What’s New in Infectious Diseases?

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Topics

- New Antibacterial Therapeutics
- Emerging Pathogens
- HIV
- Hepatitis C
Disclosures

- Research Studies
  - Pfizer – Staph aureus Vaccine Trial
  - TaiMed Biologics - Ibaluzimab

- Advisory Board
  - Viiv Healthcare
New Antibacterial Therapeutics

- Dalbavancin
- Oritavancin
- Tedizolid
- Ceftolozane/tazobactam
- Ceftazidime/avibactam
- Fecal Transplant
Incidence of Staph aureus hospitalizations in U.S.A., 2001–2009

BMC Infect Dis 2014, 14:296
Dalbavancin (Dalvance)

- Derived from Teicoplanin
- \(\frac{1}{2}\) life
  - Effective: 8.5 days
  - Terminal: 346 hrs (14 days)
- Bactericidal
- Similar spectrum to Vancomycin, active against:
  - Staphylococci
    - MSSA, MRSA, CoNS
  - Streptococci
    - resistant pneumococci
    - anaerobic strep
  - Enterococci
    - VRE with van B, C but not A
  - Corynebacterium
Dalbavancin Once Weekly Non-Inferior to Vanco/Linezolid

Table 2. Primary and Secondary Efficacy End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Dalbavancin number/total number (percent)</th>
<th>Vancomycin–Linezolid number/total number (percent)</th>
<th>Absolute Difference (95% CI) Percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISCOVER 1</td>
<td>240/288 (83.3)</td>
<td>233/285 (81.8)</td>
<td>1.5 (−4.6 to 7.9)</td>
</tr>
<tr>
<td>DISCOVER 2</td>
<td>285/371 (76.8)</td>
<td>288/368 (78.3)</td>
<td>−1.5 (−7.4 to 4.6)</td>
</tr>
<tr>
<td>Both trials</td>
<td>525/659 (79.7)</td>
<td>521/653 (79.8)</td>
<td>−0.1 (−4.5 to 4.2)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISCOVER 1</td>
<td>259/288 (89.9)</td>
<td>259/285 (90.9)</td>
<td>−1.0 (−5.7 to 4.0)</td>
</tr>
<tr>
<td>DISCOVER 2</td>
<td>325/371 (87.6)</td>
<td>316/368 (85.9)</td>
<td>1.7 (−3.2 to 6.7)</td>
</tr>
<tr>
<td>Both trials</td>
<td>584/659 (88.6)</td>
<td>575/653 (88.1)</td>
<td>0.6 (−2.9 to 4.1)</td>
</tr>
<tr>
<td>Secondary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical status</td>
<td>517/570 (90.7)</td>
<td>502/545 (92.1)</td>
<td>−1.5 (−4.8 to 1.9)</td>
</tr>
<tr>
<td>Sensitivity analysis of clinical status†</td>
<td>533/570 (93.5)</td>
<td>517/545 (94.9)</td>
<td>−1.4 (−4.2 to 1.4)</td>
</tr>
<tr>
<td>Investigator’s assessment of outcome</td>
<td>547/570 (96.0)</td>
<td>527/545 (96.7)</td>
<td>−0.7 (−3.0 to 1.5)</td>
</tr>
</tbody>
</table>

* The primary end point was the success rate at 48 to 72 hours after the initiation of therapy (i.e., early clinical response) in the intention-to-treat population. The sensitivity analysis of the primary end point was the success rate, defined as a reduction in the infection area of at least 20% at 48 to 72 hours after the initiation of therapy, in the intention-to-treat population. The secondary end points were evaluated in a pooled analysis and included success rates at the end of therapy in the clinical per-protocol population. For the pooled analysis, the weighted difference in success rates was calculated.

† The degree of fluctuance or localized heat or warmth had to be improved from baseline.
Single-Dose (1.5 g) Non-Inferior to Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection

VA Experience with Dalbavancin

• Background
  – Levels in bone > MIC for 14 days

• 8 patients treated for osteomyelitis with IV Dalbavancin
  – Former IV drug users not eligible for home IV or unwilling to do home IV

• Treated for up to 8 weeks

• No adverse events

• All with resolution of osteomyelitis

• Cost savings vs. placement in facility
Oritavancin (Orbactiv)

- Derived from Vancomycin
- $\frac{1}{2}$ life
  - Terminal 245-393 hrs (10-16 days)
- Bactericidal
- Similar spectrum to Vancomycin, active against
  - Staphylococci
    - MSSA, MRSA, CoNS
  - Streptococci
    - resistant pneumococci
    - anaerobic strep
  - Enterococci
    - VRE with van A, B, C
  - Corynebacterium
### Single Dose Oritavancin vs. Vancomycin in Acute Bacterial Skin Infections

