Scaling Up ART in Resource-limited Settings

Can we get to 15 million by 2015?

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Medical Epidemiologist
Division of Global HIV/AIDS (DGHA)
U.S. Centers for Disease Control and Prevention (CDC)
Outline

- ART Scale-up: Success, Challenges, and Targets.
- Importance of ART Scale-up for Prevention
- What strategic choices can be made?
  - When to start?
  - How to increase access?
  - ART efficiencies?
Outline

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8 million on ART by end 2011

...15 million by 2015 seems achievable
Progress of estimated ART coverage in low- and middle-income countries (2003-2010)

Estimated gap: patients eligible for ART (by current WHO guidelines) but not yet on ART

Patients receiving ART

WHO, 2011
Disparities in ART coverage between regions and populations

* 2010 HIV case reporting (18 countries)
“Last month, world leaders at the United Nations General Assembly Meeting on AIDS called for providing ART for 15 million people in low- and middle-income countries by 2015, an increase from the 6.6 million currently receiving therapy, plus additional efforts toward universal access to HIV prevention, treatment, and care. An estimated $22 billion to $23 billion annually will be needed by 2015; current spending is approximately $16 billion.”

- A.S. Fauci, Science July 1, 2011
PEPFAR Funding Realities

- **FY 2006**: $2,654
- **FY 2007**: $3,699
- **FY 2008**: $5,028
- **FY 2009**: $5,503
- **FY 2010**: $5,542
- **FY 2011 CR (Notional)**: $5,542

<table>
<thead>
<tr>
<th>Year</th>
<th>Bilateral Funding</th>
<th>Global Fund</th>
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<tr>
<td>FY 2006</td>
<td>$2,654</td>
<td>$545</td>
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<tr>
<td>FY 2007</td>
<td>$3,699</td>
<td>$724</td>
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<tr>
<td>FY 2008</td>
<td>$5,028</td>
<td>$840</td>
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<tr>
<td>FY 2009</td>
<td>$5,503</td>
<td>$1,000</td>
</tr>
<tr>
<td>FY 2010</td>
<td>$5,542</td>
<td>$1,050</td>
</tr>
<tr>
<td>FY 2011 CR (Notional)</td>
<td>$5,542</td>
<td>$1,050</td>
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</table>
The Grand Challenge: Can we treat 15 million HIV-infected patients for the cost of treating 8 million?
• ART Scale-up: Success, Challenges, and Targets.

• Importance of ART Scale-up for Prevention

• What strategic choices can be made?
  - When to start?
  - How to increase access?
  - ART efficiencies?
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D.,
Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D.,
Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D.,
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Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D.,
Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch.,
Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D.,
Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D.,
David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*
Randomized clinical trial, early vs. delayed ART

13 sites in 9 countries (5 African), enrollment 2007-2010

1763 discordant couples enrolled

HIV-infected members with $350 < \text{CD4} < 550$

Randomized to early or deferred arm:

- Early: ART started immediately
- Deferred: ART started at $\text{CD4} \leq 250$ or if clinically indicated

39 HIV transmissions observed (28 phylogenetically linked)

Analyzed HIV incidence, by randomized early and delayed ART arms and transmissions linked to the infected partner
### Table 2. Incidence of Partner-Linked and Any HIV-1 Transmission and Clinical and Composite Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Therapy</th>
<th>Delayed Therapy</th>
<th>Hazard or Rate Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Person-yr</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td><strong>Linked transmission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>1585.3</td>
<td>0.1 (0.0–0.4)</td>
</tr>
<tr>
<td>1 yr</td>
<td>1</td>
<td>819.0</td>
<td>0.1 (0.0–0.7)</td>
</tr>
<tr>
<td>2–3 yr</td>
<td>0</td>
<td>686.5</td>
<td>0.0 (0.0–0.5)</td>
</tr>
<tr>
<td>&gt;3 yr</td>
<td>0</td>
<td>79.9</td>
<td>0.0 (0.0–4.6)</td>
</tr>
<tr>
<td><strong>Any transmission‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>1585.3</td>
<td>0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>1 yr</td>
<td>2</td>
<td>819.0</td>
<td>0.2 (0.0–0.9)</td>
</tr>
<tr>
<td>2–3 yr</td>
<td>2</td>
<td>686.5</td>
<td>0.3 (0.0–1.1)</td>
</tr>
<tr>
<td>&gt;3 yr</td>
<td>0</td>
<td>79.9</td>
<td>0.0 (0.0–4.6)</td>
</tr>
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</table>

