Advances in Prevention and Treatment of HIV Infection 2018

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Objectives

- Provide an overview of challenges we face in caring for the HIV-infected in 2018
- Focus on novel areas of drug development and delivery
- Define areas of future focus in HIV-related health care
Disclosures

- NIH NIAID and NIDDK Funding
- VA ORD funding
- Department of Defense Funding
NEW HIV INFECTIONS BY REGION
(2013)

- 2.1m Global
- 94k Latin America
- 12k Caribbean
- 88k Western, Central Europe and North America
- 1.5m Sub-Saharan Africa
- 25k Middle-east & North Africa
- 110k Eastern Europe and Central Asia
- 350k Asia and Pacific

SOURCE: UNAIDS Gap Report 2014
HIV Cure
Treatment as Prevention
Simplifying treatment
Co-infection
Aging
Antiretroviral Therapy Targets

Diagram showing the stages of HIV replication within a CD4 cell, including binding sites, RNA, reverse transcriptase, protease, integrase, and host DNA.
Pre-exposure Prophylaxis (PrEP) = TDF/emtricitibine

- Federal guidelines recommend PrEP for HIV negative people with specific risk factors
  - In a serodiscordant relationship
  - In a non-monogamous relationship with an HIV negative person is a man who has sex with men and had sex without a condom in the last 6 months or has had an STI in the past 6 months
  - Does not regularly use condoms and who has sex with people of unknown HIV status who are at risk for contracting HIV
  - Anyone who has injected illicit drugs, shared drug injection equipment, or been in treatment for injection drug use in the past 6 months
- FDA approval was only for TDF/emtricitibine
- April, 2016---FDA approved TAF/emtricitibine for use in HIV infection, but did NOT approve it for PrEP
  - ? Differences in rectal/vaginal concentrations
  - Clinical trial to comparing TAF- vs TDF=based regimens are ongoing
PrEP

**Ipergay**
- Truvada taken at the time of HIV exposure
  - MSM at risk for HIV infection took two Truvada pills one day to two hours before they anticipated having sex and then one pill at 24 and 48 hours after sex
  - Annual incidence of HIV was 0.94% in the Truvada arm and 6.75% in the placebo
- **Overall effectiveness: 86%**
- DSMB unrandomized the trial
- Open label extension study
  - 334 person years of follow up
  - Only one acquisition in an individual who stopped PrEP

**Proud**
- Two year study
- Truvada given daily to half of the study population immediately, the other half a year later
- **Overall effectiveness: 86%**
- DSMB unrandomized the trial
- PROUD closed April 2016 but seeking new funding sources
- DISCOVER trial planned: TAF/emtricitidine
ANRS Prevenir: Daily vs On-Demand TDF/FTC Oral PrEP

- Multicenter, open-label, prospective cohort study in Paris

Beginning of Study
May 3, 2017

Current Analysis
July 2, 2018

End of Study
May 31, 2020

HIV-negative adults at high risk of HIV infection with inconsistent condom use; CrCl ≥ 50 mL/min; HBsAg negative in on-demand arm (N = 1594)*

Daily TDF/FTC PrEP†
(n = 724)

On-Demand TDF/FTC PrEP†
(2-1-1: 2 doses before sex, 1 dose QD for 2 days after sex)
(n = 870)

*Participants enrolled in arm of their choice with ability to switch; target enrollment, N = 3000 (85% MSM).
†Plus condoms, gels, risk reduction and adherence counseling, questionnaire on sexual behavior. Follow-up every 3 mos with STI and/or HIV testing, plasma creatinine measurement.