#### Modified intention-to-treat population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
<th>Percentage-Point Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>391/475 (82.3)</td>
<td>378/479 (78.9)</td>
<td>3.4 (-1.6 to 8.4)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>378/475 (79.6)</td>
<td>383/479 (80.0)</td>
<td>-0.4 (-5.5 to 4.7)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>413/475 (86.9)</td>
<td>397/479 (82.9)</td>
<td>4.1 (-0.5 to 8.6)</td>
</tr>
</tbody>
</table>

#### CE population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
<th>Percentage-Point Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>344/394 (87.3)</td>
<td>342/397 (86.1)</td>
<td>1.2 (-3.6 to 5.9)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>357/394 (90.6)</td>
<td>352/397 (88.7)</td>
<td>1.9 (-2.3 to 6.2)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>362/394 (91.9)</td>
<td>370/397 (93.2)</td>
<td>-1.3 (-5.0 to 2.3)</td>
</tr>
</tbody>
</table>

#### Patients infected with MRSA in intention-to-treat population with microbiologic evaluation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
<th>Percentage-Point Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>84/104 (80.8)</td>
<td>80/100 (80.0)</td>
<td>0.8 (-10.1 to 11.7)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>86/104 (82.7)</td>
<td>83/100 (83.0)</td>
<td>-0.3 (-10.7 to 10.0)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>94/104 (90.4)</td>
<td>84/100 (84.0)</td>
<td>6.4 (-2.8 to 15.5)</td>
</tr>
</tbody>
</table>

#### Patients infected with MSSA in intention-to-treat population with microbiologic evaluation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
<th>Percentage-Point Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>96/116 (82.8)</td>
<td>92/110 (83.6)</td>
<td>-0.9 (-10.6 to 8.9)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>89/116 (76.7)</td>
<td>88/110 (80.0)</td>
<td>-3.3 (-14.0 to 7.4)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>98/116 (84.5)</td>
<td>94/110 (85.5)</td>
<td>-1.0 (-10.3 to 8.3)</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>Oritavancin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Short infusion: 30 min</td>
<td>• Active against van A enterococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Active against catheter related BSI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Few drug-drug interactions</td>
<td>• Long infusion: 3 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• $pK$ data in bone, tissue</td>
<td>– Infusion reaction if shorter</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Drug-drug interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– 31% increase warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can prolong PTT and CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– No heparin within 48 hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tedizolid (Sivextro)

- Oxazolidinone antibiotic
- Prodrug
- pK
  - ½ life 12 hrs
  - Once daily
  - >90% oral bioavailable
- Bacteriostatic
  - Cidal in animal models
- Not expected to have MAOI interactions
- Microbiology
  - Staphylococci
    - MSSA, MRSA, CoNS
  - Streptococci
    - resistant pneumococci
    - anaerobic strep
  - Enterococci
  - Corynebacterium
  - Atypical mycobacteria
Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

JAMA. 2013;309(6):559-569
Should I use Tedizolid or Linezolid

Tedizolid
• Once daily
• 6 days for ABSSSI
• Potentially
  – Less MAOI interaction
  – Less hematologic effects
• May be active against some linezolid resistant strains
• No dose adjustment in hepatic or renal

Linezolid
• Now generic so lower cost
• Twice daily
• 10 days for ABSSSI
• Interaction with MAOI
• Hematologic effects
• Possible accumulation of metabolites in renal failure

Lancet Infect Dis 2010; 10: 597–602
New Agents to Treat GNRs

Ceftolozane

Ceftazidime

Tazobactam

Avibactam

Drugs. 2013 Feb;73(2):159-77.
Ceftolozane/Tazobactam (Zerbaxa)

- 1.5g (1g Ceftolozane 0.5g Tazobactam) **every 8 hours**
  - Needs renal adjustment

- FDA approved for
  - Complicated urinary tract infections
  - Complicated intra-abdominal infections

- Broad spectrum gram negative activity including
  - *Pseudomonas aeruginosa* (including MDR strains)
  - Some extended-spectrum beta-lactamases (ESBL) from the TEM-1 & 2, SHV, CTX-M and OXA groups
  - **NOT active against organisms that produce serine carbapenemases (eg., KPCs) and metallo-beta lactamases**

- Other activity includes the *Streptococcus milleri* group (*S. anginosus*, *S. constellatus*, *S. intermedius*) and *Bacteroides fragilis*
Ceftazidime/Avibactam (Avycaz)

- 2.5 gm (2 gm ceftazidime, 0.5 gm avibactam) over 2 hours **every 8 hours**
  - Renal dose adjustments required

- FDA approved for
  - Complicated urinary tract infections
  - Complicated intra-abdominal infections