Scale-up of ART, number of AIDS deaths and new HIV infections in LMIC*, 2001–2011

* LMIC = Low- and middle-income countries
Effect of ART coverage on rate of new HIV infections in a rural South African population

For every 10% increase in coverage there is a 17% decrease in individual risk

Source: Tanser F et al. CROI 2012
• ART Scale-up: Success, Challenges, and Targets.

• Importance of ART Scale-up for Prevention

• What strategic choices can be made?
  - When to start?
  - How to increase access?
  - ART efficiencies?
ART eligibility: 5 policy scenarios

Estimated millions of people eligible for ART in LMIC in 2011

1. CD4 ≤ 200
   - Recommended Since 2003

2. CD4 ≤ 350
   - Recommended since 2010

3. CD4 ≤ 350 + TasP
   - Incremental approach 2012

4. CD4 ≤ 500
   - Ongoing systematic review of evidence (GRADE review)

5. All HIV+
   - “Test and treat”

ART regardless of CD4 count for:
- Serodiscordant couples
- Pregnant women
- Key populations (SW, IDU, MSM)

11 15 23 25 32
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   “Test and treat”

ART regardless of CD4 count for:
- Serodiscordant couples
- Pregnant women
- Key populations (SW, IDU, MSM)
- Treatment of High Viral Load

11 15 23 25 32
Several countries are implementing or considering PMTCT Option B+ in Sub-Saharan Africa...

<table>
<thead>
<tr>
<th>Country</th>
<th>Current Option</th>
<th>Transition Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi</td>
<td>B+</td>
<td>Currently implementing B+ at national level. Revised treatment guidelines were approved in July 2011 and implementation began in September 2011.</td>
</tr>
<tr>
<td>Kenya</td>
<td>Mixed</td>
<td>Phased roll out of B+ beginning with high volume facilities. Most (60%) of the country receives Option A, with 40% receiving Option B. Revised PMTCT include B+, with a goal of 50% of HIV+ pregnant women on ART by Dec 2012.</td>
</tr>
<tr>
<td>Rwanda</td>
<td>B+</td>
<td>Will begin implementing Option B+ in July 2012; already treating all pregnant women CD4&lt;500.</td>
</tr>
<tr>
<td>Uganda</td>
<td>Mixed</td>
<td>Will conduct a phased rollout of B+ over a 14 month period, beginning in regions with high HIV prevalence. Aim is to transition all sites by March 2013.</td>
</tr>
<tr>
<td>Haiti</td>
<td>B</td>
<td>MOH is considering transition to Option B+ in 2012.</td>
</tr>
<tr>
<td>Namibia</td>
<td>A</td>
<td>Has had preliminary discussions about B/B+ and will be conducting a cost and benefit/feasibility analysis, although no timeframe has been set.</td>
</tr>
<tr>
<td>Zambia</td>
<td>A+ (treatment of discordant couples)</td>
<td>TWG recommended transition to B/B+ in early 2010, but has not been implemented due to lack of funding and HR challenges.</td>
</tr>
<tr>
<td>Mozambique</td>
<td>A</td>
<td>MOH endorsed piloting B+ at 241 PEPFAR PMTCT facilities with ART facilities if ARV availability can be secured.</td>
</tr>
<tr>
<td>Swaziland</td>
<td>A</td>
<td>B+ pilot studies planned; Discussions of a phased implementation are ongoing.</td>
</tr>
<tr>
<td>Cameroon</td>
<td>A</td>
<td>Planned pilot of B+ in 2 districts.</td>
</tr>
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</table>
Significant variation in ART eligibility thresholds among countries