- Predominantly MSM (98.8%), white (85.2%); median age: 36 yrs

- Primary endpoint: ≥ 15% reduction in new HIV diagnoses among MSM in Paris vs rate reported by National Surveillance network in 2016

- Secondary endpoints: PrEP adherence, sexual behavior, safety

### ANRS Prevenir: HIV Incidence

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>HIV incidence/100 PY (95% CI)</td>
<td>0 (0-0.8)</td>
<td>0 (0-0.7)</td>
</tr>
</tbody>
</table>

- Mean follow-up: 7 mos
- Overall HIV infections averted, n = 85
  - Assuming incidence of 9.17/100 PY as reported for ANRS IPERGAY study among participants in Paris
- Overall incidence of study discontinuation: 3.3/100 PY, including PrEP discontinuations of 1.5/100 PY

CDC Interim Guidance on HIV Pre-Exposure Prophylaxis

**Before initiating PrEP**

**Determine eligibility:**
- Document negative HIV antibody test immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection or reports unprotected sex with an HIV-positive person in the preceding month.
- Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding.
- Confirm that patient is at ongoing, very high risk for acquiring HIV infection.
- If any sexual partner is known to be HIV-infected, determine whether receiving antiretroviral therapy; assist with linkage to care if not in care or not receiving antiretroviral therapy.
- Confirm that calculated creatinine clearance is ≥60 mL per minute (Cockcroft-Gault formula).

**Other recommended actions:**
- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision regarding prescribing PrEP.
- Screen and treat as needed for sexually transmitted infections (STIs).
- Disclose to women that safety for infants exposed during pregnancy is not fully assessed but no harm has been reported.
- Do not prescribe PrEP to women who are breastfeeding.

**Beginning PrEP medication regimen:**
- Prescribe tenofovir disoproxil fumarate 300 mg (TDF) plus emtricitabine 200 mg (FTC) (i.e., one Truvada [Gilead Sciences] tablet) daily.
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected. For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about use during pregnancy.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC, which may serve as both treatment of active hepatitis B infection and HIV prevention.
- Provide risk reduction and PrEP medication-adherence counseling and condoms.

**Follow-up while PrEP medication is being taken:**
- Every 2–3 months, perform an HIV antibody test (or fourth generation antibody/antigen test) and document negative result.
- At each follow-up visit for women, conduct a pregnancy test and document results; if pregnant, discuss continued use of PrEP with patient and prenatal-care provider.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.

**On discontinuing PrEP** (at patient request, for safety concerns, or if HIV infection is acquired):
- Perform HIV tests to confirm whether HIV infection has occurred.
- If HIV positive, order and document results of resistance testing, establish linkage to HIV care.
- If HIV negative, establish linkage to risk reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B infection.
- If pregnant, inform prenatal-care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding.

Recommendations in black apply to both adult MSM and heterosexual-active men and women; items in blue are specific to heterosexual women.
Opposites Attract
- Australian study presented at CROI
- 135 serodiscordant gay couples
- No linked transmissions

PARTNER Study
- 888 serodiscordant couples
- HIV positive partner viral load undetectable on ART
- 38% gay men
- Followed for 1.6 years
- Total sexual encounters without a condom: 58,213 events
- HIV passage linked to partners: 0
- Note: 11 new HIV infections with genetically different HIV acquisition

IAS 2016; CROI 2015
PARTNER2: HIV Risk in Serodiscordant MSM Partners

- Multicenter, observational, prospective study of HIV serodiscordant couples in which the HIV-positive partners received suppressive ART
  - PARTNER1: 2010-2014 (MSM and heterosexuals)
  - PARTNER2: 2014-2018 (MSM only)

- Primary aim: estimate within-couple HIV transmission risk for serodiscordant MSM having condomless sex while HIV-positive partner had HIV-1 RNA < 200 copies/mL
  - No PEP or PrEP use reported by HIV-negative partner
  - Linked infections established by phylogenetic analysis of HIV-1 \textit{pol} and \textit{env} sequences isolated from plasma or PBMCs

PARTNER2: HIV Transmission

- No linked transmissions documented in ~77,000 condomless sex acts when HIV-positive MSM partner suppressed to HIV-1 RNA < 200 copies/mL