- Avibactam is a potent inhibitor of class A, class C and some class D beta-lactamases

- Broad spectrum gram negative activity including Enterobacteriaceae including **ESBLs** (TEM, SHV, CTX-M) and **KPC producers**, and Pseudomonas
  - Minimal anaerobe coverage, high MICs for *B. fragilis*

- Note - avibactam does not restore the activity of ceftazidime against *P. aeruginosa* as reliably as it does Enterobacteriaceae (likely due to other mechanisms of resistance such as porin alterations, efflux pumps, metallo-β-lactamases or OXA β-lactamases)
When to use the GNR antibiotics

- **Ceftolozane/tazobactam**
  - FDA approved
    - UTI
    - cIAI
  - Being studied in VABP
  - Renal adjustment
  - Use
    - **MDR Pseudomonas**
    - Some ESBLs
    - Not active against KPC
  - Cost $$$

- **Ceftazidime/avibactam**
  - FDA approved
    - UTI
    - cIAI
  - Being studied in VABP
  - Renal adjustment
  - Use
    - MDR Pseudomonas
    - ESBLs
    - **Active against KPC**
  - Cost $$$$$

- Need to check susceptibilities for use
Incidence of Nosocomial *Clostridium difficile* Infection

Antibiotic Classes and Their Association with Clostridium difficile infection

- Careful use of antibiotics can make a difference – antimicrobial stewardship

<table>
<thead>
<tr>
<th>Class</th>
<th>Association with C. difficile Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Very common</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Very common</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Very common</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Very common</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Very common</td>
</tr>
<tr>
<td>Other penicillins</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
# Treatment of Clostridium difficile infection

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical Manifestations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carrier</td>
<td>No symptoms or signs</td>
<td>No treatment indicated</td>
</tr>
<tr>
<td>Mild†</td>
<td>Mild diarrhea (3 to 5 unformed bowel movements per day), afebrile status, mild abdominal discomfort or tenderness, and no notable laboratory abnormalities</td>
<td>Predisposing antibiotic cessation, hydration, monitoring of clinical status, and either administration of metronidazole (500 mg three times per day) or close outpatient monitoring without the administration of antibiotics</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate nonbloody diarrhea, moderate abdominal discomfort or tenderness, nausea with occasional vomiting, dehydration, white-cell count &gt;15,000/mm³, and blood urea nitrogen or creatinine levels above baseline</td>
<td>Consideration of hospitalization and cessation of predisposing antibiotics; hydration, monitoring of clinical status, and either administration of oral metronidazole (500 mg three times per day) or first-line therapy with oral vancomycin (125 mg four times per day for 14 days)</td>
</tr>
<tr>
<td>Severe</td>
<td>Severe or bloody diarrhea, pseudomembranous colitis, severe abdominal pain, vomiting, ileus, temperature &gt;38.9°C, white-cell count &gt;20,000/mm³, albumin level &lt;2.5 mg/dl, and acute kidney injury</td>
<td>Hospitalization; oral or nasogastric vancomycin (500 mg four times per day) with or without intravenous metronidazole (500 mg three times per day), or oral fidaxomicin (200 mg twice a day for 10 days) instead of vancomycin if the risk of recurrence is high</td>
</tr>
<tr>
<td>Complicated</td>
<td>Toxic megacolon, peritonitis, respiratory distress, and hemodynamic instability</td>
<td>Antibiotics as for severe infection, and surgical consultation for subtotal colectomy or a diverting ileostomy with vancomycin colonic lavage; consideration of fecal microbial transplantation or additional antibiotics</td>
</tr>
<tr>
<td>First recurrence</td>
<td></td>
<td>Oral vancomycin (125 mg four times per day for 14 days) or oral fidaxomicin (200 mg twice a day for 10 days)</td>
</tr>
<tr>
<td>Second or further recurrence</td>
<td></td>
<td>Vancomycin in a tapered and pulsed regimen; fecal microbial transplantation, or fidaxomicin (200 mg twice a day for 10 days)</td>
</tr>
</tbody>
</table>

Rates of Cure and Changes to the Microbiota after Fecal Microbial Transplantation for Recurrent *Clostridium difficile* Infection.
Emerging Pathogens

- Ebola
- Zika
- Chikungunya
- Borrelia miyamotoi
Ebola Virus

• Filovirus
• Clinical
  – Fever, severe headache, muscle pain, weakness, fatigue, diarrhea, vomiting, abd pain, unexplained hemorrhage (bleeding or bruising)
  – Incubation: 8-10 days (range 2-21 days)
  – Mortality rate: 25-90%
Ebola
What Did We Learn