<table>
<thead>
<tr>
<th>CD4 count for ART initiation</th>
<th>≤200-350</th>
<th>≤300</th>
<th>≤350</th>
<th>≤350 + TasP</th>
<th>≤500</th>
<th>≤500 + TasP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of countries</td>
<td>1</td>
<td>1</td>
<td>43</td>
<td>12</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Results of a WHO survey (2011, n= 61 countries)
Mean CD4 count at ART initiation is below 200 in LMIC

Source: Egger M. CROI 2012

Estimates from random-effects model adjusted for age, sex and year of starting ART, 2002-2009
Provider-initiated testing and counseling (PITC) in Africa

- 42/53 countries in Africa have PITC policies\(^1\)
- High PITC acceptance by ANC\(^2\) & TB patients\(^3,4\)
- Most clinical settings in generalized epidemics not routinely offering HIV testing\(^5\)

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Scaling up HIV testing in the community

- Home-based (door-to-door)

- Campaigns plus
  - HTC-plus – malaria, TB
  - Non-communicable diseases

- Mobile outreach
  - General populations
  - Key populations
  - Work Places and Schools
High Uptake of Home-Based HTC in Kwa-Zulu Natal South Africa (CROI 2012)

- 282 households
- 743 adults in HH
- 673 (91%) accepted survey + HTC
- 203 (30%) HIV-infected
- 74 (37%) of 203 first diagnoses
- Median CD4 425/uL
The test-treat-retain cascade

Create demand for testing and treatment

Testing

Pre-ART care and support

ART eligible

ART

Adherence and viral suppression
ART optimization approaches

SHORT TERM  
Next 1-2 years

Improve currently available drugs and formulations

- Once daily FDC for 1st line (e.g., TDF/3TC/EFV)
- Heat stable once-daily boosted PI options for 2nd line (e.g., ATV/r)
- Solid pediatric formulations (sprinkles, dispersible tablets)

MEDIUM TERM  
Next 2-5 years

Add new drugs/better sequencing

- Replacement of regimen components by new drugs/classes (e.g., integrase inhibitors, NRTI pro-drugs, entry blockers)

LONG TERM  
Next 5-10 years

Use new strategies

- New therapeutic approaches (e.g., induction/maintenance, co-therapies, anti-latency drugs)

SHORT TERM  
Next 1-2 years

Improve currently available drugs and formulations
## Potential cost benefits of optimizing ARVs

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>Optimization methods</th>
<th>Present cost in USD (per patient/year)</th>
<th>Expected cost in USD (per patient/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>Process chemistry and dose optimization</td>
<td>87</td>
<td>63 ((\downarrow) 28%)</td>
</tr>
<tr>
<td>AZT</td>
<td>Dose optimization</td>
<td>89</td>
<td>60 ((\downarrow) 33%)</td>
</tr>
<tr>
<td>EFV</td>
<td>Reformulation and dose optimization</td>
<td>63</td>
<td>31 ((\downarrow) 51%)</td>
</tr>
<tr>
<td>ATV/r</td>
<td>Process chemistry and reformulation</td>
<td>355</td>
<td>125 ((\downarrow) 65%)</td>
</tr>
<tr>
<td>DRV/r</td>
<td>Process chemistry dose optimization and reformulation</td>
<td>835</td>
<td>335 ((\downarrow) 60%)</td>
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Adapted from Crawford et al, 2012
Ongoing Clinical Trials

- **Evaluation of Novel Concepts in Optimization of antiretroviral Efficiency (ENCORE)**
  - ENCORE 1 = Reduced-dose efavirenz
    - Will be fully enrolled by end of March, 2012.
  - ENCORE 2 = Reduced-dose lamivudine
    - Completed; 150 mg per day ≠ 300 mg/day
  - ENCORE 3 = Reduced-dose lopinavir/ritonavir
    - Completed; 200/50 mg BID ≠ 400/100 mg BID
- Others:
  - Reduced dose ZDV pilot (Cameroon) enrolling
  - Reduced dose d4T vs. TDF first patient enrollment anticipated for late April in South Africa
Breakthroughs in diagnostic testing and patient monitoring at point-of-care