<table>
<thead>
<tr>
<th>Sexual Behavior Reported by HIV-Negative Partner</th>
<th>Linked Transmissions, n</th>
<th>Upper 95% CI*</th>
<th>Condomless Sex Acts, n</th>
<th>CYFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sex</td>
<td>0</td>
<td>0.23†</td>
<td>76991</td>
<td>1596</td>
</tr>
<tr>
<td>Anal sex</td>
<td>0</td>
<td>0.24</td>
<td>70743</td>
<td>1546</td>
</tr>
<tr>
<td>Insertive anal sex</td>
<td>0</td>
<td>0.27</td>
<td>52572</td>
<td>1345</td>
</tr>
<tr>
<td>Receptive anal sex without ejaculation</td>
<td>0</td>
<td>0.43</td>
<td>23153</td>
<td>867</td>
</tr>
<tr>
<td>Receptive anal sex with ejaculation</td>
<td>0</td>
<td>0.57</td>
<td>20770</td>
<td>652</td>
</tr>
<tr>
<td>Any sex with an STI</td>
<td>0</td>
<td>2.74</td>
<td>6301</td>
<td>135</td>
</tr>
</tbody>
</table>

*For rate of within-couple HIV transmission per 100 CYFU. †Compared with 0.84 for MSM and 0.46 for heterosexuals in PARTNER1.

- Unlinked transmissions occurred in 15 initially HIV-negative MSM partners

Locate your local PrEP program

https://npin.cdc.gov/preplocator
HIV Vaccine

• RV144 ALVAC-HIV/AIDS VAX® B/E/alum HIV vaccine trial conducted in Thailand
  • 31% efficacy at 3.5 years
  • In this phase ½ South African trial (HVTN100), a modified vaccine expressed HIV-1 antigens matched to circulating clade C strains and bilvalent gp120 (the HVTN100 trial) in South Africa
  • 100% of HVTN recipients developed IgG binding antibodies

Meeting the "Go" Criteria: immunogenicity from HVTN100, a phase 1/2 randomized, double blind, placebo-controlled trial of clade C ALVAC® (vCP2438) and Bivalent Subtype C gp120/MF59® in HIV-uninfected South African adults. IAS 2016.
Ongoing HIV Vaccine-related Trials

• Large-scale trial in South Africa using the altered version of the Thai vaccine
  • 5400 HIV-negative men and women
  • May lead to the first licensed vaccine against HIV
  • Goal is 50% protection

• AMP (Antibody Mediated Protection) trial
  • IV infusion of a broadly neutralizing antibody
  • South Africa, U.S. and South America

Meeting the "Go"Criteria: immunogenicity from HVTN100, a phase 1/2 randomized, double blind, placebo-controlled trial of clade C ALVAC® (vCP2438) and Bivalent Subtype C gp120/MF59® in HIV-uninfected South African adults. IAS 2016.
Challenge #2: Making it Safe, and Simple

GI
- Protease inhibitors

CNS
- Efavirenz

ART

Renal
- Tenofovir disoproxil F (TDF)

Bone
- Tenofovir disoproxil F (TDF)
Relative to TDF 300 mg, TAF 25 mg has:
- Increased intracellular TFV-DP levels by ~7 fold
- Decreased circulating plasma TFV levels by 90%
Challenge #2: Making it Simple with once-daily regimens

- efavirenz/TDF/emtricitibine (Atripla)
- rilpivirine/TDF/FTC (Complera)
- rilpivirine/TAF/FTC (Odefsey)
- elvitegravir/cobicistat/TDF/FTC (Stribild)
- elvitegravir/cobicistat/TAF/FTC (Genvoya)
- dolutegravir/abacavir/ lamivudine (Triumeq)
- Bictegravir/TAF/FTC (Biktarvy)
- Dolutegravir/rilpivirine (Juluca)
- Darunavir/cobicistat/TAF/FTC (Symtuza)
### DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

<table>
<thead>
<tr>
<th>Class</th>
<th>DHHS(^1)</th>
<th>IAS-USA(^2)</th>
</tr>
</thead>
</table>
| INSTI | ▪ BIC/TAF/FTC  
       | ▪ DTG/ABC/3TC  
       | ▪ DTG + (TAF or TDF)/FTC  
       | ▪ EVG/OBI/(TAF or TDF)/FTC  
       | ▪ RAL + (TAF or TDF)/FTC | ▪ BIC/TAF/FTC  
       | ▪ DTG/ABC/3TC  
       | ▪ DTG + TAF/FTC |

Bold text identifies single-tablet regimens.

