HIV Diagnosis and Treatment Updates
ACP DC Chapter

Frank Maldarelli
HIV Dynamics and Replication Program, NCI, NIH
November 5, 2016
Disclosures

• NONE
Objectives

- HIV Testing Updates
- HIV Treatment Update
- Vaccines Progress
HIV Testing Updates
HIV-1 Infection Worldwide

Total: 36.7 million [34.0-39.8 million]
Diagnosis is a cornerstone of the medical and public health response to the HIV epidemic.

UNAIDS, 2015
WHO, 2015
Diagnosis of HIV Infection
Multi-Purpose Designs

- Patient Diagnosis
- Epidemiologic Surveillance
- Donor Screening
  - Blood
  - Tissue products
HIV Testing Updates

Who to test?
2006 CDC recommendations Revised:
Test all 15-64 year olds presenting for health care
OPT OUT strategy: Default is to TEST for HIV
US Preventive Services Task Force gives “A” recommendation for OPT OUT HIV testing
Get an "A" In HIV Screening

• The US Preventative Services Task Force (USPSTF) recommends
  • Screen for HIV infection: 15 to 65 years.
  • Younger adolescents and older adults who are at increased risk should also be screened.
  • Screen all pregnant women for HIV, including those who present in labor who are untested and whose HIV status is unknown.
  • Screening intervals based on risk

• US Preventative Services Task Force
  • DHHS Agency
  • 16 volunteer experts, generally practitioners
  • Evidence based recommendations
Get an "A" In HIV Screening

US Preventative Services Task Force (USPSTF) Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.</td>
<td>Offer or provide this service for selected patients depending on individual circumstances.</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td>
<td>Discourage the use of this service.</td>
</tr>
<tr>
<td><strong>I</strong></td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
<td>Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.</td>
</tr>
</tbody>
</table>

https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions
HIV Screening USPTF Screening Guideline

Oh, and one more thing about cost and coverage…

Under the Affordable Care Act Insurance Plans are REQUIRED to cover routine screening

Get an ”A” In HIV Screening
Diagnosis of HIV Infection

- History
  - Counseling
  - Consent
  - Confidentiality

- Physical
  - Comprehensive

- Laboratory studies
  - Correct Choice of testing
  - Correct interpretation of Results

- Follow up
  - Care linkage

Confidentiality, Counseling, Consent, Correct Testing, Correct Interpretation, Care Linkage
HIV Diagnosis

• You are seeing a 36 year old man with a long history of receptive anal intercourse, lymphadenopathy, and oral thrush. He has never been tested for HIV. Your clinic has done a rapid HIV 1/2 ELISA test and it is REACTIVE. Which of the following is the next best course of action:

A. Western Blot for HIV-1
B. Immune fluorescence test for HIV-1
C. HIV 1/2 antibody differentiation ELISA
D. No further testing is required; the patient is infected with HIV
HIV Diagnostic Testing

**HIV Screening**
- HIV 1/2 ELISA
  - Third Generation: HIV antibody
  - Fourth generation:
- Nucleic Acid testing NAT
  - Not standard viral RNA testing
  - Aptima
- HIV 1/2 antibody differentiation assay
- Result
  - Reactive
  - Non-reactive”

**HIV Confirmation**
- HIV Western blot
- HIV Immunofluorescence assay
- HIV 1/2 antibody differentiation assay
- Nucleic Acid testing NAT
  - Not standard viral RNA testing
  - Aptima
- Result:
  - Positive
  - Negative
  - Indeterminant
HIV Detection: Window Period

- **Anti-HIV Antibody**
- **p24 Antigen**
- **HIV RNA**
- **HIV Nucleic acid testing (NAT) detection**

**Time Post-Infection**
- 11 days: HIV Nucleic acid testing (NAT) detection
- 16 days: HIV p24 4th Generation assay Antibody and p24 detection
- 21 days: 3rd Generation assay Antibody only detection