• Ebola virus disease survivors frequently reported anorexia and arthralgia

• Persistence
  – Semen – detected 284 days after symptoms
  – Aqueous humour – detected 9 weeks after recovery
  – Vaginal fluids, sweat, urine, and breast milk
  – CNS symptoms 9 months after recovery

• Can be sexually transmitted

• Transfusion of plasma from convalescent donors did not improve survival
  – Neutralizing Ab levels not checked

• Patients receiving Artesunate-amodiaquine had a 31% lower risk of death than those receiving artemether-lumefantrine
Ebola
What Did We Learn

• Multilevel, interprofessional collaboration to isolate HID cases and reduce disease transmission will be crucial to contain future outbreaks\(^1\)

• Potential therapies
  – Virus-neutralizing antibody cocktail (ZMab)
  – Vesicular stomatitis virus-vectored Ebola glycoprotein vaccine (rVSV/ZEBOV-GP)
  – T-705 (favipiravir) - nucleotide analog
  – BCX4430 – nucleoside analogue

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1. Infect Control Hosp Epidemiol. 2015 Dec 8:1-6. [Epub ahead of print]
Zika Virus

- Arbovirus
- First isolated in Zika Forest Uganda 1947
- Transmitted by Aedes mosquito
- Incubation: 3-12 days
- Symptoms: mild fever, arthralgia (small joints of hands and feet), myalgia, HA, asthenia, abdominal pain, edema, lymphadenopathy, retro-orbital pain, conjunctivitis, and cutaneous maculopapular rash
- Largely limited to Africa and Asia until 2015 when spread to Brazil, Columbia, Venezuela, Mexico
- Now cases in Puerto Rico, Texas, Hawaii
Distribution of Zika Virus

Zika Virus in Travelers returning from the Cook Islands

- Conjunctivitis and Rash

Clin Infect Dis. 2015; 61 (9): 1485-1486
Zika vs. Dengue

• Conjunctivitis
  – 17/31 [55%] of ZIKA patients vs 14/148 [9%] DENGUE patients

• Absence of thrombocytopenia

• Rash
  – more common in ZIKA

Clin Infect Dis. 2015; 61 (9): 1485-1486
Zika Virus
Why is it Important

- Largely limited to Africa and Asia until 2015 when spread to Brazil, Columbia, Venezuela, Mexico
- Now in Puerto Rico, Texas, Hawaii
  - Texas case in traveler from El Salvador
  - Local transmission reported in Samoa, Puerto Rico, Mexico, Caribbean, Central and South America
- Linked to
  - Microcephaly in pregnant women with infection
    - 1200-4000 cases in Brazil (up from 150-200) coincident with outbreak
    - Brazilian government recommending that mothers delay conception
  - Guillain-Barre syndrome
- What can you do
  - Mosquito control/avoidance
  - No treatment
Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016

Emily E. Petersen, MD¹; J. Erin Staples, MD, PhD²; Dana Meaney-Delman, MD³; Marc Fischer, MD²; Sascha R. Ellington, MSPH¹; William M. Callaghan, MD¹; Denise J. Jamieson, MD¹

- Test Pregnant women for Zika in consult with health dept if
  - history of travel to an area with Zika virus transmission
  - and 2+ symptoms consistent with Zika virus disease during or within 2 weeks of travel
    - acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis
  - or have US findings of fetal microcephaly or intracranial calcifications
- All pregnant women consider postponing travel to areas where Zika virus transmission is ongoing
- If a pregnant woman travels to an area with Zika virus transmission, she should be advised to avoid mosquito bites
Chikungunya Virus

- Arbovirus (alpha virus)
- Transmitted by Aedes mosquitoes
- Incubation period is typically 3–7 days (range, 1–12 days)
- Symptoms: acute onset of fever (typically >39°C) and polyarthralgia
  - Joint symptoms are usually bilateral and symmetric
    • can be severe and debilitating
  - Other symptoms: headache, myalgia, arthritis, conjunctivitis, nausea/vomiting, or maculopapular rash
  - Clinical laboratory findings: lymphopenia, thrombocytopenia, elevated creatinine, and elevated hepatic transaminases
- Acute symptoms typically resolve within 7–10 days
- Some with persistent joint pains for months to years
- Mortality is rare and occurs mostly in older adults
Countries and territories where Chikungunya Reported 2015

http://www.cdc.gov/chikungunya/geo/index.html
Chikungunya in the U.S. - 2015

- 679 Travel associated cases
- 202 locally-transmitted cases
  - All in Puerto Rico and US Virgin Islands

Chikungunya Virus

• Treatment
  – Symptomatic – NSAIDs (if no dengue)
  – No specific treatment
## Virus Comparison