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status.
- Data are lacking for women of child-bearing age not using contraception.
- IAS-USA now lists EVG/OBI/TAF/FTC and RAL + TAF/FTC as alternative regimens owing to their lower resistance barriers and, respectively, more drug interactions and higher pill burden\(^2\).

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Two drugs?

GEMINI: Time to Virologic Suppression

*Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.

Challenge #3: Can we develop long-acting medication regimens

Injectable HIV treatment

- Low solubility crystalline drugs suspended in an aqueous vehicle
  - Cabotegravir
    - ½ life 21-50 days
  - Rilpivirine

Muller et al., European Journal of Pharmaceutics and Biopharmaceutics, 2011
Injectable HIV treatment

- **LATTE-2**
  - Cabotegravir and rilpivirine given as nanosuspension, long-acting IM regimens
  - Phase 2b; 309 patients
  - 92% remained suppressed at week 48
  - Q4 week injections led to lower rates of virologic non-response compared to Q8 week injections
    - Going into phase 3 using q4 week injections
    - Also under study for use as PrEP

### Week 48 Snapshot Study Outcomes (ITT-ME)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CAB LA + RPV LA Q8W (n=115)</th>
<th>CAB LA + RPV LA Q4W (n=115)</th>
<th>Oral CAB 30 mg + ABC/3TC (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%HIV-1 RNA &lt;50 c/mL at W48</td>
<td>92%** (2.9:-6.6, 12.4)</td>
<td>91%** (2.0:-7.6, 11.6)</td>
<td>89%</td>
</tr>
<tr>
<td>Discontinued due to lack of efficacy (PDVF)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Discontinued due to Other Reasons while Not Suppressed</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Data in window not &lt;50 c/mL</td>
<td>1 (7%)</td>
<td>1 (&lt;1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Non-response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued due to AE or Death</td>
<td>1 (&lt;1%)</td>
<td>6 (5%)**</td>
<td>2 (4%)*</td>
</tr>
<tr>
<td>Discontinued due to Other Reasons while Suppressed</td>
<td>1 (&lt;1%)</td>
<td>3 (3%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

### Other Results

<table>
<thead>
<tr>
<th>Category</th>
<th>CAB LA + RPV LA Q8W (n=115)</th>
<th>CAB LA + RPV LA Q4W (n=115)</th>
<th>Oral CAB 30 mg + ABC/3TC (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of injections</td>
<td>2126</td>
<td>1725</td>
<td>NA</td>
</tr>
<tr>
<td>Number of ISR events</td>
<td>1017 (80%)</td>
<td>245 (19%)</td>
<td>1135 (89%)</td>
</tr>
<tr>
<td>Grade 1 – mild (%)</td>
<td>1381 (99%)</td>
<td>1381 (99%)</td>
<td>1381 (99%)</td>
</tr>
<tr>
<td>Grade 2 – moderate (%)</td>
<td>245 (19%)</td>
<td>245 (19%)</td>
<td>245 (19%)</td>
</tr>
<tr>
<td>ISR Duration ≤7 days</td>
<td>1135 (89%)</td>
<td>1135 (89%)</td>
<td>1135 (89%)</td>
</tr>
<tr>
<td>Median CD4+ cells/mm³</td>
<td>449</td>
<td>499</td>
<td>518</td>
</tr>
<tr>
<td>Baseline</td>
<td>+248 (152, 347)</td>
<td>+258 (133, 355)</td>
<td>+307 (199, 566)</td>
</tr>
</tbody>
</table>

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**Challenge #4: Co-infection**

