ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals
Approach for the Newly Diagnosed HIV Positive Patient

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Objectives

Detail strategies for TEST and TREAT approaches

Discuss the first-line ART regimens for treatment naïve individuals.

Review clinical considerations when selecting an initial ART regimen

Describe follow-up monitoring of patients newly started on ART
CDC’s new recommendations for HIV testing in laboratories capitalize on the latest available technologies to help diagnose HIV infections earlier – as much as 3-4 weeks sooner than the previous testing approach. Early diagnosis is critical since many new infections are transmitted by people in the earliest (“acute”) stage of infection.

By putting the latest testing technology to work in laboratories across the United States, we can help address a critical gap in the nation’s HIV prevention efforts.

**Step 1:** “Fourth generation” HIV test
*Detecting HIV sooner*

Detects HIV in the blood earlier than previously recommended antibody tests by identifying the HIV-1 p24 antigen, a viral protein which appears in the blood sooner than antibodies.

- **Negative**
  - Diagnosis: HIV-negative
  - Final Step: Nucleic Acid Test (NAT)
    - *Acute HIV-1 Infection*
    - Ensures accurate detection of early infection or indicates a false positive from the fourth generation test.
  - Diagnosis: HIV Infection

**Step 2:** HIV-1/HIV-2 antibody differentiation immunoassay
*Diagnosing HIV-1 vs. HIV-2*

- Produces results faster than the previously recommended Western Blot.
- Distinguishes between HIV-1 and HIV-2, which the previously recommended Western Blot cannot do – this distinction can have important treatment implications for a patient.

**Step 3:** Nucleic Acid Test (NAT)
*Acute HIV-1 infection or “false positive”?

Interpret Test Results as HIV-1 or HIV-2

- Interpretation based on NAT results ensures accurate detection.

This graphic is designed to illustrate key concepts of the new testing approach in laboratories. For more detail, please see the full guidelines here: http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf.
The Newly Diagnosed Patient

• Delivering the results vs. post result visit

• Connect clients to needed services:
  – HIV treatment support
    • Peer, pharmacist, adherence groups
  – Partner services
  – Other relevant services (e.g. drug treatment)

• Address patient feelings and/or concerns

• To treat or not to treat?
The Movement to Test and Treat

https://hptn.org/research/studies/hptn065

Test and Treat Conceptual Framework

Population -> TEST
- Test site
- Counsel
- L2C -> TREAT
- Care site

Decrease in HIV Transmission
Decrees in Community Viral Load Are Accompanied by Reductions in New HIV Infections in San Francisco

Moupali Das1,2, Priscilla Lee Chu1, Glenn-Milo Santos1, Susan Scheer1, Eric Vittinghoff2, Willi McFarland1,2, Grant N. Colfax1,2

1 San Francisco Department of Public Health, San Francisco, California, United States of America; 2 University of California San Francisco, San Francisco, California, United States of America

Figure 3. Mean CVL and New HIV Infections, 2004–2008. There was a statistically significant decline in annual measures of mean CVL from 2004–2008 (p = 0.037). Newly diagnosed cases of HIV (shown in red with △) decreased in San Francisco from 798 (2004) to 434 (2008) (p<0.005). The point estimates of HIV incidence (shown in dark red with △) using the CDC methods also declined from 935 [95% CI 658–1212] in 2006, to 792 [552–1033] in 2007 and 621 [462–781] in 2008, although the change was not statistically significant (trend p = 0.29). The reductions in annual measures of mean CVL were significantly associated with decreases in newly diagnosed and reported HIV cases from 2004–2008 (p=0.003). Longitudinal reductions in estimated HIV incidence were consistent with the trends in mean and total CVL, but the association in the meta-regression was not statistically significant (p>0.3).

doi:10.1371/journal.pone.0011068.g003
Improvements in the Continuum of Care

Estimated percentage of HIV infected adults/adolescents engaged in selected stages of the continuum of care, Maryland 2010-2013

- HIV Infected: 100%
- HIV Diagnosed: 86%
- Linked to HIV Care: 70%
- Retained in HIV Care: 50%
- On ART: 32%
- Suppressed VL: 32%

