Evolving HIV Treatment Paradigms
What we need to know

Benjamin Young
International Association of Providers of AIDS Care
Washington, DC, USA
Evolving HIV Treatment Paradigms

When/who to treat
Better medicines
Easier adherence
Diagnostics
Task shifting
“...the available evidence renders the discussion on when to start ART unnecessary and that, instead, efforts should be aimed at offering treatment as soon as possible.”
The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection

Edward M. Gardner, Margaret P. McLees, John F. Steiner, Carlos del Rio, and William J. Burman

1Denver Public Health and 2Kaiser Permanente Colorado, Denver, 3University of Colorado Denver, Aurora, Colorado, and 4Rollins School of Public Health of Emory University, and 5Emory Center for AIDS Research, Atlanta, Georgia
New combinations, superior tolerability

EVALVING ART
Evolving ART Combinations

NNRTI-Based Regimen:
- EFV/TDF/FTC $^a$ (AI)

PI-Based Regimens:
- ATV/r plus TDF/FTC $^a$ (AI)
- DRV/r plus TDF/FTC $^a$ (AI)

INSTI-Based Regimens:
- DTG plus ABC/3TC $^a$ (AI)—only for patients who are HLA-B*5701 negative
- DTG plus TDF/FTC $^a$ (AI)
- EVG/cobi/TDF/FTC—only for patients with pre-ART CrCl >70 mL/min (AI)
- RAL plus TDF/FTC $^a$ (AI)
## Evolving ART Combinations

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI</strong></td>
<td><strong>NRTI</strong></td>
</tr>
<tr>
<td>EFV&lt;sup&gt;(i)&lt;/sup&gt;</td>
<td>ABC/3TC&lt;sup&gt;(vii)&lt;/sup&gt; or TDF/FTC</td>
</tr>
<tr>
<td>RPV&lt;sup&gt;(ii)&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI/r</strong></td>
<td></td>
</tr>
<tr>
<td>ATV/r&lt;sup&gt;(iv)&lt;/sup&gt;</td>
<td>ABC/3TC&lt;sup&gt;(vii)&lt;/sup&gt; or TDF/FTC</td>
</tr>
<tr>
<td>DRV/r&lt;sup&gt;(iv)&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INSTI</strong></td>
<td></td>
</tr>
<tr>
<td>EVG + COBI</td>
<td>FTC/TDF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>TDF/FTC or ABC/3TC</td>
</tr>
</tbody>
</table>
Relative Efficacy of HIV Prevention Strategies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction in HIV Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 052 (ARV treatment as prevention)</td>
<td>96%</td>
</tr>
<tr>
<td>iPrEx (FTC/TDF) in MSM</td>
<td>44%</td>
</tr>
<tr>
<td>Subjects with detectable drug levels</td>
<td>94%</td>
</tr>
<tr>
<td>Partners PrEP (FTC/TDF) in discordant couples</td>
<td>75%</td>
</tr>
<tr>
<td>Subjects with detectable drug levels</td>
<td>90%</td>
</tr>
<tr>
<td>Condoms in heterosexuals</td>
<td>80%</td>
</tr>
<tr>
<td>Condoms in US MSM</td>
<td>70%</td>
</tr>
<tr>
<td>TDF2 (FTC/TDF) in men &amp; women</td>
<td>62%</td>
</tr>
<tr>
<td>Medical male circumcision</td>
<td>54%</td>
</tr>
<tr>
<td>STD treatment</td>
<td>42%</td>
</tr>
<tr>
<td>CAPRISA 004 (1% TFV vaginal gel) in women</td>
<td>39%</td>
</tr>
<tr>
<td>FEM-PrEP (FTC/TDF) in women, VOICE (FTC/TDF, TDF, TFV vaginal gel) in women</td>
<td>Not Significant</td>
</tr>
<tr>
<td>HIV vaccine (RV144)</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy (%)

0  10  20  30  40  50  60  70  80  90  100
PrEP Guidelines: USA

- PrEP is recommended as one prevention option for:
  - Sexually-active adult MSM (IA)
  - Adult heterosexually-active men and women (IA)
  - Adult injection drug users (IA)

US Public Health Service
PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014
A CLINICAL PRACTICE GUIDELINE
Evolving ART Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Dolutegravir (n=411)</th>
<th>Raltegravir (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological success</td>
<td>361 (88%)</td>
<td>351 (85%)</td>
</tr>
<tr>
<td>Virologic non-response*</td>
<td>20 (5%)</td>
<td>31 (8%)</td>
</tr>
<tr>
<td>Data in window not &lt;50 copies per mL</td>
<td>8 (2%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>5 (1%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Discontinued for other reasons while HIV-1 RNA not &lt;50 copies per mL</td>
<td>2 (&lt;1%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Change in ART</td>
<td>5 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>No virological data at week 48</td>
<td>30 (7%)</td>
<td>29 (7%)</td>
</tr>
<tr>
<td>Discontinued because of adverse event or death</td>
<td>9 (2%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Discontinued for other reasons†</td>
<td>21 (5%)</td>
<td>23 (6%)</td>
</tr>
</tbody>
</table>

Data are n (%), by US Food and Drug Administration snapshot analysis. ART=antiretroviral therapy. *Virological failure. †Protocol deviation, lost to follow-up, or withdrawal of consent.