- HCV infection is a leading cause of morbidity and mortality among patients with HIV-1
  - rapid progression of liver disease
  - increased risk of cirrhosis, end-stage liver disease, and HCC
- Treatment of HIV slows HCV progression and is recommended for all HIV-infected individuals
HIV Co-infection Studies

• Astral-5
  • Once daily fixed dose combination of sofosbuvir/velpatasvir
  • Given for 12 weeks
  • 95% cure rate

• TURQUOISE-I (part 2)
  • PROD=paritaprevir, ritonavir, ombitasvir, dasabuvir for 12/24 weeks
  • Genotype 1, 4 only
  • 98/100% cure rates
# Treatment-Naive Genotype 1a Without Cirrhosis

## Recommended and alternative regimens listed by evidence level and alphabetically for:

## Treatment-Naive Genotype 1a Patients Without Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs(^a) for elbasvir</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^b)</td>
<td>8 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is &lt;6 million IU/mL</td>
<td>8 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

| \(^a\) Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. |
| \(^b\) This is a 3-tablet coformulation. Please refer to the prescribing information. |
| \(^c\) The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV co-infection for patients on antiretroviral therapy. |
# Regimens Not Recommended for Patients with HIV/HCV Coinfection

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral treatment interruption to allow HCV therapy is <strong>not</strong> recommended.</td>
<td>III, A</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir should <strong>not</strong> be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.</td>
<td>III, B</td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir should <strong>not</strong> be used with atazanavir, ritonavir-containing antiretroviral regimens, efavirenz, or etravirine.</td>
<td>III, B</td>
</tr>
<tr>
<td>Sofosbuvir/velpatsavir should <strong>not</strong> be used with efavirenz, etravirine, or nevirapine.</td>
<td>III, B</td>
</tr>
<tr>
<td>Sofosbuvir/velpatsavir/voxilaprevir should <strong>not</strong> be used with ritonavir-boosted atazanavir, efavirenz, etravirine, or nevirapine.</td>
<td>III, B</td>
</tr>
<tr>
<td>Sofosbuvir-based regimens should <strong>not</strong> be used with tipranavir.</td>
<td>III, B</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir plus dasabuvir should <strong>not</strong> be used with darunavir, efavirenz, ritonavir-boosted lopinavir, ritonavir-boosted tipranavir, etravirine, nevirapine, cobicistat, or rilpivirine.</td>
<td>III, B</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should <strong>not</strong> be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy.</td>
<td>III, B</td>
</tr>
<tr>
<td>Ribavirin should <strong>not</strong> be used with didanosine, stavudine, or zidovudine.</td>
<td>III, B</td>
</tr>
<tr>
<td>Simeprevir should <strong>not</strong> be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.</td>
<td>III, B</td>
</tr>
</tbody>
</table>
# Drug Interactions Between DAAs and ARV Drugs—Recommended Regimens