2010 2011 2012 2013
<table>
<thead>
<tr>
<th>Factor</th>
<th>2007</th>
<th>2009</th>
<th>2010</th>
<th>2012</th>
<th>2013/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treat &lt;350</td>
<td></td>
<td>Treat &lt;350</td>
<td>Treat &lt;350</td>
<td>Rec for all</td>
<td>Treat</td>
</tr>
<tr>
<td>• Risks/benefits if &gt;350</td>
<td></td>
<td>Rec 350 - 500</td>
<td>&gt;500 optional</td>
<td>&lt;350 (AI)</td>
<td>Rec for all</td>
</tr>
<tr>
<td>• &gt;500 optional</td>
<td></td>
<td></td>
<td></td>
<td>350 -500 (AII)</td>
<td>&lt;350 (BIII)</td>
</tr>
<tr>
<td>• &gt;500 optional (panel split)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Everyone</td>
</tr>
<tr>
<td>Viral load (copies/mL)</td>
<td>No specific viral load</td>
<td>No specific viral load</td>
<td>No specific viral load</td>
<td>No specific viral load</td>
<td>No specific viral load</td>
</tr>
<tr>
<td>Other factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pregnant women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HBV co-infected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HIVAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treat to prevent infection</td>
<td></td>
<td></td>
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</tbody>
</table>
Benefits of early ART

• Prevention of complications
  – Including non-communicable diseases

• Prevent sexual transmission

• Prevent mother to child transmission

• Preserve immune function
<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Drug(s)</th>
</tr>
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<tbody>
<tr>
<td>'80-'84</td>
<td>First AIDS cases reported in United States</td>
</tr>
<tr>
<td>'85-'89</td>
<td>Zidovudine (NRTI)</td>
</tr>
<tr>
<td>'90-'94</td>
<td>Didanosine (NRTI), Zalcitabine (NRTI), Stavudine (NRTI)</td>
</tr>
<tr>
<td>'95-'99</td>
<td>Lamivudine (NRTI), Saquinavir (PI), Nevirapine (NNRTI), Ritonavir (PI)</td>
</tr>
<tr>
<td>'00-'04</td>
<td>Indinavir (PI), Zidovudine (NRTI), Delavirdine (NNRTI), Efavirenz (NNRTI)</td>
</tr>
<tr>
<td>'05-'09</td>
<td>Atazanavir (PI), Tenofivir DF (NRTI), Emtricitabine (NRTI), Enfuvirtide (FI)</td>
</tr>
<tr>
<td>'10-'14</td>
<td>Maraviroc (EI), Kaletra (FDC), Darunavir (PI)</td>
</tr>
<tr>
<td>'15-'16</td>
<td>Complera (FDC), Descovy (FDC), Odefsey (FDC)</td>
</tr>
</tbody>
</table>

**Drug Class Abbreviations:**

- EI: Entry Inhibitors
- FI: Fusion Inhibitors
- INSTI: Integrase Inhibitors
- NNRTI: Non-nucleoside reverse transcriptase inhibitors
- NRTI: Nucleoside reverse transcriptase inhibitors
- PI: Protease inhibitor
- PE: Pharmacologic enhancer
- FCD: Fixed Dose Combination

**Note:** drugs in gray are no longer recommended for use
Current ARV Medications with Generic (Trade) Names:

- NRTI
  - Abacavir (Ziagen)
  - Emtricitabine (Emtriva)
  - Lamivudine (Epivir)
  - Tenofovir (Viread) / TAF

- NNRTI
  - Efavirenz (Sustiva)
  - Rilpivirine (Edurant)

- PI
  - Atazanavir (Reyataz)
  - Darunavir (Prezista)
  - Dolutegravir (Tivicay)
  - Elvitegravir* (Stribild)

- Integrase Inhibitor (II)
  - Raltegravir (Isentress)

- Fusion Inhibitor
  - Enfuvirtide (Fuzeon)

- CCR5 Antagonist
  - Maraviroc (Selzentry)
Deeks, et al, 2015; Nature Reviews
Choosing the Regimen

• Review baseline labs including genotype
• Review co-morbid diseases including age
• Assess adherence potential

• Synthesize this information for regimen selection

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2016
Baseline laboratory evaluations

- CD4 T-cell count (CD4 count);
- Plasma HIV RNA (viral load);
- Complete blood count, chemistry profile, transaminase levels, BUN, and creatinine, urinalysis;
- Serologies for hepatitis A, B, and C viruses;
- HLA-B5701
  - Abacavir regimens – only need once
- Fasting blood glucose and serum lipids
- Genotypic resistance testing at entry into care, regardless of whether ART will be initiated immediately.
  - For patients who have HIV RNA levels <500 to 1,000 copies/mL, viral amplification for resistance testing may not always be successful