**Relative Level**
- 8-30 X MORE Infectious

CDC 2014
HIV-1/2 antigen/antibody combination immunoassay

(+) -> Negative for HIV-1 and HIV-2 antibodies and p24 Ag

(-) ->

HIV-1/HIV-2 antibody differentiation immunoassay

HIV-1 (+) HIV-1 (-) HIV-1 (+) HIV-1 (-) or indeterminate
HIV-2 (-) HIV-2 (+) HIV-2 (+) HIV-2 (-)
HIV-1 antibodies detected HIV-2 antibodies detected HIV antibodies detected

HIV-1 NAT

(+) indicates reactive test result
(-) indicates nonreactive test result
NAT: nucleic acid test

HIV-1 NAT (+) Acute HIV-1 infection HIV-1 NAT (-) Negative for HIV-1

No issues with detection of any HIV-1 Subtype or group O

CDC, 2014
HIV Treatment Update
HIV-1 Infection Worldwide

Total: 36.7 million [34.0-39.8 million]
People undergoing antiretroviral therapy: 17 million

North America and western and central Europe
2.4 million

On Therapy: 1.4 million

Eastern Europe and central Asia
1.5 million

On Therapy: 2.1 million

Middle East and North Africa
230,000

[160,000-330,000]

On Therapy: 38,200

Latin America and the Caribbean
2.0 million

On Therapy: 1.1 million

Western and central Africa
6.5 million

On Therapy: 1.8 million

Eastern and southern Africa
19.0 million

On Therapy: 10.2 million

Asia and the Pacific
5.1 million

On Therapy: 2.1 million

UNAIDS, 2015

WHO, 2015
Effect of Introduction of Antiretroviral Therapy

Decreased Mortality

MMWR, 2011
HIV Replication Cycle

Attachment

Fusion

Uncoating

Reverse transcription

Integration into Host Genome

Viral Expression

Maturation

HIV DNA
Antiretroviral Drug Development

Attachment Inhibitor: Maraviroc

Fusion Inhibitor: Enfuvirtide

Uncoating

NRTI/NNRTI

HIV DNA

Integrase Inhibitors

Viral Expression

Protease inhibitors
Antiretroviral Development

SO MANY CHOICES
What do I do?
There are Guidelines
https://aidsinfo.nih.gov/guidelines
http://www.aidsetc.org
Goals

• Reduce morbidity and mortality

• Prevent complications

• Suppress HIV RNA levels

• Prevent Transmission
When to Start Antiretroviral Therapy

- ART is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection
- A1 recommendation RCT
- Optimal time for initiating therapy is
  - As soon as possible
  - As indicated in setting of clinical and psychological factors
- Therapy is indefinite
- Adherence is a key discussion
Before You Start

- History
  - Co-morbidity
    - Pregnancy
    - Coinfection HCV, HBV, TB
    - Opportunistic infection
    - Cardiovascular disease
    - Hyperlipidemia
  - Patient preferences
- Physical
- Laboratory examinations
  - HIV RNA
  - CD4
  - Resistance testing: genotype
  - HLAB*5701 testing
What to Start

• Recommended
  • Easy to use
  • Durable virologic efficacy
  • Favorable tolerability and toxicity profiles

• Alternative
  • Effective but have potential disadvantages, limitations in certain patient populations, or less supporting data
  • May be the optimal regimen for individual patients

• Other
  • Reduced virologic activity; limited supporting data; or greater toxicities, higher pill burden, more drug interactions, or other limiting factors
What to Start

• 3 main categories:
  • 1 INSTI + 2 NRTIs
  • 1 PK-boosted PI + 2 NRTIs
  • 1 NNRTI + 2 NRTIs

• Combination of INSTI, boosted PI, or NNRTI + 2 NRTIs is preferred for most patients

• NRTI pair should include 3TC or FTC

• Recommendations based mostly on rates of HIV RNA suppression and severity of adverse effects

• Individualize regimen choice
What to Start

• 3 main categories:
  • 1 INSTI + 2 NRTIs
  • 1 PK-boosted PI + 2 NRTIs
  • 1 NNRTI + 2 NRTIs

