Fall ID and HIV Conference Updates

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Disclosures (Dr. Meyerowitz)

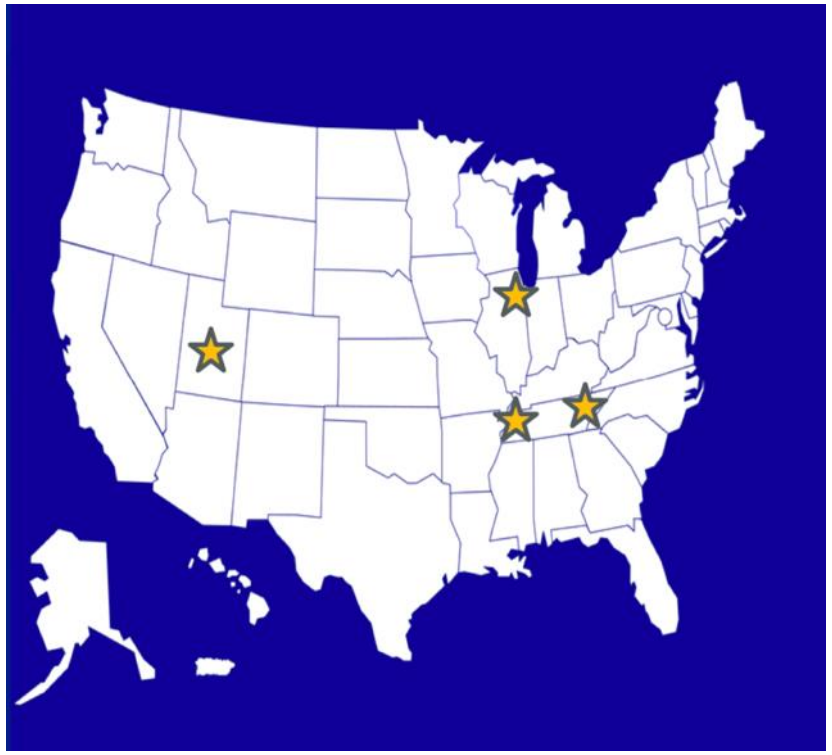
- None
- I am borrowing or adopting slides from presenters at IDWeek (lecturer is cited in each case)

Disclosures (Dr. Gandhi)

- Scientific advisory board: Merck. Educational grants to MGH from Gilead, Viiv, Janssen, Theratechnologies

EPIC Study: Pneumonia Etiology - 1

- Lecture presented by Dr. Seema Jain on October 5
- Enrolled 1/1/2010 – 6/30/2012
- 5 adult hospitals in Chicago and Nashville
- 3 peds hospitals Nashville, Salt Lake City, Memphis