Green indicates coadministration is safe; yellow indicates dose change or additional monitoring is warranted; pink indicates combination should be avoided.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-boosted etazanavir (ATZ)</td>
<td>▲ LDV ▲ ATZ³</td>
<td>▲ VEL ▲ ATZ³</td>
<td>▲ ELB ▲ GRZ ▲ ATZ</td>
<td>▲ GLE ▲ PIB ▲ ATZ</td>
<td>▲ VOX ▲ ATZ³</td>
</tr>
<tr>
<td>Ritonavir-boosted darunavir (DRV)</td>
<td>▲ LDV ▲ DRV³</td>
<td>▲ VEL ▲ DRV³</td>
<td>▲ ELB ▲ GRZ ▲ DRV³</td>
<td>▲ GLE ▲ PIB ▲ DRV³</td>
<td>▲ VOX ▲ DRV³</td>
</tr>
<tr>
<td>Ritonavir-boosted lopinavir (LPV)</td>
<td>No data³</td>
<td>▲ VEL ▲ LPV³</td>
<td>▲ ELB ▲ GRZ ▲ LPV</td>
<td>▲ GLE ▲ PIB ▲ LPV</td>
<td>No data³</td>
</tr>
<tr>
<td>Ritonavir-boosted tipranavir (TPV/r)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Elavirenz (EFV)</td>
<td>▲ LDV ▲ EFV³</td>
<td>▲ VEL ▲ EFV³</td>
<td>▲ ELB ▲ GRZ ▲ EFV³</td>
<td>▲ GLE ▲ PIB ▲ EFV³</td>
<td>No data³</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>▲ LDV ▲ RPV</td>
<td>▲ VEL ▲ RPV</td>
<td>▲ ELB ▲ RPV</td>
<td>▲ GLE ▲ PIB ▲ RPV</td>
<td>▲ VOX ▲ RPV³</td>
</tr>
<tr>
<td>Etravirine (ETV)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data³</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>▲ LDV ▲ RAL</td>
<td>▲ VEL ▲ RAL</td>
<td>▲ ELB ▲ RAL</td>
<td>▲ GLE ▲ PIB ▲ RAL</td>
<td>No data</td>
</tr>
<tr>
<td>Cobicistat-boosted elvitegravir (COB)</td>
<td>▲ LDV ▲ COB³</td>
<td>▲ VEL ▲ COB³</td>
<td>▲ ELB ▲ COB</td>
<td>▲ GLE ▲ PIB ▲ COB</td>
<td>▲ VOX ▲ COB³</td>
</tr>
<tr>
<td>Dolutegravir (DTG)</td>
<td>▲ LDV ▲ DTG</td>
<td>▲ VEL ▲ DTG</td>
<td>▲ ELB ▲ DTG</td>
<td>▲ GLE ▲ PIB ▲ DTG</td>
<td>No data³</td>
</tr>
<tr>
<td>Tenofovir Alafenamide (TAF) / Entecavir (FTC)/Bicitravir (BIC)</td>
<td>▲ LDV ▲ BIC</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>▲ VOX ▲ BIC³</td>
</tr>
<tr>
<td>Maraviroc (MVC)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data³</td>
</tr>
<tr>
<td>Tenofovir (TFV) disoproxil fumarate</td>
<td>▲ LDV ▲ TFV³</td>
<td>▲ VEL ▲ TFV³</td>
<td>▲ ELB ▲ TFV³</td>
<td>▲ TFV</td>
<td>▲ TFV³³</td>
</tr>
<tr>
<td>Tenofovir (TFV) alafenamide</td>
<td>▲ LDV ▲ TFV³</td>
<td>▲ VEL ▲ TFV³</td>
<td>No data</td>
<td>▲ TFV</td>
<td>▲ TFV³³</td>
</tr>
</tbody>
</table>

³ Caution only with tenofovir disoproxil fumarate. ³³ Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered.

³³ Avoid tenofovir disoproxil fumarate in patients with an eGFR <80 ml/min; tenofovir concentrations may exceed those with established renal safety data in individuals on drug- or nucleoside-containing regimens. ³ Shown as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.
# Treatment Recommendations for Patients With HIV/HCV Coinfection

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed).</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily daclatasvir (refer to information above for dose) plus sofosbuvir (400 mg), with or without ribavirin, is a recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals. Refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for treatment duration.</td>
<td>I, B</td>
</tr>
</tbody>
</table>

## Regimens Not Recommended for Patients With HIV/HCV Coinfection

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir for 8 weeks is not recommended, regardless of baseline HCV RNA level.</td>
<td>IIb, C</td>
</tr>
</tbody>
</table>
Challenge #5: Aging

• By 2030, 3 of every 4 HIV-infected patients are expected to be 50 years or older
  • 1/3 of those will have at least 3 age-related disease
  • Severe age-related diseases are highly prevalent in treated HIV-infected adults
    • Most studies suggest a 1.5 to 2-fold increased risk of MI
    • Higher prevalence of low bone mineral density and fractures (age-adjusted fractures was 2-3.7 times higher than general population in the HOPS Study)
  • Increase in neurocognitive disorders=HIV-associated neurocognitive disorders (HAND)
  • Non-AIDS defining cancers have emerged in the aging HIV population
    • anal cancer: 10-30 fold increase
    • HCC:2-5 fold increase
    • lung cancer
    • melanoma