<table>
<thead>
<tr>
<th>Chikungunya</th>
<th>Dengue</th>
<th>Zika</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Fever</td>
<td>Fever/High fever</td>
<td>Fever</td>
</tr>
<tr>
<td>Severe arthralgia</td>
<td>Severe headache</td>
<td>Rash</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Joint pains</td>
<td>Joint pain</td>
</tr>
<tr>
<td>Rash</td>
<td>Neutropenia</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Thrombocytopenia</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shock</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

- Presentation can be similar.
- Use predominant symptoms and/or travel history to help
- Diagnosis may have to rely on diagnostic tests
Borrelia Miyamotoi

- First human case identified in Russia in 2011
- Prevalence in ticks 1-5%
- Cases present similarly to Human Granulocytic Anaplasmosis

Clin Microbiol Infect. 2015 Jul;21(7):631-639
Relationship of Borrelia Species

B. miyamotoi LB-2001 (USA)

B. miyamotoi FR64b (Japan)

B. turicatae

B. parkeri

B. hermsii (Genomic group I)

B. hermsii (Genomic group II)

B. crocidurae

0.02

B. burgdorferi

B. afzelii
Geographic Distribution of Tick vectors of Borrelia miyamotoi

- Vectors in US: Ixodes scapularis and pacificus
Clinical Features of 51 Patients with Borrelia miyamotoi

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value*</th>
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</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>55 (12-82)</td>
</tr>
<tr>
<td>Male</td>
<td>29 (57)</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>49 (96)</td>
</tr>
<tr>
<td>Headache†</td>
<td>49 (96)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42 (84)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>39 (76)</td>
</tr>
<tr>
<td>Malaise/fatigue</td>
<td>42 (82)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms‡</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Cardiac/respiratory symptoms§</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
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</tr>
</tbody>
</table>
Lab Findings in 51 Patients with Borrelia miyamotoi

- Elevated liver enzyme levels, neutropenia, and thrombocytopenia

- Treatment: Doxycycline
  - Some reports of slower resolution of clinical symptoms than with HGA or Lyme

*Ann Intern Med. 2015;163:91-98*
HIV

• Treat All
• New Drugs
• New Strategies
• PrEP
The HIV Incidence in the U.S. Has Not Changed

Estimated New HIV Infections

START Trial
Reduction in Events when ART started with CD4 > 500 vs. 350

No. at Risk
<table>
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<tr>
<th></th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
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<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
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<tbody>
<tr>
<td>Immediate init</td>
<td>2326</td>
<td>2302</td>
<td>2279</td>
<td>2163</td>
<td>1801</td>
<td>1437</td>
<td>1031</td>
<td>757</td>
<td>541</td>
<td>336</td>
<td>110</td>
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<tr>
<td>Deferred init</td>
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<td>2326</td>
<td>2281</td>
<td>2135</td>
<td>1803</td>
<td>1417</td>
<td>1021</td>
<td>729</td>
<td>520</td>
<td>334</td>
<td>103</td>
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Estimated Percentage
<p>| | | | | | | | | | | | |</p>
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</thead>
<tbody>
<tr>
<td>Immediate init</td>
<td>0.2</td>
<td>0.6</td>
<td>0.8</td>
<td>0.9</td>
<td>1.2</td>
<td>1.5</td>
<td>2.0</td>
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<td>3.1</td>
<td>3.7</td>
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<tr>
<td>Deferred init</td>
<td>0.5</td>
<td>1.2</td>
<td>1.8</td>
<td>2.4</td>
<td>3.3</td>
<td>4.1</td>
<td>4.6</td>
<td>5.3</td>
<td>5.9</td>
<td>7.4</td>
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</tbody>
</table>
## Treatment Guidelines
### When to Start

<table>
<thead>
<tr>
<th>Agency</th>
<th>Treatment Recommendation</th>
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</thead>
<tbody>
<tr>
<td>DHHS</td>
<td>Treat All</td>
</tr>
<tr>
<td>IAS-USA</td>
<td>Treat All</td>
</tr>
<tr>
<td>BHIVA</td>
<td>Treat All</td>
</tr>
<tr>
<td>EACS</td>
<td>Treat All</td>
</tr>
<tr>
<td>WHO</td>
<td>Treat All</td>
</tr>
</tbody>
</table>

Guidelines only differ in the strength of recommendation for different conditions but all recommend to treat everyone with HIV.