- Point-of-care CD4 is just emerging
  - 3 products available and 1 prequalified
- Point-of-care testing for VL and EID is imminent
- Affordability is key
Summary (1)

• Global progress on scale-up of ART has been extraordinary. Current trends in scale-up suggest that 15 million is possible

• Further scale-up must address disparities and inequities (countries, key populations)

• ART funding gap is a significant barrier: we need to do more with less

• With new evidence and new policies, the number of persons eligible for ART will increase
Summary (2)

• To reach targets, innovative HIV testing strategies will be needed, combined with effective linkage to and retention in care.

• ART optimization (dose reductions, cheaper formulations) may be a mechanism to continue scale-up in a challenging economic environment.

• Use of point of care Technologies may facilitate faster enrollment of ART-eligible persons (POC CD4) and easier treatment monitoring (POC viral load).

• ARVs for treatment and prevention are a powerful tool towards ending the HIV epidemic.
# Acknowledgements

<table>
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<tr>
<th>Jon Kaplan</th>
<th>Simon Agolory</th>
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<td>Gundo Weiler</td>
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<td>Tim Hallett</td>
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Linkage and Retention: Where have all the patients gone?

Jonathan E. Kaplan, M.D.

HOPE Conference

October 9, 2012
Continuum of HIV Care and Treatment

1. Delivery of HIV + test result
2. CD4 count, clinical staging
3. Eligible for ART
4. Start ART
5. Stable on ART
Continuum of HIV Care and Treatment

Delivery of HIV + test result
CD4 count, clinical staging
Eligible for ART
Start ART
Stable on ART

41%
54%
32%
10%
Definitions

• Pre-ART care: all services provided between testing positive for HIV and dispensing of first dose of ARVs
• Linkage to care: transition from HIV diagnosis to enrollment in HIV care
• Retention in care/treatment: patient generally maintains expected schedule for visits, lab tests, etc. before and after initiation of ART
Barriers and Solutions
Individual-level barriers

- Fear/stigma/denial
- Non-supportive family
- Time away from children, work
- Lack of education about HIV, including how to access services
- Perceived lack of value of services
- Co-morbidities (e.g., IDU, ETOH abuse)
- Distance, transport
Structural barriers

• Inconvenient hours
• Long waiting times
• Unfriendly staff
• Separate service sites
• Unclear referral mechanisms
• Registration fees
Individual-level solutions

- Support groups
- HIV education
- Information on how to access services
- Cash/non-cash incentives
Structural solutions

• Decentralization
• More convenient clinic hours
• More clinical, psychological, and social services*
• Community support groups, case managers*
• Various technologies:
  - POC CD4*
  - cell phone/text messaging*

* Literature to support
An Intervention Addressing Multiple Challenges to Adherence: From Efficacy to Effectiveness

Distribution of Antiretroviral Treatment Through Self-Forming Groups of Patients in Tete Province, Mozambique

Tom Decroo, MD,* Barbara Telfer, MPH,* Marc Biot, MD, MSc,* Jacob Maïkéré, MD, MSc, PhD,† Sergio Dezembro,* Luisa Isabel Cumba, MD,‡ Carla das Dores, MD,§ Kathryn Chu, MD, MSc,¶ and Nathan Ford, MPH, PhD§¶

*J Acquir Immune Defic Syndr • Volume 56, Number 2, February 1, 2011
A Different Approach

• Community adherence support groups (CASG)
  – Establish treatment groups with up to 6 members
  – Stable non-pregnant adults on ART
  – One representative from the group visits the health facility every month and does the following:
    • Clinical assessment and CD4 count
    • Provides feedback to the health facility about the five other members of the group
    • Obtains lab results for other members
    • Collects one month’s worth of ARV’s for each group member
Results from MSF-Tête Pilot