Challenge #5: Aging

Challenge #5: Aging

- San Francisco cohort (IAS 2016)
  - Geriatric assessments among HIV-infected individuals >50
  - 40% reported difficulty with daily activities
  - 30% reported had only poor to fair quality of life
  - 41% reporting falls and a high prevalence of issues with balance

- Stroke incidence is high in the HIV-infected (CROI 2016)
  - Viral load and CD4 cell count significantly associated
  - Women with HIV about twice the stroke risk of HIV-negative women
  - Elevated BP, CD4 count <200, and age were the strongest and most common risk predictors in people with HIV

- START trial
  - Analysis showed that individuals >50 (as well as all subgroups in the START trial) benefit from immediate treatment (IAS 2016)
CVD Risk in HIV-infected Patients Is Beyond That Predicted by Traditional Risk Factors

In the VACS cohort, the HR of MI was 1.48 in HIV vs non-HIV veterans after adjusting for FRS, comorbidities, and substance use (95% CI 1.27-1.72).

(Freiberg, 2013)
Early initiation of ART

- Early therapy appears to reduce, but not eliminate, the HIV reservoir
  - **CHER trial** (Payne et al. Abstract 35. CROI 2015)
    - Infants with HIV randomized to immediate therapy vs delayed
    - 400 infants in South Africa
    - HIV DNA measured from PBMCs
    - Early treatment led to lower levels of proviral DNA in immune cells
  - **ANRS PRIMO cohort** (Ghosn et al. Abstract 373, CROI 2015)
    - 327 adults with primary HIV infection
    - Earlier ART started, the faster HIV DNA reservoirs decreased

- Conclusion: start ART as early as is feasible
Challenge #6: The “Cure”

The reservoir: the complex, challenging barrier to cure

Quiescent, but replication-competent, proviral genomes
What does treatment do to the reservoir?

Challenge #6: The “Cure”

- "Berlin Patient" -- now known to be Timothy Ray Brown -- remains free of any detectable HIV in his blood, gut tissue, and other reservoir sites 8 years after receiving a bone marrow transplant containing stem cells from a donor with the CCR5-Δ32 mutation
  - Repeated chemotherapy
  - Stem cell transplant
  - GVHD
  - Donor lacked CCR5 expression

PLoS Pathog 9, e100..47 (2013)
Novel Approaches

- Targeted nucleases
  - Genetic scissors
    - CRISPR/Cas9
    - Zn-finger nucleases
Gene editing and CCR5

- Autologous cells targeted ex vivo by modification or deletion of the CCR5 gene
- Propagated ex vivo and transfused back into the patient
- Preliminary data (N Engl J Med 2014;370:901-10)
  - Increase in the CCR5-negative population in lymphoid tissues and blood
  - Blood levels of HIV DNA decreased in most patients

• What is needed to clear this infection? Multimodality approach.

- Find the latent virus
- Induce viral protein expression
- Clear the virus with robust immune responses
- Keep it clear
Latency Reversal Agents (LRAs) to activate immune recognition

• Target the quiescent but replication-competent proviral genomes to induce activation
  • Histone deacetylase inhibitors
    • Panobinostat
    • vorinostat
  • Histone demethylase inhibitors
  • BET bromodomain inhibitors
  • PKC agonists
    • bryostatin
Caveats...

- Multiple mechanisms for latency
  - transcriptional repression due to removal of histone acetylation or methylation
  - availability of transcription factors
  - the integration site of the provirus
  - the availability of the LRA to the infected tissues and cells
CURE

- ART
- Therapeutic Vaccines
- Reservoir Depletion
- Immune Activation
Conclusions

- Prevention of HIV is now available and appear highly safe and effective

- Novel formulations of existing drugs and development of new, long-acting agents are emerging

- Vaccine initiatives may soon come to fruition

- The Cure presents the greatest challenge to the field and will likely require a multipronged approach