are living with HIV (2011) and the red dots represent countries conducting research.
Higher mortality for mothers in Zimbabwe even when their CD4 cell counts are at higher level (ZIVTAMBO study)


Data: Hargrove AIDS 2010; Model: Williams JID 2006
**Risk of non-AIDS morbidity and mortality**

- HIV may be associated with serious non-AIDS defining events
  - Cardiovascular
  - Renal
  - Liver
  - Non-AIDS malignancies

- At higher CD4 counts non-AIDS events are much more common than AIDS events

- Does ART use reduce risk of some serious non-AIDS events?

Slide courtesy of A Phillips
CD4 highly variable in HIV-negative people

Mean (95%) Range (95%)

Ethiopia Guinea Bissau Nigeria S. Africa Tanzania Uganda Zambia Botswana

Williams et al. J Infect Dis. 2006; 194: 1450-8; Bussman et al. Clinical and Diagnostic Laboratory Immunology 2004
Likelihood of achieving normal CD4+ cell count on ART depends on baseline level

Johns Hopkins HIV Clinical Cohort

ATHENA National Cohort

University of Chicago Press. All rights reserved. http://www.journals.uchicago.edu/toc/cid/current.
ART reduces sexual transmission of HIV: meta-analysis shows no transmission <400 copies per ml

Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas

Note. Data have been adjusted for reporting delays and missing risk-factor information.
Impact of ART: Significant Decrease in Mother-to-Child Transmission of HIV since 2010

Progress needed to reach virtual elimination of MTCT by 2015
Current Trajectory

UNAIDS Global Report 2012
Ongoing and planned TasP studies: feasibility, impact and key populations

- Countries in blue are high HIV incidence countries (2011)
- Red dots represent countries with ongoing/planned research on early ART and the yellow dots represent countries with research on combination HIV prevention strategies
ART as prevention

- Testing and ART impacts HIV incidence and survival
- Elimination is feasible

Granich, Gilks, Dye, De Cock, Williams *Lancet* 2008
Available funding and costs:
We appear to be in the right ball park....

Blue: 17% global funding (UNAIDS)
Brown: 17% projected funding (UNAIDS)
Green: Universal testing + immediate ART
Red: <350 with universal voluntary testing

UNAIDS. Financial resources required to achieve universal access to HIV prevention, treatment, care and support.
ART policy vs. funding conundrum

Can we afford to shift policy to provide earlier ART?

Can we afford not to?
WHO 2013 Guidelines
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  – Strategic use to maximize treatment & prevention benefits
  – Symptomatic and CD4 ≤ 350 as a priority
  – CD4-independent situations for ART initiation:
    • TB-HIV and HBV-HIV
    • pregnant women (*Option B*++)
    • sero-discordant couples
    • children < 5 years of age
• No specific recommendations for key populations
Rapid transitioning to Option B+

Early 2013

Legend
- Green: Actively implementing or phased roll-out underway
- Light green: MOH endorsed, preparing for roll-out
- Yellow: Operational planning, piloting, or costing underway
- Red: Considering B+
- Dark red: No immediate plans to implement B+

Source: PEPFAR PMTCT/Pediatrics TWG, Updated February 28, 2013

Figure 1: Patients newly initiated on ART and total ART clinic registrations per quarter

Total ART clinic registrations include patients who transferred between sites. This results in double counting of patients at the national level. For 'patients newly initiated on ART' every patient is only counted once.

Option B+: early 2013

Slide courtesy of CDC
However beautiful the strategy, you should occasionally look at the results

--Winston Churchill
Resources available for HIV in low- and middle-income countries, 2002–2012 and 2015 target*


Source: UNAIDS estimates.
Re-think how we spend the money
Re-think focus:
eMTCT, Testing. ART, VMMC
Re-think targets: *programmatic tipping point*: on treatment equals new infections
Re-think when to start ART: test and treat for key populations or everyone?

Over a 5 year period, a 5.2% increase in costs* would result in 12.7% additional deaths averted and a 28.4% decrease in new infections**