Table 2: Patients with plasma HIV-1 RNA less than 50 copies per mL at week 48

Raffi, et al., Lancet, 2013
Evolving first-line ART: Integrase Inhibitor-based Treatments

- **Dolutegravir**
  - DTG superior to EFV (SINGLE; Walmsley, New Engl J Med, 2013)
  - DTG superior to DRV/r (FLAMINGO, Clotet, Lancet 2014)

- **Elvitegravir**
  - EVG/c/TDF/FTC switch superior to continued PI/r ART (STRATEGY studies, Pozniak, Lancet ID 2014)

- **Raltegravir**
  - RAL superior to EFV (STARTMRK 5 year analysis; Rockstroh, JAIDS 2013)
  - RAL superior to DRV/r and ATV/r (ACTG 5257 (Landovitz, CROI2014))
Perfection not required

EVOLVING ADHERENCE
“I am on ART for the past 2 years, I always take it at the same time, everyday, but one day, I missed my pill by 15 minutes. Does it mean that I will become drug resistant? I am very worried.”

-Question on TheBody.com
Evolving Adherence

• Newer medications are better
• Perfection not required
  – 90% (maybe lower?) adherence is adequate
  – Stopwatch not required
• Substance dependency doesn’t prevent adherence or ART success
Better Medications and Adherence

Better medications: fewer barriers to engagement in care, retention on ART and human resources needed to deliver care

- Fewer pills (4 single tablet regimens)
- Fewer doses (most regimens once-daily)
- Fewer dietary restrictions (some)
- Fewer side effects ($\text{INSTI} < \text{NNRTI} \leq \text{PI/r}$)
- Fewer drug-drug interactions (some)
Lower pill burden associated with both better adherence and virological suppression.

Adherence but not virological suppression was slightly better with once- vs twice-daily regimens.
Once vs Twice Daily: ACTG 5257

Cumulative Incidence of Virologic or Tolerability Failure

- ATV/r vs RAL: 15% (10%, 20%)
- DRV/r vs RAL: 7.5% (3.2%, 12%)
- ATV/r vs DRV/r: 7.5% (2.3%, 13%)

*Consistent results seen with TLOVR at a 200 copies/ml threshold
PrEP Adherence: Good but not perfect is ok

HIV Incidence and Drug Concentrations

Follow-up %  
26%  
Risk Reduction  
44%  
95% CI  
-31 to 77%  
86 to 100% (combined)

Grant WAC Melbourne 2014;  
Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

IAPAC  
INTERNATIONAL ASSOCIATION OF PROVIDERS OF AIDS CARE
What to test and when to test

EVOLVING DIAGNOSTICS
Viral load testing: WHO 2013

7.3.2 Monitoring the response to ART and the diagnosis of treatment failure

New recommendations

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (strong recommendation, low-quality evidence).

- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (strong recommendation, moderate-quality evidence).
CD4 monitoring:
After 2 years on ART with consistently suppressed viral load:
- CD4 count 300-500 cells/mm$^3$: *Every 12 months (BII)*
- CD4 count >500 cells/mm$^3$: *CD4 monitoring is optional (CIII)*

HIV RNA monitoring:
Clinicians may extend the interval of viral load testing to 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable (*AIII*).
Building human capacity

Evolving task shifting
Exploiting social capital to address stigma and engagement in care

Hickey, Adherence 2014
Nurses and peer counselors were not inferior to physicians in providing ART follow-up care to postpartum women, an approach that may help deliver treatment to many more HIV-infected people.
“Expansion of primary-care nurses’ roles to include ART initiation and represcription can be done safely, and improve health outcomes and quality of care, but might not reduce time to ART or mortality.”

Fairall, Lancet 2012
Ending epidemic AIDS

EVOLVING TARGETS
Normal Life Expectancy?

- Pre-HAART Era (Mono/Dual Therapy)
  - +8 years
  - HIV+ 2000-2002

- HAART Era (Triple Therapy)
  - +36 years
  - HIV+ 2003-2006
  - +51 years
  - HIV+ 2006-2007
  - +55 years
  - HIV+ 2010

- +60 years
  - HIV uninfected
Healthy Aging and HIV

Comorbidity distribution

<table>
<thead>
<tr>
<th>Condition</th>
<th>HIV negative</th>
<th>HIV positive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>20%</td>
<td>35%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>15%</td>
<td>22%</td>
<td>0.005</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10%</td>
<td>18%</td>
<td>0.003</td>
</tr>
<tr>
<td>Peripheral arterial insufficiency</td>
<td>5%</td>
<td>7%</td>
<td>0.003</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10%</td>
<td>12%</td>
<td>0.022</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>5%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>3%</td>
<td>5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>2%</td>
<td>4%</td>
<td>0.006</td>
</tr>
<tr>
<td>Reduced renal function</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>1%</td>
<td>2%</td>
<td>0.001</td>
</tr>
<tr>
<td>Fracture / Osteoporosis</td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Schouten, XIX IAC, 2012
Evolving Targets

THE TREATMENT TARGET

90% diagnosed
90% on treatment
90% virally suppressed

UNAIDS, 2014
Evolving HIV Treatment Paradigms: Summary

- Treat all
- HIV medications are safer and better tolerated
- Medication adherence doesn’t require perfection
- Among stable patients, lab monitoring may be less frequent
- Task shifting works = larger role for nurses
- Evolving targets
Educational Matters
Evolving HIV Treatment Paradigms
What we need to know

Benjamin Young
International Association of Providers of AIDS Care
Washington, DC, USA