# U.S. FDA Approved Antiretroviral Drugs 2015

<table>
<thead>
<tr>
<th>NRTI/NtRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Nevirapine</td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Delavirdine</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Efavirenz</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Etravirine</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Rilpivirine</td>
<td>Lopinavir/r</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td></td>
<td>Atazanavir</td>
</tr>
<tr>
<td>Tenofovir</td>
<td><img src="#" alt="Integrase Inhibitors" /></td>
<td>Fosamprenavir</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td><img src="#" alt="Integrase Inhibitors" /></td>
<td>Tipranavir</td>
</tr>
<tr>
<td>ZDV/ABC/3TC</td>
<td><img src="#" alt="Integrase Inhibitors" /></td>
<td>Darunavir</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td><img src="#" alt="Integrase Inhibitors" /></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC/EFV*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC/RPV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Integrase Inhibitors**: Dolutegravir, ABC/3TC/Dolutegravir*, Raltegravir, TDF/FTC/Elvitegravir/Cobicistat*, TAF/FTC/Elvitegravir/Cobicistat*
- **Entry Inhibitors**: Enfuvirtide, Maraviroc

*Multiple class coformulation
DHHS Guidelines Changes
Recommended Regimens

2014

• NNRTI-Based:
  – EFV/TDF/FTC (AI)
  – If RNA < 100,000
    • EFV + ABC/3TC (AI)
    • RPV/TDF/FTC (AI)

• PI-Based:
  – ATV/r + TDF/FTC (AI)
  – DRV/r + TDF/FTC (AI)
  – If RNA < 100,000
    • ATV/r + ABC/3TC (AI)

• INSTI-Based:
  – DTG + ABC/3TC (AI)
  – DTG + TDF/FTC (AI)
  – EVG/cobi/TDF/FTC (AI)
  – RAL + TDF/FTC (AI)

2015

• INSTI-Based
  – DTG/ABC/3TC (AI)
  – DTG + TDF/FTC (AI)
  – EVG/c/TDF/FTC (AI)
  – RAL + TDF/FTC (AI)

• PI-Based:
  – DRV/r + TDF/FTC (AI)

• Other regimens moved to alternative
Association Between Efavirenz as Initial Therapy for HIV-1 Infection and Increased Risk for Suicidal Ideation or Attempted or Completed Suicide

An Analysis of Trial Data

Katie R. Mollan, MS; Marlene Smurzynski, PhD; Joseph J. Eron, MD; Eric S. Daar, MD; Thomas B. Campbell, MD; Paul E. Sax, MD; Roy M. Gullick, MD; Lumine Na, MS; Lauren O’Keefe, BS; Kevin R. Robertson, PhD; and Camlin Tierney, PhD

Results:
- Virologic Failure
  - RAL=ATV=DRV
- Tolerability Failure
  - ATV > RAL=DRV
- Virologic and Tolerability Failure
  - ATV > DRV > RAL
Future Changes in ART/Guidelines?

• Modified by
  – Toxicities
  – Co-morbidities
  – Aging
  – New agents/strategies

• Will Move to
  – Better tolerability
  – Less side effects/toxicities
  – Better PK – once daily/weekly/monthly
  – May need less than 3 agents
Doravirine – New NNRTI

- Once daily NNRTI
- Minimal Lipid or CNS Effects
- Active against NNRTI mutations:
  - K103N,
  - Y181C,
  - E138K, K101E

FIG 1 Structures of MK-1439 (A), EFV (B), RPV (C), and ETR (D).
**Tenofovir Alafenamide**

- Prodrug of Tenofovir
- Converted intracellularly to TFV
- Higher TFV levels in PBMC than TDF
- Less Toxicity than TDF
  - Less affect on BMD, Creatinine

![Chemical structures of Tenofovir, Tenofovir DF, and GS 7340](image-url)

EVG/Cobi/FTC + TDF vs. TAF – 48 wks

Attachment Inhibitor Prodrug BMS-663068 in Antiretroviral-Experienced Subjects: Week 48 Analysis

Thompson et al, 22nd CROI, Seattle, WA 2015, Abstract 545
Ibalizumab for Treatment of HIV

- **Ibalizumab**
  - humanized IgG4 monoclonal antibody (MAb) administered via IV infusion
  - Binds to domain 2 of CD4 so no immunosuppression
  - Entry inhibitor

*Curr Opin HIV AIDS. 2015 May;10(3):144-50.*
Inhibition of Telomerase Activity and Telomere Shortening in PBMCs with N(t)RTIs

“TDF was the only NRTI tested that enhanced shortening of TL at therapeutic concentrations”

Leeansyah et al, J Infect Dis 2013;207:1157–65
GARDEL: LPV/r + 3TC Noninferior to Triple ART at Wk 48 and Wk 96

- Safety and tolerability also similar between treatment arms

Cahn P, et al. EACS 2015. Abstract 961. Adapted From Clinical Care Options

Wk 48 difference: +4.6%
(95% CI: -2.2 to 11.8; \(P = .171\))