Cohort of 1384 ART patients in 12 health facilities in Tête Province

- 291 groups formed
- 12-month retention: 97.5%
- Mortality: 0.2%
- LTFU: 2.3%
- Median follow-up time: 12.9 months
Community Adherence Support Groups
Impact at Health Facility

- Reduced number of stable ART patients accessing the health facility
- Increased capacity of health facility to enroll new patients
- Increased amount of time staff can dedicate to sick or complex patients
- Decreased congestion at the pharmacy
- Decreased acuity of consultations and admissions due to earlier access to health services
- Improved reporting of patient outcomes

Community Adherence Support Groups
Impact on Patient

- Decreased number of health facility visits
- Improved self-monitoring of clinical conditions
- Improved psychosocial support
- Stigma reduction
- Early warning system for illness
- Improved monitoring and resources to address adherence problems
- Provide a social safety net
- Income generation
- Family testing
- Community education
Scale-up Study for Effectiveness

- Government of Mozambique piloting the model in all 11 provinces
  - 3-6 health facilities per province
  - 3 tiers
    - >1000 patients
    - 500-1000 patients
    - <500 patients

- Non-pregnant, stable adults (or on adult ARV doses)

- 12-month pilot with national scale-up pending the results of retrospective evaluation
Integrated Access to Care and Treatment (I ACT): Overview and Goals

• I ACT is a program being implemented in South Africa to help teach skills to people living with HIV (PLWH) to understand the disease and manage their health care.

• The program is introduced nationally to close an identified gap within the continuum of care for PLWH. I ACT was developed to promote the early recruitment and retention of PLWH into care and support programs in order to alleviate the large numbers of people lost to follow up from the time of diagnosis to the beginning of treatment.

• I ACT is a structured, closed Support Group Curriculum that is finite and is
Integrated Access to Care and Treatment (I ACT): Training Content

- Content is presented by a trained Support Group Facilitator
- Training of Support Group Facilitators takes eleven days, and includes both content and facilitation skills
- The current content in I ACT includes the following:
  1. HIV/AIDS, tuberculosis and other opportunistic infections, sexually transmitted infections
  2. HIV treatment, adherence counseling
  3. Acceptance of HIV status
  4. Disclosure of HIV status to others
  5. Nutrition and other principles of healthy living
  6. Safer sex/prevention
Integrated Access to Care and Treatment (I ACT) implementation

- The Provincial Department of Health (DOH) provides overall direction, and District DOHs are responsible for implementation, with technical assistance and support from external partners such as NASTAD and CARE.

- The I ACT group can be implemented in both health facility and community settings. In some provinces the project is more community-based, with recruitment by community-based organizations. In others, the project is more facility-based, with recruitment directly from HIV clinics.

- The focus for I ACT support groups is pre-ART patients, especially newly diagnosed PLWH (CD4 > 350). Those who meet South African criteria for ART initiation are counseled and enrolled in drug readiness.
Retention ≠ Adherence: Additional Factors to Consider

• Drug regimen
• Frequency of dosing
• Side effects
• Belief in efficacy
• Frequency of refills
• Stockouts
Continuum of HIV Care and Treatment

1. Delivery of HIV + test result
2. Enroll in HIV care
3. Eligible for ART
4. Start ART
5. Stable on ART

41% 54% 32% 10%
Key References

• Linkage and retention cascade

• Interventions
  – Self-forming adherence groups: 98% retention, 2% deaths
    (Decroo JAIDS 2011)
  – Text messages increased patients with > 90% ART adherence from
    40% to 53% (Pop-Eleches AIDS 2011)
  – Use of peer health workers reduced virologic failure (Chang PloS One
    2010)
  – Point of care CD4 testing reduced loss between enrollment and CD4
    determination (Jani Lancet 2011)
  – Weekly two-way SMS in Kenya improved HIV RNA suppression (Lester
    Lancet 2010)
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