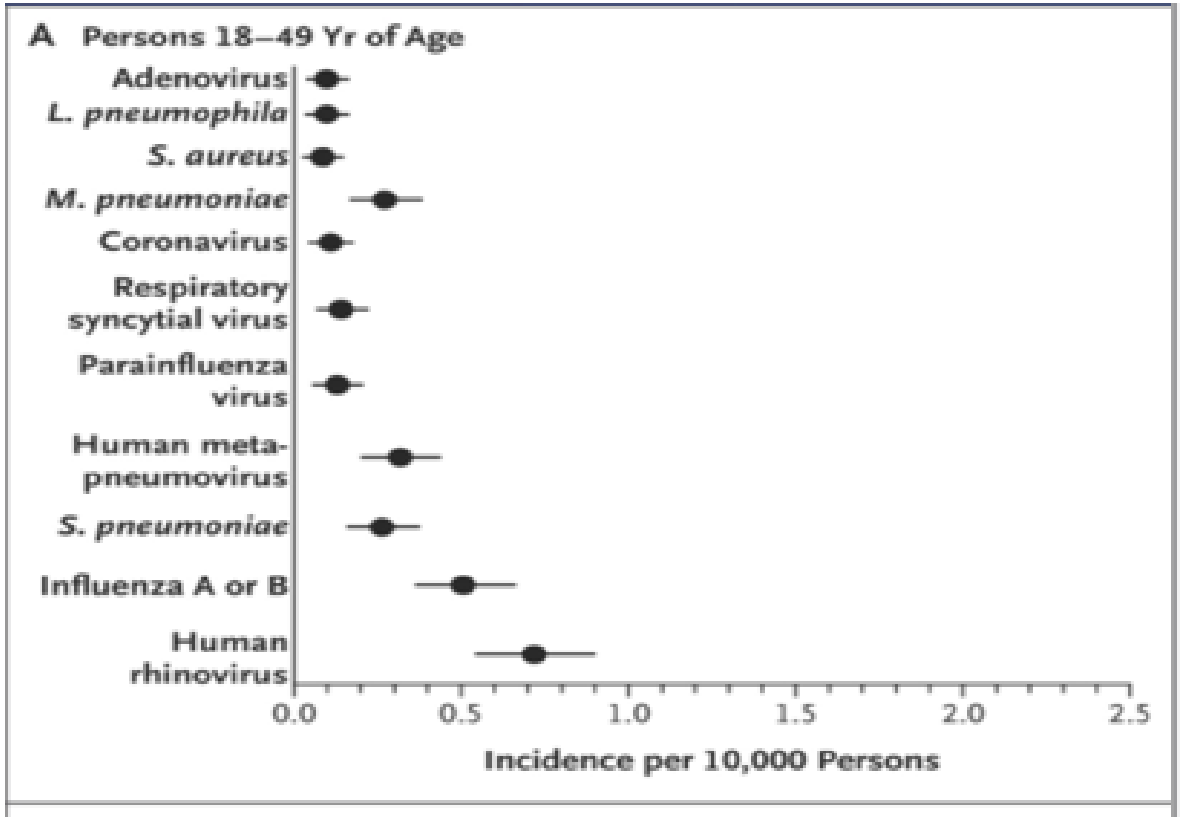


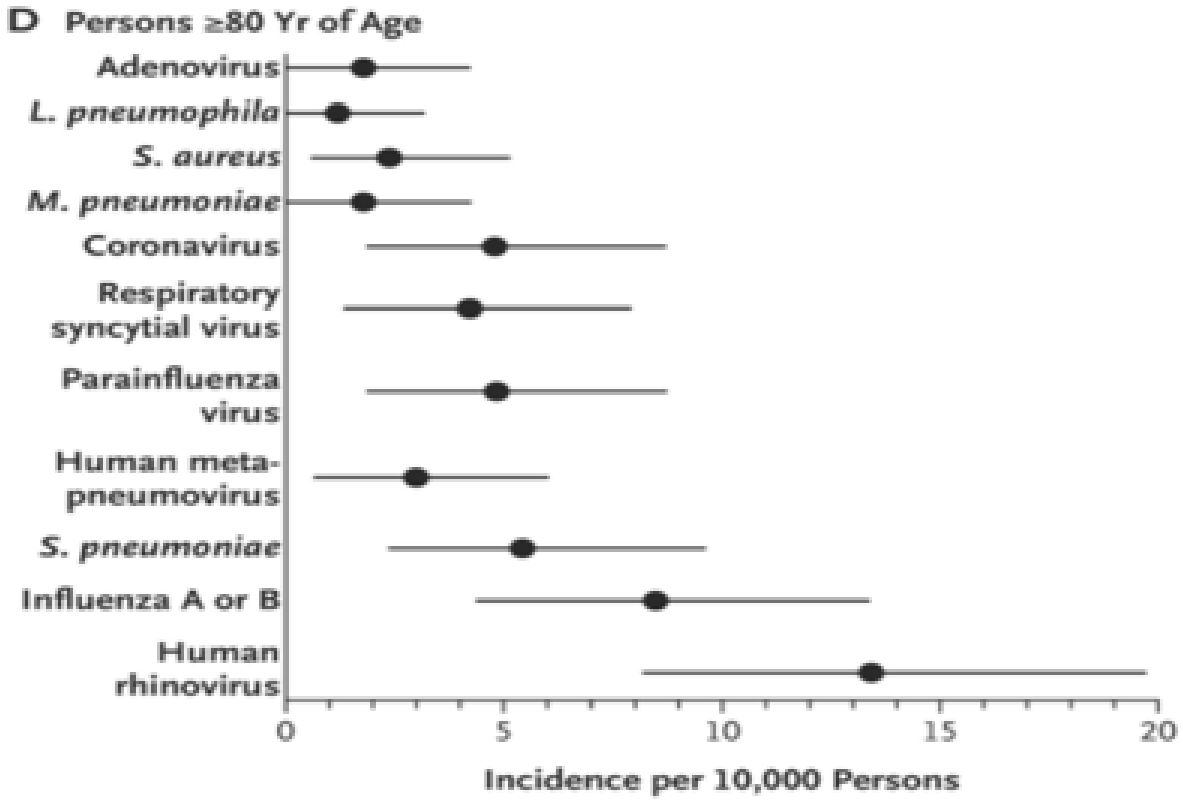
EPIC Study: Pneumonia Etiology - 2

- Hospitalized patients (without recent prior hospitalization
- Evidence of infection (fever, leukocytosis)
- Evidence of respiratory illness (cough, shortness of breath)
- Radiographic evidence of pneumonia
- Excluded patients with severe immunosuppression and cystic fibrosis

- Enrolled patients got extensive testing
  - Urine antigen tests
  - Cultures from multiple sites
  - Acute and convalescent serology for certain organisms
  - Molecular based testing of nasopharyngeal swabs and of sputum cultures and BALs when available

EPIC Study: Pneumonia Etiology - 3





EPIC Study: Pneumonia Etiology - 4

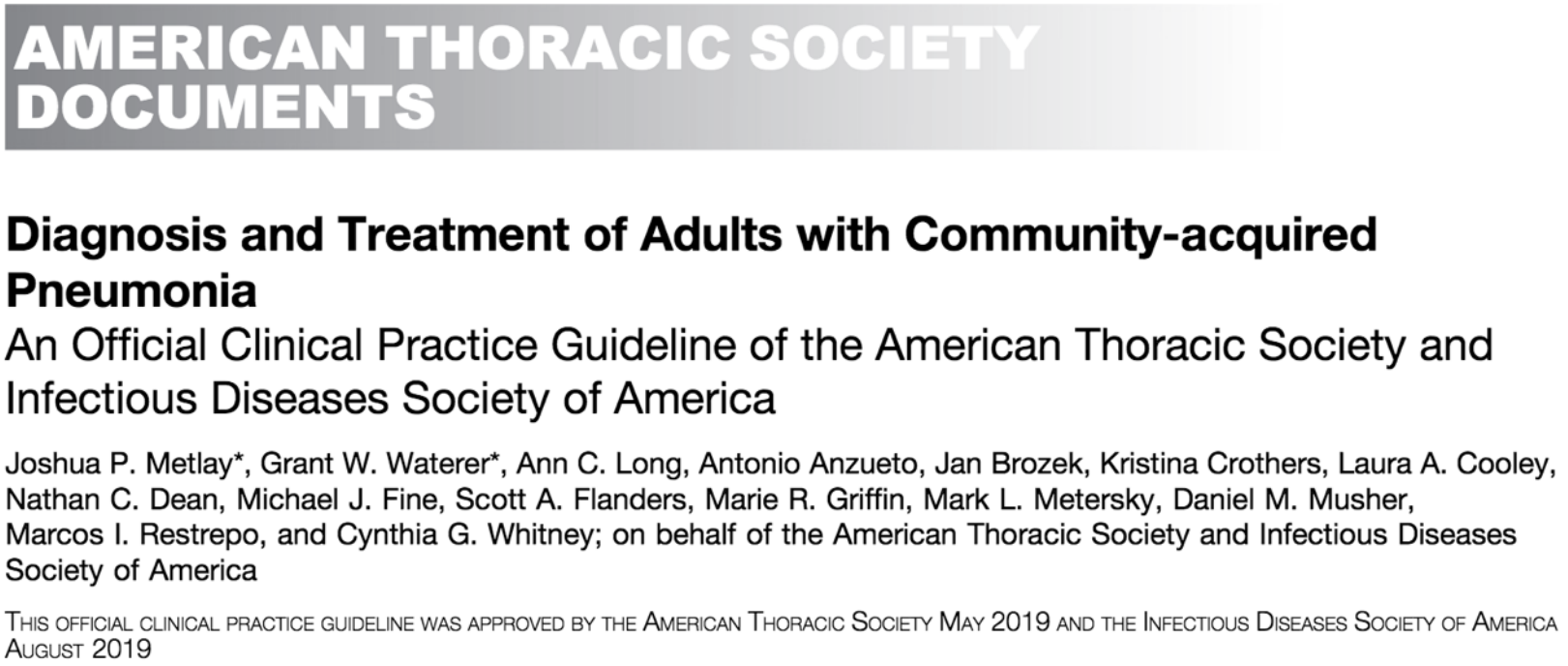
- If any pathogen was detected, pneumonia more likely to be severe
- Strep pneumonia was detected in 4% of patients not in the ICU and 8% of patients in the ICU (statistically significant = $p<0.05$)
- Staph aureus detected in 1% of non-ICU patients and 5% of ICU patients (statistically significant)
- Parainfluenza 1-3 detected in 3% of non-ICU and 4% of ICU patients (p 0.04)
- Enterobacteriaceae detected in 1% of non-ICU patients and 3% of ICU patients (statistically significant)
- Legionella detected only rarely, in 2% of non-ICU patients and 1% of ICU patients (not statistically significant)

EPIC Study: Pneumonia Etiology - 5

- Older adults with much higher incidences of pneumonia compared to younger people
- Pathogen detected only 38% of the times with 3% co-detections
- Viruses detected in 27% of adults (most common rhinovirus, influenza, human metapneumovirus)
- Bacterial detected in 14% of adults, with S. pneumoniae most common
- Wonder about under detection of bacteria since many patients received antibiotics prior to sample collection

Review of New CAP Guidelines - 1

- Lecture called: ”Strengths and Pitfalls of Treatment Guidelines for CAP: New 2019 Recommendations” by Dr. Michael Niederman (pulmonologist at Cornell)



Review of New CAP Guidelines - 2

- The new guidelines answer 16 questions with supporting evidence for each recommendation
- Highly readable

Question 1: In Adults with CAP, Should Gram Stain and Culture of Lower Respiratory Secretions Be Obtained at the Time of Diagnosis?

Recommendation. We recommend not obtaining sputum Gram stain and culture routinely in adults with CAP managed in the outpatient setting (strong recommendation, very low quality of evidence).