Wk 96 difference: +5.9%
(95% CI: -2.3 to 14.1; \(P = .165\))
**PADDLE: All Pts Virologically Suppressed by Wk 8 of Dolutegravir + Lamivudine**

- Included 4 pts with HIV-1 RNA > 100,000 copies/mL at BL

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Screen</th>
<th>BL</th>
<th>Day 2</th>
<th>HIV-1 RNA, copies/mL</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 6</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 24</th>
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<td>266</td>
<td>97</td>
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<tr>
<td>162</td>
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<td>268</td>
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<td>&lt; 50</td>
<td>Not done</td>
<td>&lt; 50</td>
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<tr>
<td>Not done</td>
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<tr>
<td>106,320</td>
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<td>168</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Figueroa MI, et al. EACS 2015. Abstract 1066. Reproduced with permission. Adapted from Clinical Care Options
Cabotegravir + RPV after induction with CBV + NRTIs

pK of Cabotegravir (IM or SC) and Rilpivirine (IM)

28 pts

25/28 VL < 50 cp/mL
- All <50cp/ml
- All <20cp/ml except 37 cp/mL (1)
- 1 blip W4 (52 cp/mL)

3 virological failures

W12 : 1 pt
VL 138/469 cp/mL

W24 : 2 pts
- VL : 2220 cp/mL
- VL : 291 cp/mL

Katlama C et al. EACS 2015, Oral PS4/4
Trials Demonstrating a Benefit of PrEP TDF/FTC resulted in 49-92% Reduction in HIV

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

Lancet. 2013;381:2083-90
CDC/USPHS and WHO Recommend PrEP

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014
A CLINICAL PRACTICE GUIDELINE

WHO EXPANDS RECOMMENDATION ON ORAL PRE-EXPOSURE PROPHYLAXIS OF HIV INFECTION (PrEP)

NOVEMBER 2015
## Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th></th>
<th>Men Who Have Sex With Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detecting substantial risk</td>
<td>• Sexual partner with HIV</td>
<td>• Sexual partner with HIV</td>
<td>• HIV-positive injecting partner</td>
</tr>
<tr>
<td>of acquiring HIV infection:</td>
<td>• Recent bacterial STD</td>
<td>• Recent bacterial STD</td>
<td>• Sharing injection equipment</td>
</tr>
<tr>
<td></td>
<td>• High number of sex partners</td>
<td>• High number of sex partners</td>
<td>• Recent drug treatment (but currently injecting)</td>
</tr>
<tr>
<td></td>
<td>• History of inconsistent or no condom use</td>
<td>• History of inconsistent or no condom use</td>
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</tr>
<tr>
<td></td>
<td>• Commercial sex work</td>
<td>• Commercial sex work</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lives in high-prevalence area or network</td>
<td></td>
</tr>
<tr>
<td>Clinically eligible:</td>
<td>• Documented negative HIV test before prescribing PrEP</td>
<td>• No signs/symptoms of acute HIV infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No signs/symptoms of acute HIV infection</td>
<td>• Normal renal function, no contraindicated medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Normal renal function, no contraindicated medications</td>
<td>• Documented hepatitis B virus infection and vaccination</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>status</td>
<td></td>
</tr>
<tr>
<td>Prescription</td>
<td>Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90 day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>supply</td>
<td></td>
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<tr>
<td>Other services:</td>
<td>Follow-up visits at least every 3 months to provide:</td>
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</tr>
<tr>
<td></td>
<td>• HIV test, medication adherence counseling, behavioral risk</td>
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</tr>
<tr>
<td></td>
<td>reduction support, side effect assessment, STD symptom</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• At 3 months and every 6 months after, assess renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Every 6 months test for bacterial STDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Do oral/rectal STD testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Assess pregnancy intent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pregnancy test every 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Access to clean needles/syringes and drug treatment services</td>
<td></td>
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</tbody>
</table>

# US Public Service: PrEP for the Prevention of HIV Infection

<table>
<thead>
<tr>
<th>Specific tests</th>
<th>MSM</th>
<th>Heterosexual Women and Men</th>
<th>IDU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral/rectal Gonorrhea and Chlamydia NAAT, and syphilis serology</td>
<td>Assess pregnancy intent Pregnancy test every 3 months</td>
<td>Access to clean needles/ syringes and drug treatment services</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other services</th>
<th>MSM</th>
<th>Heterosexual Women and Men</th>
<th>IDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3 months</td>
<td>HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At 3 months and every 6 months thereafter</th>
<th>MSM</th>
<th>Heterosexual Women and Men</th>
<th>IDU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assess renal function</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Every 6 months</th>
<th>MSM</th>
<th>Heterosexual Women and Men</th>
<th>IDU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test for bacterial STIs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HCV