<table>
<thead>
<tr>
<th>Years</th>
<th>Deaths averted</th>
<th>Current Strategy</th>
<th>CD4 500 + Test-treat KP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>8,500</td>
<td>9,000</td>
<td>10,000</td>
</tr>
<tr>
<td>2014</td>
<td>9,000</td>
<td>9,500</td>
<td>10,500</td>
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<tr>
<td>2015</td>
<td>10,000</td>
<td>10,500</td>
<td>11,500</td>
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<tr>
<td>2016</td>
<td>11,500</td>
<td>12,000</td>
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<tr>
<td>2017</td>
<td>12,500</td>
<td>13,000</td>
<td>13,500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of new infections</th>
<th>Current Strategy</th>
<th>CD4 500 + Test-treat KP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>7,000</td>
<td>6,500</td>
<td>6,000</td>
</tr>
<tr>
<td>2014</td>
<td>6,000</td>
<td>5,500</td>
<td>5,000</td>
</tr>
<tr>
<td>2015</td>
<td>5,000</td>
<td>4,500</td>
<td>4,000</td>
</tr>
<tr>
<td>2016</td>
<td>4,000</td>
<td>3,500</td>
<td>3,000</td>
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<tr>
<td>2017</td>
<td>3,000</td>
<td>2,500</td>
<td>2,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years</th>
<th>Total costs difference between current strategy and proposed best case scenario</th>
<th>Current Strategy</th>
<th>CD4 500 + Test-treat KP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>$30</td>
<td>$40</td>
<td>$50</td>
</tr>
<tr>
<td>2014</td>
<td>$40</td>
<td>$50</td>
<td>$60</td>
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<tr>
<td>2015</td>
<td>$50</td>
<td>$60</td>
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<tr>
<td>2016</td>
<td>$60</td>
<td>$70</td>
<td>$80</td>
</tr>
<tr>
<td>2017</td>
<td>$70</td>
<td>$80</td>
<td>$90</td>
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</tbody>
</table>

Investing an additional 12.7M $ would result in
6,391 deaths averted and
7,586 fewer new infections

- Additional costs may be underestimated as current resources were assumed to be able to absorb the new ART and pre-ART patients. *
- * EPI impact calculated with Spectrum, with conservative assumptions
Re-think delivery: SEARCH Uganda community trial of test and treat

Approach: Multidisease “Community Health Campaign” HIV + other diseases

Principles:
- community led
- high throughput
- health services for children/adults

Findings:
- Adults with HIV 8%
- Hypertension 12%
- Diabetes 3.5%

Chamie, PLOS Med, 2012
Re-think strategy for “concentrated epidemics” and key populations

Annual new HIV infection

Annual AIDS death

ART and HTC cost

Periodic testing and immediate treatment (PTIT)

Kato M et al. Unpublished data
Re-think M and E strategy: the OODA Loop

Speed matters...and our feedback loop is slow
Fail fast vs. global consensus
Conclusion

• Prevention matters—combination will be required
• Treatment prevents illness, death, transmission
• Global testing and treatment scale-up plan with practical measurable milestones (think end game)
• Speed—slow scale up is not an option for millions, remove complexity and barriers to access
• Innovation—community delivery, consider standardized franchise model
• People first, community engagement
Public health is purchasable. Within a few natural and important limitations any community can determine its own health.

--Hermann M. Biggs
(29 Sep 1859 - 28 Jun 1923)
New York City's Public Health Officer and public health pioneer
Policy matters
PARTNERS Study: CROI 2014

• 16,400 occasions of sex in the gay men and 28,000 in the heterosexuals

• Zero transmissions within couples from a partner with an undetectable viral load

• Upper bounds of confidence intervals suggest that risk is not zero

Press conference at CROI 2014.
Photo by Liz Highleyman, hivandhepatitis.com

Significantly higher employment at CD4≥500 among adults

- Compared to CD4<200, CD4≥500 associated with
  - 5.8 more days/month
  - 2.2 more hours/day (40% more than ref. mean of 5.5)

<table>
<thead>
<tr>
<th>Regression model coefficients</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome:</strong></td>
<td><strong>Days worked in the past month</strong></td>
<td><strong>Hours worked on usual day in past</strong></td>
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<tr>
<td>CD4&lt;200</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>CD4 200-349</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>CD4 350-499</td>
<td>4.8</td>
<td>0.9</td>
</tr>
<tr>
<td>CD4 ≥500</td>
<td>5.8**</td>
<td>2.2*</td>
</tr>
<tr>
<td>Observations</td>
<td>107</td>
<td>107</td>
</tr>
</tbody>
</table>

- Linear regression model with age, age-squared, and sex included as controls
- ** p<0.05, * p<0.10
- Reference group has CD4<200

Those with CD4≥500 worked nearly 1 week/month more than those with CD4<200, and as much as HIV-uninfected adults

Thirumurthy, Health Affairs, 2012
REVIEW OF HIV/AIDS, TUBERCULOSIS AND MALARIA LANDSCAPE
FOR THE GLOBAL FUND STRATEGY 2012-2016