Review of New CAP Guidelines - 3

- Q1: No routine sputum gram stain / culture. Caveat: severe CAP or if being treated empirically for MRSA/PsA should have
- Q2: No routine blood cultures, though yes in severe CAP
- Q3: No routine pneumococcal urinary Ag or Legionella urinary Ag (no proven benefit). Patients with severe CAP can still have these (low quality of evidence)

Define: Severe CAP

Severe CAP = at least 1 major or at least 3 minor criteria

Table 1. 2007 Infectious Diseases Society of America/American Thoracic Society Criteria for Defining Severe Community-acquired Pneumonia

Validated definition includes either one major criterion or three or more minor criteria

Minor criteria

- Respiratory rate $\geq$ 30 breaths/min
- Pa_{O2}/F_{IO2} ratio $\leq$ 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (blood urea nitrogen level $\geq$ 20 mg/dl)
- Leukopenia* (white blood cell count $<$ 4,000 cells/μl)
- Thrombocytopenia (platelet count $<$ 100,000/μl)
- Hypothermia (core temperature $<$ 36°C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria

- Septic shock with need for vasopressors
- Respiratory failure requiring mechanical ventilation

Review of New CAP Guidelines - 4

- Q4: Test for influenza with nucleic acid amplification test when influenza is circulating in the community
- Q5: Do NOT withhold empiric antibiotics for pneumonia (radiographically confirmed) with low procalcitonin
- Q6: Use Pneumonia Severity Index rather than CURB-65 in addition to clinical judgement to determine need for hospitalization. PSI better at identifying low risk patients who can be safely managed at home

Score	Risk	Disposition
≤70	Low risk	Outpatient care
71-90	Low risk	Outpatient vs. Observation admission
91-130	Moderate risk	Inpatient admission
>130	High risk	Inpatient admission

Review of New CAP Guidelines - 5

- Q7: Use clinical judgement and IDSA/ATS 2007 severity criteria to help determine patient disposition in hospital (i.e. ICU versus floor). Patients mis-triaged have significantly higher mortality
- Q8: Outpatient initial antibiotic regimens:

Table 3. Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia

	Standard Regimen
No comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa*[*]	Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is <25%)[†]
With comorbidities[‡]	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline[§] OR monotherapy with respiratory fluoroquinolone[‖]

Review of New CAP Guidelines - 6

- Q9: In inpatient setting:

Table 4. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*
Nonsevere inpatient pneumonia*	β-Lactam + macrolide[†] or respiratory fluroquinolone[‡]	Add MRSA coverage[§] and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*[‖] and obtain cultures to allow deescalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against MRSA if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for *P. aeruginosa* only if culture results are positive
Severe inpatient pneumonia*	β-Lactam + macrolide[†] or β-lactam + fluroquinolone[‡]	Add MRSA coverage[§] and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*[‖] and obtain cultures to allow deescalation or confirmation of need for continued therapy	Add MRSA coverage[§] and obtain nasal PCR and cultures to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*[‖] and obtain cultures to allow deescalation or confirmation of need for continued therapy

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

*As defined by 2007 ATS/IDSA CAP severity criteria guidelines (*see* Table 1).

[†]Ampicillin + sulbactam 1.5–3 g every 6 hours, cefotaxime 1–2 g every 8 hours, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 hours AND azithromycin 500 mg daily or clarithromycin 500 mg twice daily.

[‡]Levofloxacin 750 mg daily or moxifloxacin 400 mg daily.

[§]Per the 2016 ATS/IDSA HAP/VAP guidelines: vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h).

[‖]Per the 2016 ATS/IDSA HAP/VAP guidelines: piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), imipenem (500 mg every 6 h), meropenem (1 g every 8 h), or aztreonam (2 g every 8 h). Does not include coverage for extended-spectrum β-lactamase–producing Enterobacteriaceae, which should be considered only on the basis of patient or local microbiological data.

Review of New CAP Guidelines - 7

- Q10: No additional anaerobic coverage for aspiration pneumonia unless lung abscess or empyema
- Q11: Don’t use old HCAP criteria for expanded coverage in CAP. The most consistently strong risk factor for infection with MRSA/PsA is prior infection with these organisms, especially if of the respiratory tract, and if recent hospitalization with antibiotics.
  - MRSA nares swab negative has good negative predictive value (no need for MRSA coverage
  - If positive, need to get a deep sample to confirm need to treat MRSA pneumonia (not a good positive predictive value)

Review of New CAP Guidelines - 8

- Q12: No routine steroids (though can use if for other indication like refractory shock). Higher mortality in severe influenza + steroids
- Q13: Give oseltamivir to ALL who test positive for influenza (regardless of how many days they have had symptoms), including inpatients and outpatients
- Q14: Do not withhold antibiotics for patient who tests positive for influenza. About 10% have co-infection. Can discontinue antibiotics at 48-72 hours if no evidence of bacteria from deep specimen and severe influenza

Review of New CAP Guidelines - 9

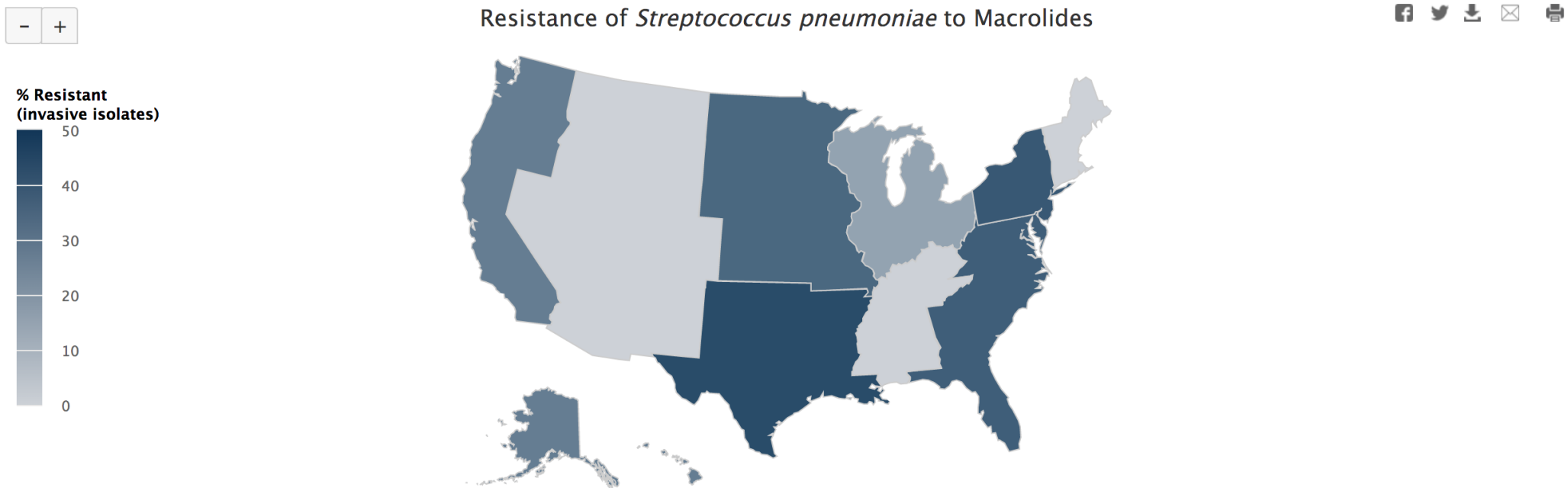
- Q15: Therapy should be for 5 days. MRSA/PsA should be 7 days. If patients are slow to respond or have complicated pneumonia (bacteremia, meningitis, etc), can extend course accordingly
- Q16: No routine follow up chest imaging