- Cure
- Duration of therapy
- Therapy for Multiple Genotypes
- Need for Ribavirin
HCV Is Prevalent and Under-diagnosed in the US

Institute of medicine: Hepatitis and Liver Cancer: A national strategy for prevention and control 2010
Most HCV Patients are Untreated

- Total U.S. Population with chronic HCV infection: 3,000,000
- HCV Detected: 50%
- Referred to Care: 32-38%
- HCV RNA test: 20-23%
- Underwent liver biopsy: 12-18%
- Treated: 7-11%
- Successfully Treated: 5-6%

Holmberg SD. NEJM 2013.
HCV Deaths Surpass Those from HIV

Age-adjusted Mortality Rates of HIV and Hepatitis C: United States, 1999-2010

- 16,600 deaths (Hepatitis C)
- 8,369 deaths (HIV)

Advances in Chronic Hepatitis C Treatment

Standard Interferon (IFN) 1991
Add Ribavirin 1998
Pegylated IFN 2001
Directly Acting Antivirals 2011

Sustained Virologic Response (%)

IFN 6 mos 16
IFN 12 mos 34
IFN/RBV 6 mos 42
IFN/RBV 12 mos 39
PegIFN 12 mos 55
PegIFN/RBV 12 mos 70+
PegIFN/RBV/DAA

Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, 2011.
IFN-Free Regimens for Genotype-I HCV Infection - Treatment Naive

### IFN-Free Regimens for Genotype-I HCV Infection - Treatment Experienced

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1b NR ABT450/r ABT 267</td>
<td>36/40</td>
</tr>
<tr>
<td>G1 SOF LDV RBV 12 W F3/F4</td>
<td>25/25</td>
</tr>
<tr>
<td>G1 SOF LDV GS-9669 12 W F3/F4</td>
<td>26/26</td>
</tr>
<tr>
<td>G1 SOF LDV 12 W F3/F4</td>
<td>70</td>
</tr>
<tr>
<td>G1 IP SOF LDV RBV 12 W F3/F4</td>
<td>21/21</td>
</tr>
<tr>
<td>G1 IP SOF LDV RBV 12 W F3/F4</td>
<td>95</td>
</tr>
<tr>
<td>G1 IP SOF LDV RBV 12 W F3/F4</td>
<td>90</td>
</tr>
<tr>
<td>G1 SMV SOF RBV 12 W F0-F2</td>
<td>13/14</td>
</tr>
<tr>
<td>G1 SMV SOF RBV 24 W F0-F2</td>
<td>14/15</td>
</tr>
<tr>
<td>G1 SMV SOF RBV 12 W F0-F2</td>
<td>26/27</td>
</tr>
<tr>
<td>G1 SMV SOF RBV 24 W F0-F2</td>
<td>19/24</td>
</tr>
</tbody>
</table>

Red: Pearl-1, ABT450/r + ABT 267; Lawitz et al. AASLD 2013, A75.
Orange: Electron: sofosbuvir (SOF)/ledipasvir (LDV) + RBV; Gane et al. AASLD 2013, A73.
Green: Cosmos: sofosbuvir (SOF)/simeprevir (SMV) + RBV; Jacobson et al. AASLD 2013, ALB3.
High SVR with Six week regimen

Kohli A,,,,,,, Kottilil The Lancet 2015
Sofosbuvir With Velpatasvir in Treatment-Naive Noncirrhotic Patients With Genotype 1 to 6 Hepatitis C Virus Infection

A Randomized Trial

Gregory T. Everson, MD; William J. Towner, MD; Mitchell N. Davis, DO; David L. Wyles, MD; Ronald G. Nahass, MD; Paul J. Thuluvath, MD; Kyle Etzkorn, MD; Federico Hinestrosa, MD; Myron Tong, MD, PhD; Mordechai Rabinovitz, MD; John McNally, PhD; Diana M. Brainard, MD; Lingling Han, PhD; Brian Doehle, PhD; John G. McHutchison, MD; Timothy Morgan, MD; Raymond T. Chung, MD; and Tram T. Tran, MD

Chart Title

- Genotype 1
- Genotype 2, 4, 5, and 6
- Genotype 3

Annals Intern Med 2015 Dec 1;163(11):818-26
RBV or not RBV?

![Bar chart showing SVR (%)](image)
Successful Treatment of HCV Is Associated With Improved Outcomes

Sustained Virologic Response is durable
- 99% stay HCV negative for > 10 years

Conclusions

- New therapeutics are available for resistant bacteria but must be used judiciously to maintain their activity

- New pathogens continue to surface

- All HIV patients should be treated to prolong life and reduce transmission

- ART and PrEP can help to reduce new HIV transmissions

- HCV is curable with relatively short term therapy