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2016
Resistance Testing Decision Tree

Resistance Options

Genotype
- Baseline (Pre-ART)

Trofile Assay (MVC)
- Non-response Non-adherence

Phenotype
- Limited treatment options
- Complex resistant patterns

INSTI (Optional)

Choosing the Right ART Regimen for Your Patient: A Patient Centered Approach

Joint decision

08

01 Side Effects

02 Drug Drug Interactions

03 Costs / Copays

04 Adherence / Dosing

05 Resistance

06 Co-Morbidity

07 Preference

08 Preference / Dosage
Treating HIV....the 3-2-1 principle

- At least 3 different DRUGS
- At least 2 different CLASSES
- Try for once daily DOSING

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2016
Begin with the “Nuc” backbone

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2016

<table>
<thead>
<tr>
<th>Drug</th>
<th>Key Points</th>
</tr>
</thead>
</table>
| TDF/FTC  | - Once-daily and in combination dosing  
            - High virologic efficacy  
            - Active against HBV  
            - Potential for renal and bone toxicity |
| TAF/FTC  | - Once-daily and in combination  
            - High virologic efficacy  
            - NO approval for HBV co-infection  
            - Improved renal and bone toxicity profile |
| ABC/3TC  | - Once-daily dosing  
            - Must be HLA-B*5701 negative  
            - Possible risk of cardiovascular events**  
            - Possible inferior efficacy if baseline HIV RNA >100,000 copies/mL |
1st line ART regimen (single tablet)

**Triumeq**
- Well tolerated
- Must be HLA-B5701 negative
- High barrier to resistance

**Odefsy / Complera**
- Well tolerated
- Take with meals
- Avoid if VL > 100,000 copies/mL
- PH sensitive

**Stribild**
- Well tolerated
- Drug-drug interactions (CYP450)
- Cobi – incr Cr; avoid if CrCl<70

**Genvoya**
- Well tolerated
- Must be HLA-B5701 negative (ABC)
- Do not use if known INSTI resistance

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2016
1st line ART regimen (2 tabs / once daily)

**Darunavir/cobi + Descovy**
- 3 pills once daily
- Very forgiving regimen (Great for ? adherence)
- Generally well tolerated
- Drug-drug interactions

**Atazanavir/rtv + Descovy**
- 3 pills once daily
- Hyperbilirubinemia
- PH sensitive
- Drug-drug interactions

**Dolutegravir + Descovy**
- 2 tablets once daily
- Well tolerated

**Cobicistat co-formulation:**
- Darunavir/cobi
  - Prezcobix

**BENEFITS:**
- Lower pill burden

**NEGATIVES:**
- Artificial rise in Creat

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2015
Considerations

- Patients should be willing and able to:
  - commit to treatment
  - understand benefits, risks
  - understand importance of adherence

- Patients or providers may elect to defer ART
  - limited reason why this should occur

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2016
Factors Associated with Adherence Challenges

- Regimen complexity and pill burden
- Low literacy/numeracy
- Younger age
  - Some challenges of older age (eg, polypharmacy, vision loss, cognitive impairment)
- Nondisclosure of HIV status
- Stigma
- Psychosocial stressors
- Active drug use or alcoholism
- Mental illness
- Cognitive impairment
- Lack of patient education
- Medication adverse effects
- Treatment fatigue
- Cost and insurance coverage issues
Factors Associated with Adherence Success

- Regimen simplicity, once-daily dosing
- Low pill burden
- Good tolerability
- Older age
- Multidisciplinary care (e.g., with case managers, social workers, pharmacists, psychiatric care providers)
- Directly observed therapy

- Trusting patient-provider relationship
- Use of motivational strategies
Monitoring viral load

• More important than CD4 count for ongoing monitoring

• Complete baseline viral load testing before initiation of ART

• Check viral load
  – Within 4 weeks after start or change of ART
  – Every 3-4 months for stable, but newer patients
  – Every 6-12 months for long term adherent patients
Case Study #1