Summary

- Sputum culture and gram stain only if high risk for MRSA or PsA
- Do not without initial therapy based on procalcitonin
- Use 2007 guideline major/minor severity criteria and clinical judgment when deciding ICU versus floor
- Weak recommendation for outpatient macrolide monotherapy if no co-morbidities (chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia) and if *S pneumo* macrolide resistance , <25%
- Support for outpatient quinolone monotherapy for those with co-morbidities but not otherwise healthy individuals
- Recommend against inpatient beta-lactam monotherapy (ie add a macrolide)
- No routine additional anaerobic coverage for aspiration pneumonia
- No routine steroids for severe CAP or influenza CAP
- Don’t without antibiotics in proven influenza CAP
- Duration 5-days

United States

Resistance Map | Resistance Trend | Resistance Chart | Use Map | Use Trend | Use Chart | ? Help



Center for Disease Dynamics, Economics & Policy (cddep.org)

Data includes aggregated resistance rates for isolates (includes intermediate resistance) from blood and cerebrospinal fluid (i.e., invasive) from inpatients of all ages. Because of differences in scope of collections and testing methods, caution should be exercised in comparing across countries. For more details see methodology.

Antibiotic use data are shown in prescriptions per 1,000 individuals. View data as defined daily doses (DDD)

Country boundaries/designations do not represent CDDEP opinion concerning the legal status of any country, territory, city, or area of its authorities, or concerning the delimitation of its frontiers or boundaries.

Hide Errorbars

https://resistancemap.cddep.org/CountryPageSub.php?country=United+States

At MGH, 64% of *Strep pneumo* are sensitive to macrolides according to the Antibiogram

Critiques of CAP Guidelines

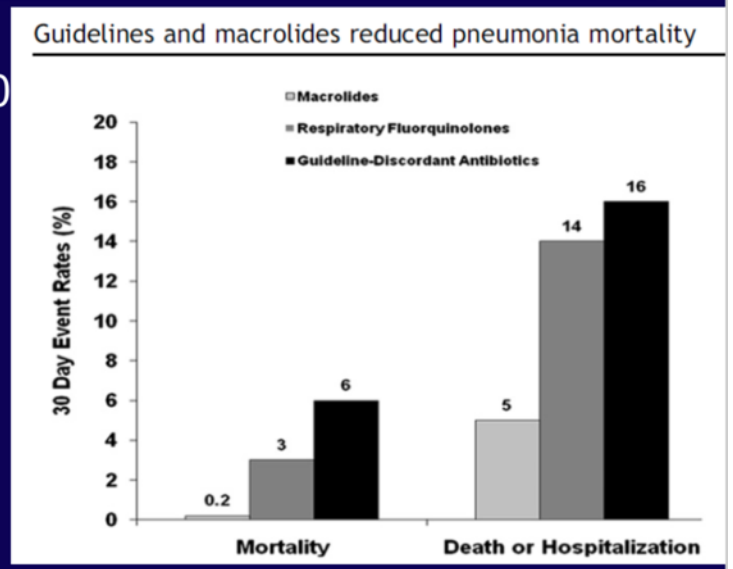
- There is some good data that other minor criteria (not reflected in 2007 formula correlate with pneumonia severity: hyponatremia, thrombocytosis (not just thrombocytopenia) and abnormal arterial CO2 (both hypocapnia and hypercapnia)
- While procalcitonin has not been shown to help determine whether a patient with pneumonia should receive antibiotics or impacted the duration of antibiotics, there may be a role for it in helping triage borderline hospitalized patients to ICU versus floor

Critiques of CAP Guidelines

- There is some good data for outpatient macrolide monotherapy which has a weaker recommendation in these guidelines
- Note that Canada has estimated 8-30% *S pneumo* macrolide resistance

Outpatient Macrolide Monotherapy: Safe for all groups of outpatients?

- 2973 CAP outpatients in Canadian EDs, 2000 -02
- At 30 days: 1% died, 8% admitted
- 2845 guideline concordant therapy
- 947 quinolone, 1832 macrolide (24 as combo rx)
  - Lower mortality with macrolide (4 vs 25 pts)



Asadi L, et al. Resp Med 2012; 106:451-8

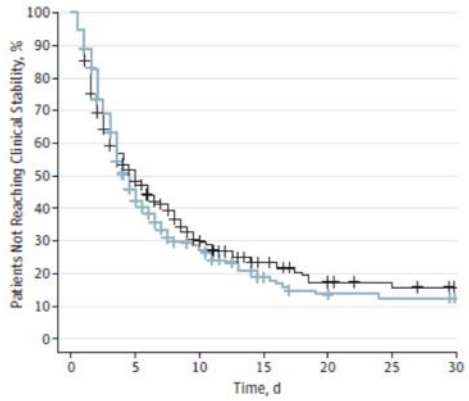
Critiques of CAP Guidelines

- Guidelines say no beta lactam monotherapy for inpatients with CAP although there is some good data suggesting this may be ok for inpatients with non-severe CAP

Randomized Trial of BL/M vs. BL Montherapy in CAP

- Open label, multicenter trial with 580 patients (moderately severe)
- Beta-lactam/macrolide vs. Beta-lactam alone (add macrolide for proven Legionella)
- Primary endpoint : Time to clinical stability (HR, BP, Temp, RR, Oxygenation)
- Non-inferiority of monorx NOT proven for CS (66.4 % vs. 58.8%, day 7 , CS for combo vs mono)
- Combination best if atypical pathogen or more ill (PSI IV)
- Garin N, et al. JAMA Intern Med 2014; 174:1894-1901

Figure 2. Proportions of Patients Not Reaching Clinical Stability



Black line indicates monotherapy arm; blue line, combination arm. $P = .44$ (log-rank test).

Critiques of CAP Guidelines

- Beta lactam macrolide combination better than beta lactam fluoroquinolone combination for severe CAP
- (Guidelines recommend these equally)

Routine Macrolide Use In Severe CAP?

- Meta-analysis of macrolide use in severe CAP
- 28 studies, nearly 10,000 patients
- Mortality risk of 0.82 with macrolide (21% vs 24% (p=0.02)
- Higher benefit if risk adjusted
- Trend of BL/M being better than BL/F

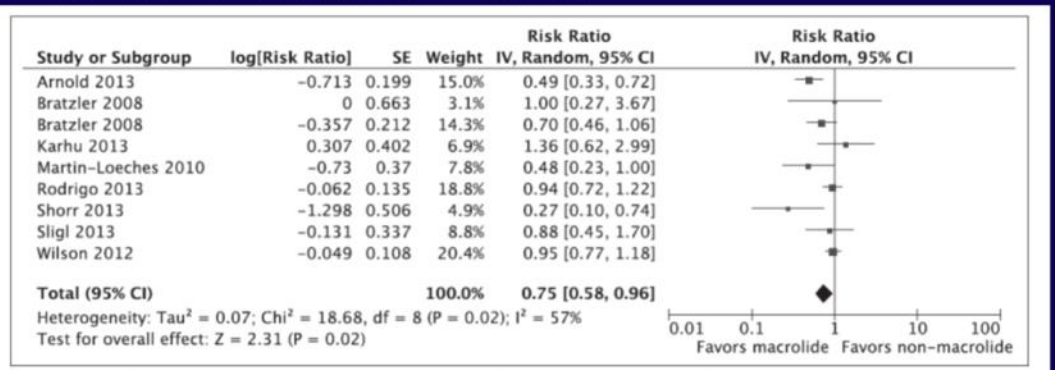


Figure 3. Macrolide versus nonmacrolide therapy and mortality in critically ill patients with community-acquired pneumonia: pooled adjusted risk estimates ($n = 9$).