Exhibit 5: HIV/AIDS – Likelihood and impact of new interventions

<table>
<thead>
<tr>
<th>Type</th>
<th>Existing</th>
<th>Anticipated</th>
<th>Timing</th>
<th>Likelihood</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>N/A</td>
<td>RV144, HVTN 505</td>
<td>2020+</td>
<td></td>
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<tr>
<td>Prevention</td>
<td>Condoms, Male Circumcision</td>
<td>Treatment as Prevention (discordant couples)</td>
<td>2011</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Oral PReP (for MSMs)</td>
<td>2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male circumcision devices</td>
<td>2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatments</td>
<td>ARV</td>
<td>Treatment 2.0</td>
<td>2011</td>
<td></td>
<td></td>
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<tr>
<td>Diagnostics</td>
<td>CD4, viral load</td>
<td>Point of care</td>
<td>2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Couples testing</td>
<td>2011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Projected incident cases (M)
Projected deaths (M)

HIV in South Africa: test and treat starting in 1995

Accountability and the dreaded retrospectoscope

Williams 2010
HIV control: challenges

- Political will—leadership and funding
  - “Coordination”—simplify current complexity
- Scale-up plan with practical measurable milestones
- Focus—prioritize interventions, geography/people
- Speed—slow scale up is not an option for millions
- Innovation—private sector, community delivery, franchise model
- Delivery—standardized approach, clear practical guidelines, people first, community engagement
- Robust supply chain, simplify commodities
- Better M and E and surveillance
CD4 Count Profile of Cohort and TB Risk

- 1000 cells/ul
- TB rate = 1.5/100pys

- 500 cells/ul
- TB rate >4.2-5.5/100pys

- 200 cells/ul
- TB rate 9.3-16.8/100pys

Duration of ART (months)

Percentage of patients with CD4 below contour

Slide courtesy of Steve Lawn
Positive but low correlation between GDP per capita and ART eligibility criteria for asymptomatic people
Numbers of people living with HIV, new HIV infections, and AIDS deaths, 2001-2012

NEW HIV INFECTIONS, GLOBAL, 2001–2012

PEOPLE LIVING WITH HIV, GLOBAL, 2001–2012

AIDS DEATHS, GLOBAL, 2001–2012

New infections

People living with HIV

Deaths
Ghana: As HIV treatment coverage rose, new HIV infections and AIDS-related deaths fell, 2005-2012

*Coverage is based on the 2006 and 2010 WHO guidelines.*
Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas

Note. Data have been adjusted for reporting delays and missing risk-factor information.
2000 subjects (500 per site)  
Thailand, Uganda, Kenya, Tanzania

Mean # timepoints before peak = 4 (range: 3-6)  
Mean # timepoints after peak = 8 (range: 6-11)
When to start ART?  
A matter of perspective

1-4 years earlier significant period

1-4 years earlier now appears like a short period

Slide adapted from Julio Montaner
When to start?

- **Advantages:**
  - Reduces mortality and extends lifespan
  - Prevents AIDS-related events and OIs
  - Reduces non-AIDS related events
  - Improves immune function
  - Reduces transmission

- **Disadvantages:**
  - Does not cure HIV
  - Side effects and toxicity
  - Pill burden/quality of life
  - Lifelong adherence
  - Resistance may develop
  - Cost ($$) – for drugs and for monitoring

Slide courtesy of D. Riedel
Morbidity prevention:
Providing ART decreases the risk of TB by 65% across all CD4 levels

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>ART</th>
<th></th>
<th>Control</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TB cases</td>
<td>PY at risk</td>
<td>TB cases</td>
<td>PY at risk</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>All baseline CD4 counts</td>
<td>9</td>
<td>375.1</td>
<td>82</td>
<td>848.2</td>
<td>0.19 (0.09 - 0.38)</td>
</tr>
<tr>
<td>Badri (2002)</td>
<td>17</td>
<td>1661.9</td>
<td>33</td>
<td>1641.8</td>
<td>0.51 (0.28 - 0.91)</td>
</tr>
<tr>
<td>Cohen (2011)</td>
<td>221</td>
<td>11627</td>
<td>155</td>
<td>3865</td>
<td>0.41 (0.31 - 0.54)</td>
</tr>
<tr>
<td>Golub (2009)</td>
<td>44</td>
<td>952</td>
<td>200</td>
<td>2815</td>
<td>0.36 (0.25 - 0.51)</td>
</tr>
<tr>
<td>Golub (2009)</td>
<td>6</td>
<td>162.6</td>
<td>9</td>
<td>80.9</td>
<td>0.11 (0.03 - 0.48)</td>
</tr>
<tr>
<td>Jerene (2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10 (0.02 - 0.45)</td>
</tr>
<tr>
<td>Lannoy (2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.20 (0.10 - 0.60)</td>
</tr>
<tr>
<td>Miranda (2007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33 (0.11 - 0.94)</td>
</tr>
<tr>
<td>Samandari (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.19 (0.03 - 1.09)</td>
</tr>
<tr>
<td>Santoro-Lopes (2002)</td>
<td>1</td>
<td></td>
<td>42</td>
<td></td>
<td>0.50 (0.28 - 0.83)</td>
</tr>
<tr>
<td>Severe (2010)</td>
<td>18</td>
<td></td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhou (2009)</td>
<td>57</td>
<td>5186</td>
<td>40</td>
<td>985</td>
<td>0.40 (0.26 - 0.61)</td>
</tr>
<tr>
<td><strong>All studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.35 (0.28 - 0.44)</strong></td>
</tr>
</tbody>
</table>