- Physical Exam: lymphadenopathy
- BMI: 26 kg/m²

- Baseline Diagnostic Data:
  - CD4+: 385 cells/µL (20 %)
  - HIV RNA: 76,000 copies/mL
  - HIV Genotype: no resistance
  - eGFR: 110 ml/min/1.73²
    - (serum Cr: 0.6 mg/dL)
  - HLA*B5701: negative

19 y/o female
- Newly diagnosed
- No primary partner
- On OCP
- No other PMH
The Decision on ART Regimen

A. 2 nucleosides + elvitegravir / cobicistat
B. 2 nucleosides + rilpivirine
C. 2 nucleosides + dolutegravir
D. 2 nucleosides + darunavir / cobicistat
Case #1 - continued

• Started on fixed-dose combination of tenofovir alefenomide/ emtricitabine/ elvitegravir/cobicistat (Genvoya)

• 4 weeks after starting therapy the patient returns for follow up.
  – Doing well with no acute complaints
Repeat Labs: Week 4

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ T-Cell Count (%)</td>
<td>420 cells/m$^3$ (21%)</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>&lt; 20 copies/mL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 mg/dL</td>
</tr>
<tr>
<td>eGFR</td>
<td>69 mL/min/1.73m$^2$</td>
</tr>
<tr>
<td></td>
<td>** From baseline 110 mL/min/1.73m$^2$</td>
</tr>
</tbody>
</table>
What is the best next step?

A. Continue treatment; monitor renal function
B. Stop ART due to renal toxicity
C. Switch to raltegravir with tenofovir/emtricitabine
D. Switch to abacavir/lamivudine with dolutegravir
Effect of Elvitegravir/cobicistat on Serum Creatinine

Case #1- Follow-up

- Patient remains on tenofovir/emtricitabine/elvitegravir/cobicistat

- eGFR remains stable $> 60$ ml/min/1.73$^2$

- HIV remains fully suppressed
Case Study # 2 – 42 year old male

• Physical Exam: Unremarkable
  – HTN, DM well controlled with no target organ damage
  – LDL cholesterol = 115 mg/dL

• Baseline Diagnostic Data:
  – CD4+: 540 cells/µL (20 %)
  – HIV RNA: 123,000 copies/mL
  – HIV Genotype: no resistance
  – eGFR: 89 ml/min/1.73^2
    • (serum Cr: 1.1 mg/dL)
  – HLA*B5701: negative

  – New HCV Diagnosis
    • Normal ALT, AST
    • HCR RNA 1.3 million copies / mL
The Decision on ART Regimen #2

A. 2 nucleosides + elvitegravir / cobicistat
B. 2 nucleosides + rilpivirine
C. 2 nucleosides + dolutegravir
D. 2 nucleosides + darunavir / cobicistat
Peripheral nervous system
  – Neuropathy, myopathy

Morphologic

Metabolic

• Glucose disorders
  – Insulin resistance
  – Impaired glucose tolerance
  – Hyperglycemia/diabetes

• Lipid elevations
  – ↓ HDL, ↑ triglycerides
  – ↑ cholesterol

• Hyperlactatemia
  – Lactic acidosis

Cardiovascular

• Myocardial infarction

Renal

• TDF toxicity

Preventing & Monitor for Long-Term Complications Associated with ART
Be on the look out: Drug-Drug Interactions are COMMON

- Ritonavir (used with PI)
  - CYP450 Inhibitor!
    - fluticasone
    - warfarin
    - rifampin
    - sildenafil (Viagra)
  - New formulation should be taken with food

- EFV decreases Methadone by up to 67%

- Atazanavir
  - Must have acidic PH
    - Avoid PPI or H2 Blockers

- Several HIV agents must have dosing changes to be used together

http://www.hiv-druginteractions.org (UK)
Drug Interactions: Effect of ARVs on Drug Metabolism

Induced by: RTV, NFV, LPV, EFV, NVP, TPV, ETR
Inhibited by: RTV, NFV, IDV, APV, SQV, ATV, DRV, DLV, COBI

Induced by: RTV, NFV, EVG
Inhibited by: DLV, ATV, ETR

Induced by: EFV, NVP
Inhibited by: RTV, COBI

Induced by: RTV, NFV
Inhibited by: EFV, DLV, ETR

Induced by: RTV, NFV?
Inhibited by: ATV

Induced by: 1A2, 2E1, 2A6, 2B6, 2C8
Inhibited by: 3A4

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