• Combination of INSTI, boosted PI, or NNRTI + 2 NRTIs is preferred for most patients

• NRTI pair should include 3TC or FTC

• Recommendations based mostly on rates of HIV RNA suppression and severity of adverse effects

• Individualize regimen choice
What to Start

• Substantial choices
• Opportunity to individualize regimen
• Cooperative relationship
• If you treat this process like a menu, the process will treat you like a patron
What NOT to Do: IFFY situations

- IF CD4 <200 there are higher rates of failure on
  - Rilpivirine + raltegravir
  - Darunavir and Raltegravir

- IF CD4 >250 (women) or >400 cells/µl (men)
  - NO Neviripine; has high frequency of hepatic dysfunction

- If HIV Viremia >100,000 copies/ml plasma there are higher rates of virologic failure on
  - Rilpivirine based therapy
  - ABC
  - Darunavir + raltegravir

- IF HLA-B*5701 POSITIVE
  - NO ABACAVIR
What NOT to Do: IFFY situations

- IF Chronic renal failure
  - Avoid tenofovir

- IF Osteoporosis
  - Avoid tenofovir

- IF Psychiatric Illness
  - Avoid Rilpivirine or Efavirenz

- IF Pregnant
  - GUIDELINES; EFV
  - INVOLVE Colleagues
What NOT to Do: IFFY situations

- IF Liver Disease with cirrhosis
  - Dose modifications
  - Involve colleagues

- IF HBV
  - Tenovovir/TAF and 3TC or FTC
  - Entecavir if no TDF or TAF
  - Interrupting therapy may lead to rebound HBV/hepatitis

- IF HCV
  - Current recommendations

- IF TB
  - NO rifampin with protease inhibitors
  - Increase raltegravir or dolutegravir dose
  - NO TAF with Rifamycins
  - Need PPI: use rifabutin instead of rifampin
# What NOT to Do

## High rate of early virologic failure
- ddI + TDF

## Inferior virologic efficacy
- ABC + 3TC + ZDV as 3-NRTI regimen
- ABC + 3TC + ZDV + TDF as 4-NRTI regimen
- ddI + (3TC or FTC)
- Unboosted ATV, FPV, or SQV
- DLV
- NFV
- TPV/r

## High incidence of toxicities
- ZDV + 3TC
- d4T + 3TC
- ddI + TDF
- NVP
- IDV/r
- RTV as sole PI
What NOT to Do

- ARV components NOT recommended:
  - ddI + d4T
  - ddI + TDF
  - FTC + 3TC
  - d4T + ZDV
  - DRV, SQV, or TPV as single PIs (unboosted)
  - ATV + IDV
What to Start: Updates

• REMOVED: lopinavir/ritonavir (LPV/r) plus 2-NRTI regimens
  • larger pill burden
  • greater toxicity
What to Start: Updates

• TAF/FTC was added as a 2-NRTI option
  • Recommended and Alternative regimens,
  • Non-inferiority studies
    • effective in achieving or maintaining virologic suppression as tenofovir disoproxil fumarate (TDF)-containing regimens
    • more favorable effects on markers of bone and renal health.
New Antiretrovirals Update
Integrase Strand Transfer Inhibitors (INSTI)

- Block essential step in HIV replication
- Three FDA approved INSTIs
  - Raltegravir
  - Elvitegravir
    - Requires boosting cobicistat
  - Dolutegravir
    - Activity against some raltegravir and elvitegravir resistant strains
TAF (GS-7340)

Next Generation Prodrug of Tenofovir

tenofovir
tenofovir disoproxil fumarate
tenofovir alafenamide

Gut → Plasma → Lymphoid Cells

TDF → TDF/TFV
TAF → TAF
TFV
TAF
TFV-MP
TFV-DP

Lee AAC 2005; Birkus AAC 2007
Tenofovir Alafenamide

• Oral prodrug of tenofovir
  • Activity against HIV-1, -2, HBV
  • All HIV-1 subtypes
  • Potency may be greater than TDF
    • Higher intracellular levels
    • Clinical activity against resistant variants remains under study
  • Selection profile is identical to TDF
    • K65R
Tenofovir Alafenamide in Renal Impairment