Sligl W, et al. Crit Care Med 2014; 42:420-32

Critiques of CAP Guidelines

PVL Positive S. Aureus Pneumonia: Do We Need An Anti-Toxin Therapy ?

- 133 with PVL positive *Staphylococcal* CAP
  - 29 MRSA
  - 104 MSSA
- 39% mortality
- 64% mechan ventilated.
- 33.7% got antitoxin (linezolid, clindamycin or rifampin), with reduced mortality (6.1% vs. 52.3%, $p < 0.001$)
- Sicot N, et al. Clin Microbiol Infect 2012; 19: E142-148

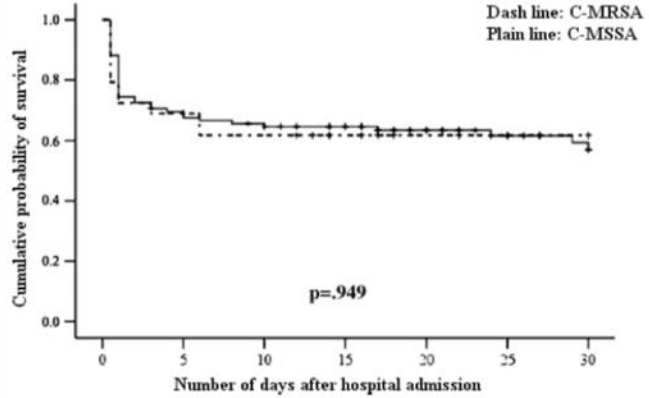
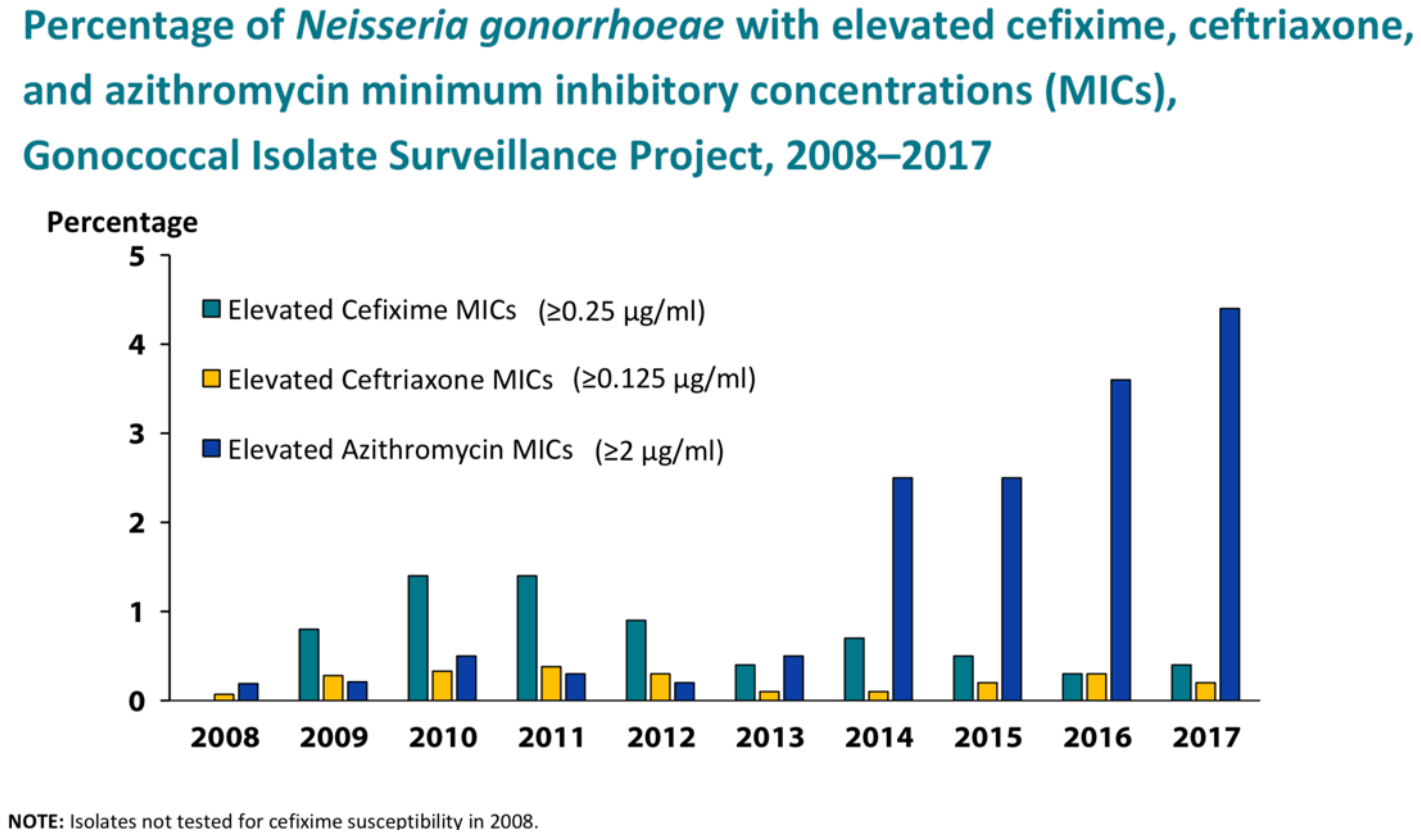


FIG. 1. Kaplan–Meier survival curves after 30 days for patients with community-acquired, Panton–Valentine-positive, *Staphylococcus aureus* necrotizing pneumonia according to methicillin susceptibility.

Questions?