Effect: Z = 9.19, p < 0.001; Heterogeneity: I² = 31% (22% - 44%), p = 0.154

*Suthar et al 2012, Plos Med*
When to start ART…or how late is too late?

**Observational data**

### Risk of Death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Oparil 2002</td>
<td>0.20 [0.07, 0.55]</td>
<td>0.20 [0.07, 0.55]</td>
</tr>
<tr>
<td>Plettenberg 2011</td>
<td>0.27 [0.06, 1.23]</td>
<td>0.27 [0.06, 1.23]</td>
</tr>
<tr>
<td>Gallant 2011</td>
<td>0.48 [0.10, 2.27]</td>
<td>0.48 [0.10, 2.27]</td>
</tr>
<tr>
<td>CASCADE 2011</td>
<td>0.51 [0.33, 0.79]</td>
<td>0.51 [0.33, 0.79]</td>
</tr>
<tr>
<td>HIV CAUSAL Coll 2010</td>
<td>0.55 [0.41, 0.74]</td>
<td>0.55 [0.41, 0.74]</td>
</tr>
<tr>
<td>ART Cohort Coll 2003</td>
<td>0.56 [0.30, 1.05]</td>
<td>0.56 [0.30, 1.05]</td>
</tr>
<tr>
<td>Kitahata 2009</td>
<td>0.59 [0.44, 0.79]</td>
<td>0.59 [0.44, 0.79]</td>
</tr>
<tr>
<td>Egger 2002</td>
<td>0.61 [0.36, 1.05]</td>
<td>0.61 [0.36, 1.05]</td>
</tr>
<tr>
<td>Palella 2003</td>
<td>0.70 [0.13, 3.85]</td>
<td>0.70 [0.13, 3.85]</td>
</tr>
<tr>
<td>Phillips 2001</td>
<td>0.71 [0.35, 1.43]</td>
<td>0.71 [0.35, 1.43]</td>
</tr>
<tr>
<td>ART Cohort Coll 2009</td>
<td>0.84 [0.65, 1.08]</td>
<td>0.84 [0.65, 1.08]</td>
</tr>
<tr>
<td>Sterne 2009 (1)</td>
<td>0.89 [0.63, 1.25]</td>
<td>0.89 [0.63, 1.25]</td>
</tr>
<tr>
<td>HIV CAUSAL 2011</td>
<td>0.99 [0.72, 1.37]</td>
<td>0.99 [0.72, 1.37]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.66 [0.55, 0.79]</td>
<td>0.66 [0.55, 0.79]</td>
</tr>
</tbody>
</table>

### Risk of Progression to AIDS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>ART Cohort Coll 2003</td>
<td>0.61 [0.42, 0.88]</td>
<td>0.61 [0.42, 0.88]</td>
</tr>
<tr>
<td>CASCADE 2011</td>
<td>0.75 [0.49, 1.14]</td>
<td>0.75 [0.49, 1.14]</td>
</tr>
<tr>
<td>Egger 2002</td>
<td>0.75 [0.55, 1.02]</td>
<td>0.75 [0.55, 1.02]</td>
</tr>
<tr>
<td>Garcia 2004</td>
<td>0.44 [0.14, 1.42]</td>
<td>0.44 [0.14, 1.42]</td>
</tr>
<tr>
<td>HIV CAUSAL 2011</td>
<td>0.72 [0.60, 0.88]</td>
<td>0.72 [0.60, 0.88]</td>
</tr>
<tr>
<td>Merito 2006</td>
<td>0.78 [0.38, 1.61]</td>
<td>0.78 [0.38, 1.61]</td>
</tr>
<tr>
<td>Opravil 2002</td>
<td>0.28 [0.12, 0.67]</td>
<td>0.28 [0.12, 0.67]</td>
</tr>
<tr>
<td>Phillips 2001</td>
<td>0.79 [0.50, 1.24]</td>
<td>0.79 [0.50, 1.24]</td>
</tr>
<tr>
<td>Sterne 2009 (1)</td>
<td>0.78 [0.64, 0.96]</td>
<td>0.78 [0.64, 0.96]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.72 [0.65, 0.81]</td>
<td>0.72 [0.65, 0.81]</td>
</tr>
</tbody>
</table>
When to start?