• Oral prodrug of tenofovir
  • Activity against HIV-1, -2, HBV
  • All HIV-1 subtypes
  • Potency may be greater than TDF
    • Higher intracellular levels
    • Clinical activity against resistant variants remains under study
  • Selection profile is identical to TDF
    • K65R
TAF in Renal Impairment

65% on Tenofovir at baseline

Switched NRTI to TAF

88-94% remained suppressed over 96 wk

Wohl AIDS 2016
TAF in Renal Impairment

Results: Bone Mineral Density
Changes From Baseline to Week 96

Spine

Hip

*Baseline vs Week 96 (2-sided Wilcoxon signed-rank test).
Results: eGFR\textsubscript{CKD-EPI,sCr}
Changes From Baseline to Week 96

Results: eGFR\textsubscript{CKD-EPI,cysC}
Changes From Baseline to Week 96

*Baseline vs Week 96 (2-sided Wilcoxon signed-rank test).
Current Concepts and Controversies

• New drug pipeline
  • Maturation inhibitors
  • Attachment inhibitors
    • BMS
    • Antibodies
• Simplification regimens
• Single drug therapy after duppression of viremia?
HIV Vaccine

• Prevent HIV infection
• Therapeutic vaccines
HIV Vaccine

• Killed
  • Recombinant subunit
  • Modified envelope
  • Peptide
  • DNA
  • Recombinant vector

• Live attenuated
  • NOT Live HIV
  • Replicons of other viruses with HIV components
RV144 Vaccine Trial Prime + boost

Per Protocol
- 36,720 person-years
- 86 infections
  - Vaccine: 36
  - Placebo: 50
- VE: 26.2%, p=0.16
- 95% CI: -13.3, 51.9

Modified ITT
- 52,985 person-years
- 125 infections
  - Vaccine: 51
  - Placebo: 74
- VE: 31.2%, p=0.04
- adj. 95% CI: 1.1, 52.1

ITT
- 52,985 person-years
- 132 infections
  - 7 prevalent
  - Vaccine: 56
  - Placebo: 76
- VE: 26.4%, p=0.08
- 95% CI: -4.0, 47.9

Newer version stronger adjuvant Thailand
New Therapies
Sustained virologic control in SIV+ macaques after antiretroviral and α4β7 antibody therapy


Fig. 1. Control of plasma and GIT viral loads. Plasma viral loads from Rhesus macaques infected with SIVmac239 and treated with antiretroviral therapy and α4β7 antibody therapy. The y-axis represents the log plasma viral RNA concentration (copies/ml).
Summary- Vaccines

• Results are not definitive

• Trials are ongoing

• Durability of protection will be a concern

• Research priority

The development of a safe and effective HIV vaccine would be the ultimate game-changer - Anthony Fauci
Summary- HIV Diagnosis

• Get an “A” in HIV Screening
• Be a physician not a technician
  • Counseling, Confidentiality, and Consent
• Be Alert
  • Mind the GAP
  • 4th generation ag/ab or NAT tests for optimum screening of HIV
• No test is perfect but some tests are better
  • Western Blot is replaced
  • HIV 1/2 antibody differentiation assay is new standard
    • Provides HIV-2 confirmatory
• Language is important
  • Screening tests are “Reactive” or “Non-reactive”
  • Confirmatory tests are Positive or Negative or Indeterminate
  • Physicians
    • May not always be positive
    • But their language is ALWAYS positive
Summary - HIV Treatment

- Regimens are improving
  - TAF
  - INSTI

- Resistance is neither futile nor a thing of the past

- You are NEVER ALONE
  - Guidelines
  - Phone-a-Pharmacist
    - Drug interactions are CRITICAL
Questions?

• Contact information
  • Fmalli@mail.nih.gov
  • 301-846-5611

*If you see pus, think of us*