• **Advantages:**
  - Reduces mortality and extends lifespan
  - Prevents AIDS-related events and OIs
  - Reduces non-AIDS related events
  - Improves immune function
  - Reduces transmission

• **Disadvantages:**
  - Does not cure HIV
  - Side effects and toxicity
  - Pill burden/quality of life
  - Lifelong adherence
  - Resistance may develop
  - Cost ($$) – for drugs and for monitoring

Slide courtesy of D. Riedel
Campaigns against Guinea Worm

Guinea worm eradication

[Images of water being poured, people carrying water, and a jar containing Guinea worms]
Campaigns against preventable blindness

Preventable blindness
ART addresses all parts of classic infectious disease triangle

Host

Pathogen

Environment
Timeline on projects with early ART (≥500)

Randomized trials

- HPTN 071 PopART
- SEARCH - Sustainable East Africa Research for Community Health
- START - Strategic Timing of Antiretroviral Treatment
- ANRS 12249 TasP - Impact of Immediate Versus South African Recommendations Guided ART Initiation on HIV Incidence
- ANRS TEMPRANO - Early ART and/or IPT against TB in HIV-infected adults

Implementation/observational studies

- MaxART –TasP Implementation Study (Planned)
- TasP Approaches in Shiselweni, Swaziland
- EARLI - Early HIV Therapy in Patients With High CD4 Cell Counts
- MSF Treatment as Prevention KwaZulu-Natal, South Africa
Countries with studies on early ART (≥ 500)

Red dots represent the countries with research on early ART.
Time from HIV seroconversion to CD4 <500 is median of 1.2 years

CASCADE: Lodi et al, CID 2011

Median year (95% CI):
< 500: 1.19 (1.12-1.26)
<350: 4.19 (4.09-4.28)
<200: 7.93 (7.76-8.09)
Estimated annual AIDS deaths per 1000 people living with HIV
Scenarios of ARV eligibility: WHO vision

Source: WHO 2014
Early ART for asymptomatic people living with HIV

- **≤200 cells/mm³**: Countries such as Afghanistan, Brazil, and China.
- **200-350 cells/mm³**: Countries like India, Pakistan, and Russia.
- **≤350 cells/mm³**: Countries such as Argentina, Australia, and Brazil.
- **>500 cells/mm³**: Countries like Italy, Japan, and South Korea.
- **Irrespective of CD4 count**: Countries such as France, Germany, and Spain.

Source: published policy
Malawi: each cohort is doing better than the last

**Figure 6:** Group cohort survival analysis: Proportion of patients retained alive on ART 12, 24, 36, 48, 60, 72, 84 and 96 months after ART initiation
Mapping local epidemiology, interventions and financing to monitor impact
Coverage of ART among eligible people living with HIV
Kenya (2007 KAIS)

Among those who knew status and were eligible 92% were on ART
Community studies suggest population-level impact of ART

BC Canada

Taiwan

San Francisco

Free ART

Wood et al. BMJ 2009;338b:1649
Fang et al. JAIDS 2004;190:879-85
Das et al.
Mean CD4 is highly variable across populations.

CD4 levels recorded among HIV-negative people

Smallpox eradication 1796 to 1977: Edward Jenner to Merca Town, Somalia
HPTN 052 Results

**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/mm³ and VL >50,000 copies/ml at transmission
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

p < 0.001

Cohen NEJM 2011
Bridging the chasm: can we scale to 90-90-90?

- Science
- Policy
- Technology
- Service delivery
- Getting into the cloud and crowd sourcing data
- Community and behavioral economics
Over 7 day period more than 47,000 (80%) of the 15-49 population attended the campaign and 41,040 were tested for HIV. Over 18,000 men received an HIV test.
PARTNERS Study: CROI 2014

• 16,400 occasions of sex in the gay men and 28,000 in the heterosexuals

• Zero transmissions within couples from a partner with an undetectable viral load

• Upper bounds of confidence intervals suggest that risk is not zero