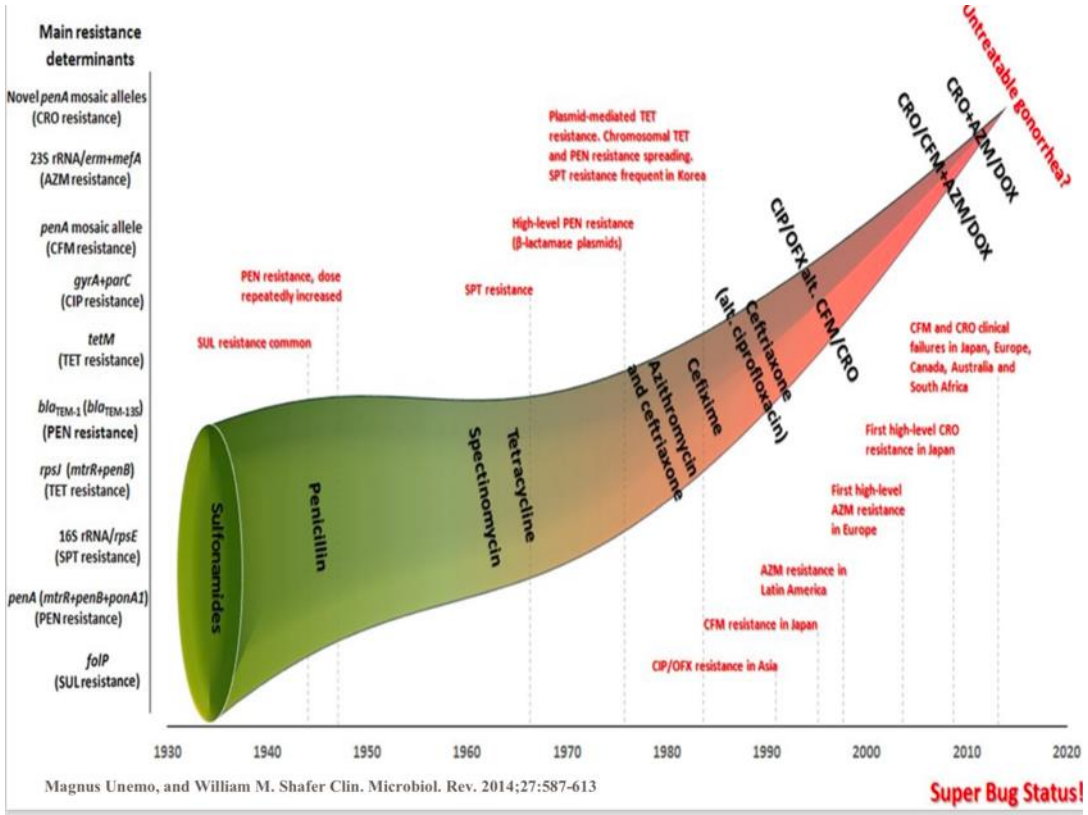
Epidemiology of MDR Gonorrhea

Slide from Dr. Robert D. Kirkcaldy



Treatment of Gonorrhea - 1

Slide from Dr. Stephanie N. Taylor

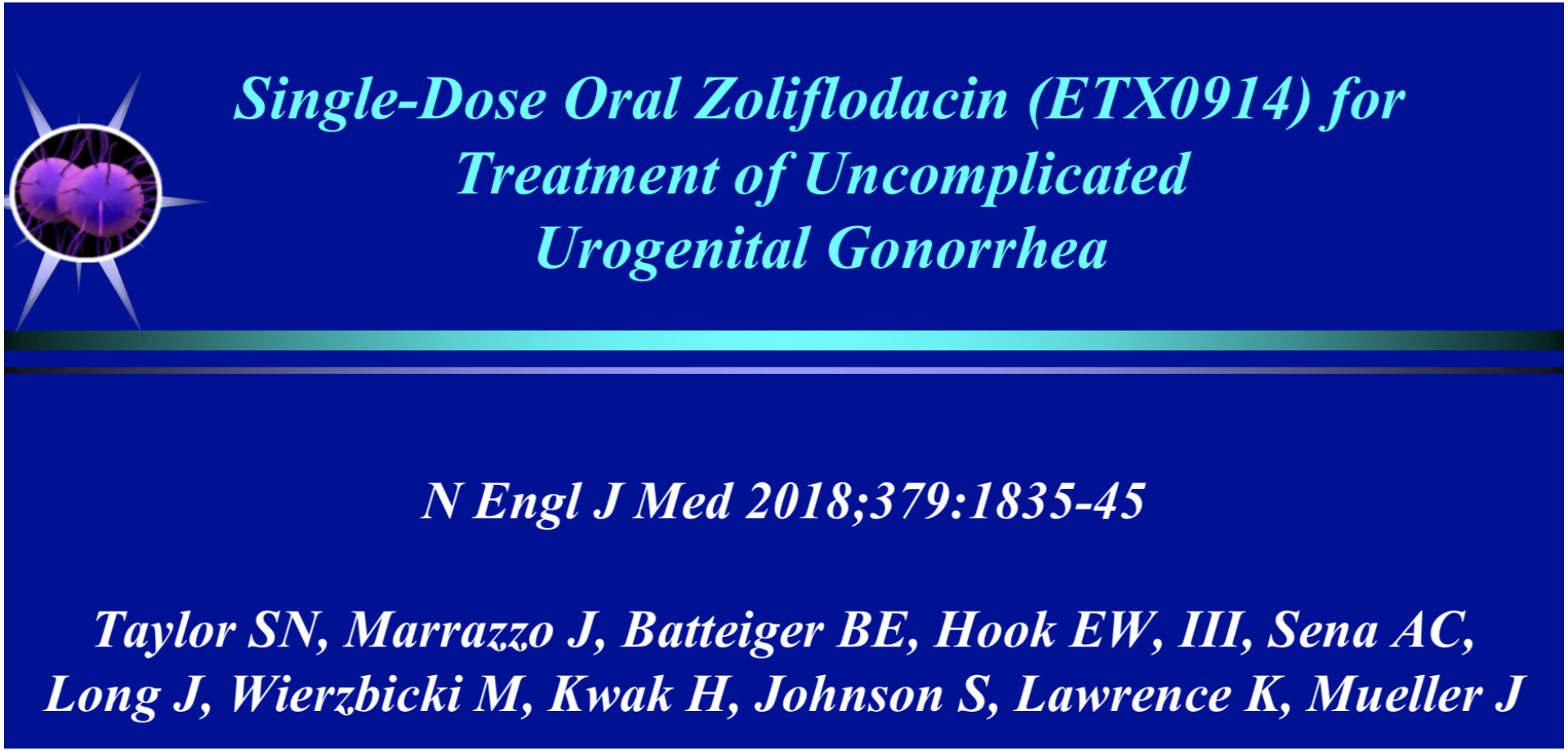


Treatment of Gonorrhea - 2

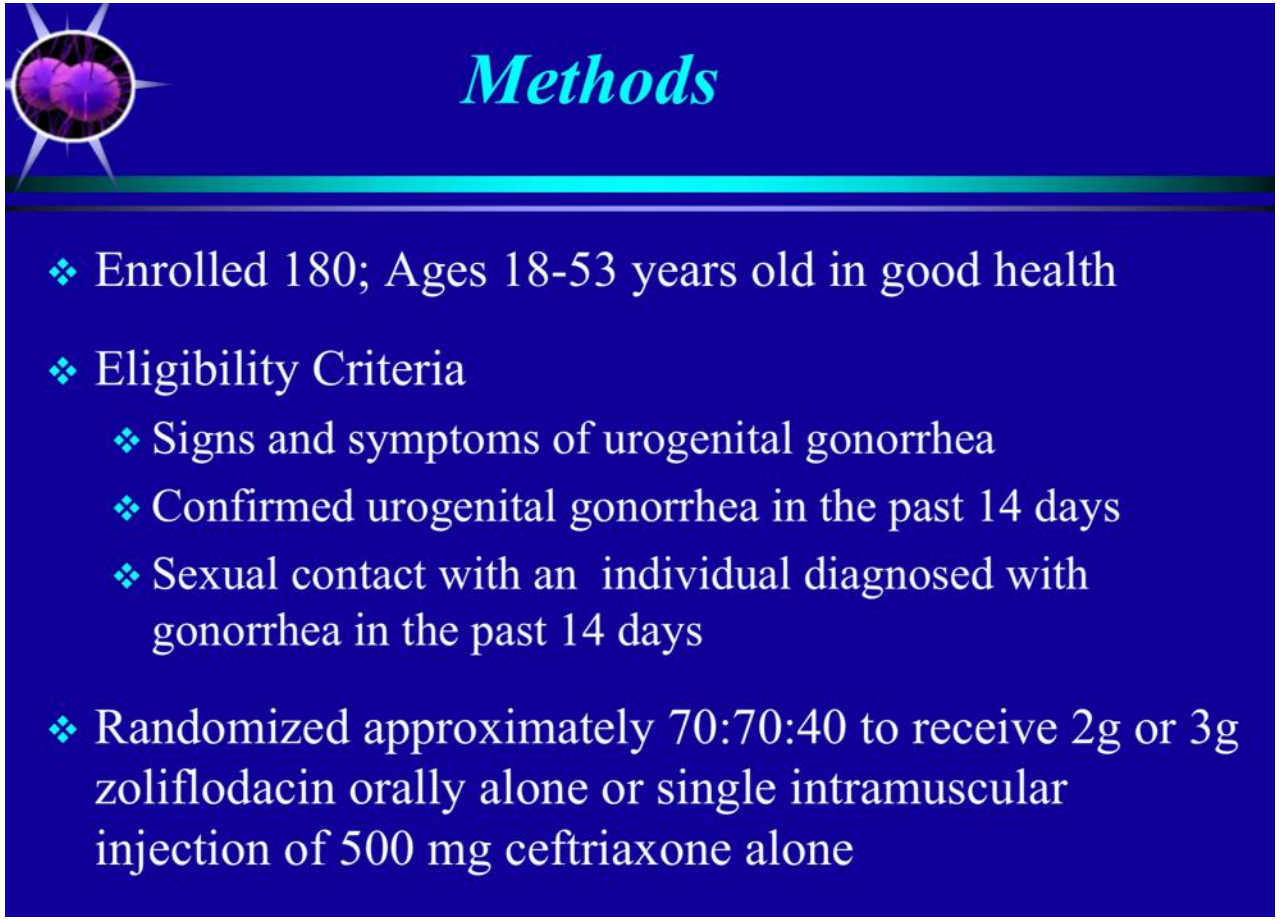
Current Guidelines:

- 250 mg IM ceftriaxone + 1 g PO azithromycin or 7 days doxycycline 100 mg BID
- For ceftriaxone allergic patients: 240 mg IM gentamicin + 2 g PO azithromycin or 320 mg Gemifloxacin + 2 g azithromycin

Treatment of Gonorrhea - 3



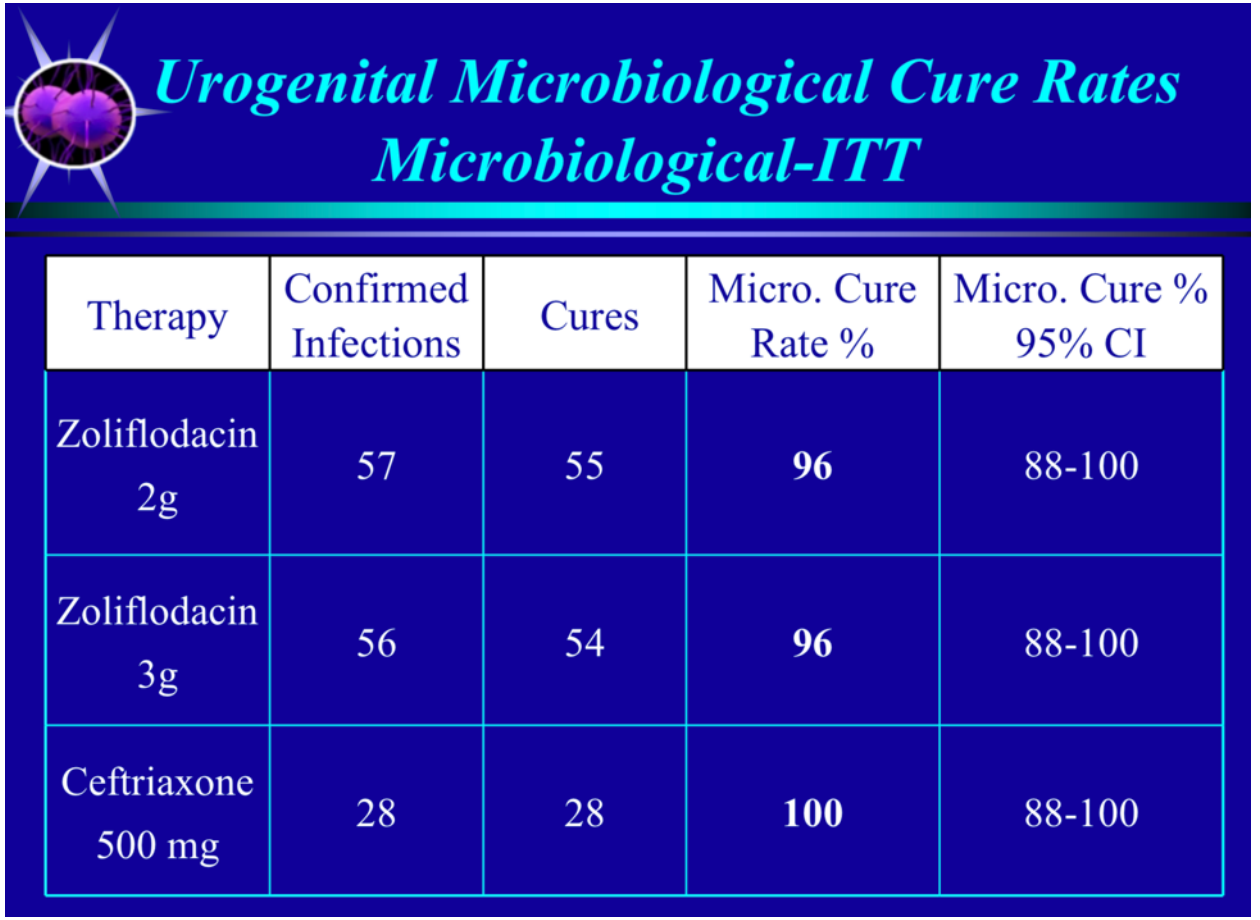
Treatment of Gonorrhea - 4



Treatment of Gonorrhea - 5

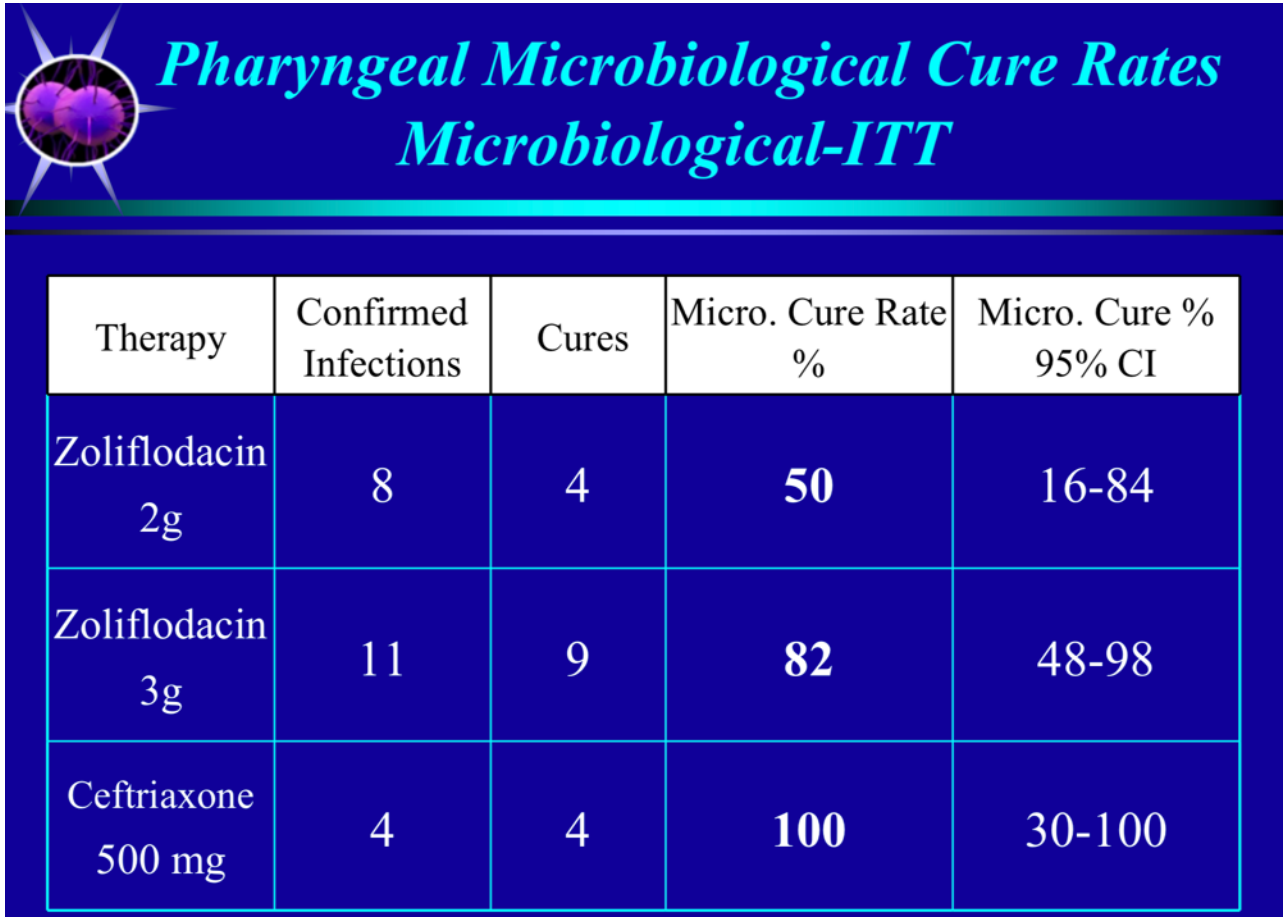
Mean Age – 29 years	n	%
Male	167	93
Female	13	7
Heterosexual	90	54
Homosexual/Gay	66	40
Bisexual	11	6
Non-Hispanic	167	93
Hispanic	13	7
Black/African American	107	59
White	58	32
Multi-racial/Other/Hawaiian/Native American/Alaskan Nat./Asian	15	9

Treatment of Gonorrhea - 6



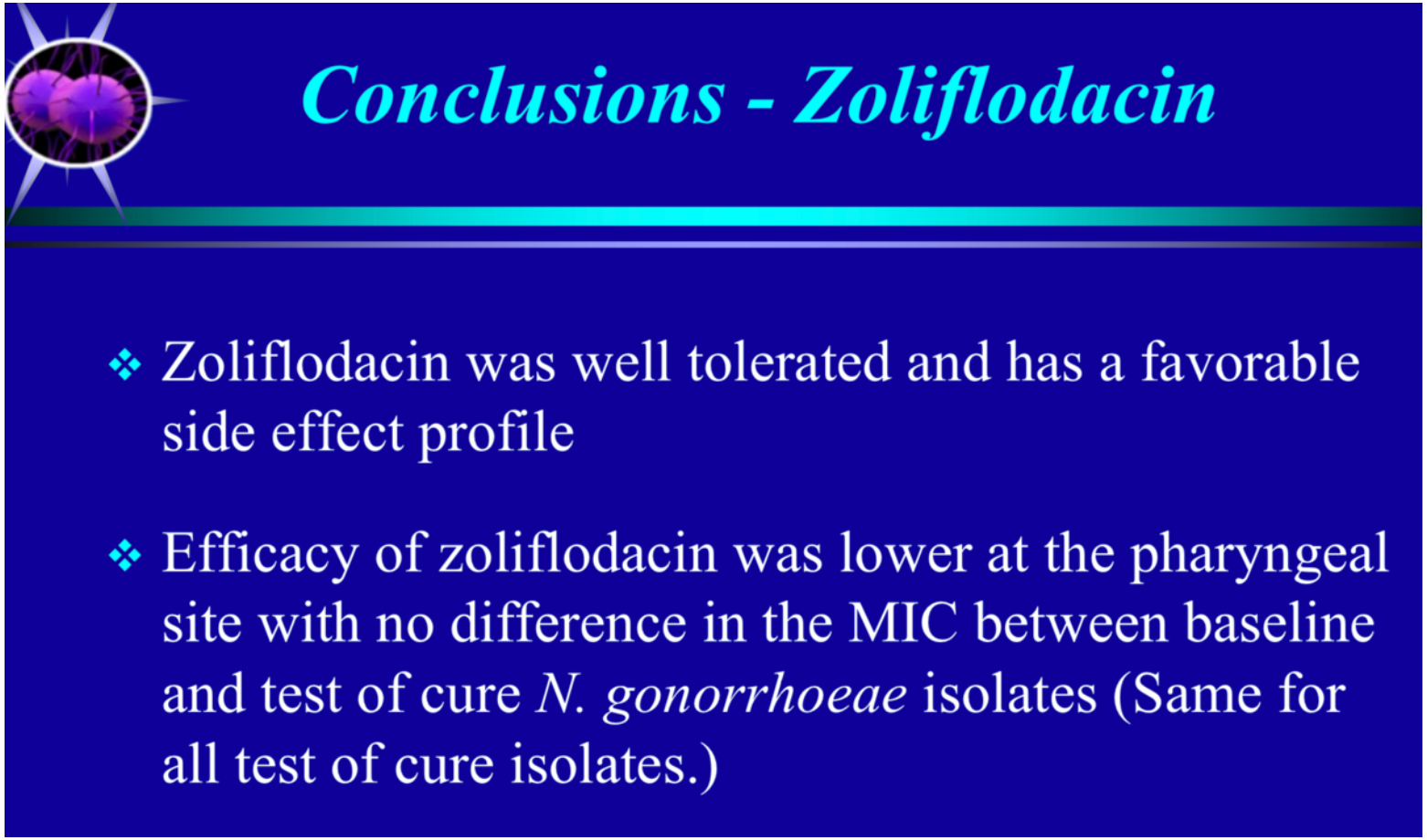
Therapy	Confirmed Infections	Cures	Micro. Cure Rate %	Micro. Cure % 95% CI
Zoliflodacin 2g	57	55	**96**	88-100
Zoliflodacin 3g	56	54	**96**	88-100
Ceftriaxone 500 mg	28	28	**100**	88-100

Treatment of Gonorrhea - 7



Therapy	Confirmed Infections	Cures	Micro. Cure Rate %	Micro. Cure % 95% CI
Zoliflodacin 2g	8	4	**50**	16-84
Zoliflodacin 3g	11	9	**82**	48-98
Ceftriaxone 500 mg	4	4	**100**	30-100

Treatment of Gonorrhea - 8



Phase 3 trials begin this fall

Treatment of Gonorrhea - 9

Treatment of Gonorrhea - 10

Mean Age – 33 years	n	%
Male	101	95
Female	5	5
Black/African American	47	48
White	45	46
Multi-racial/Other/Hawaiian/Native American/Alaskan Nat./Asian	14	6

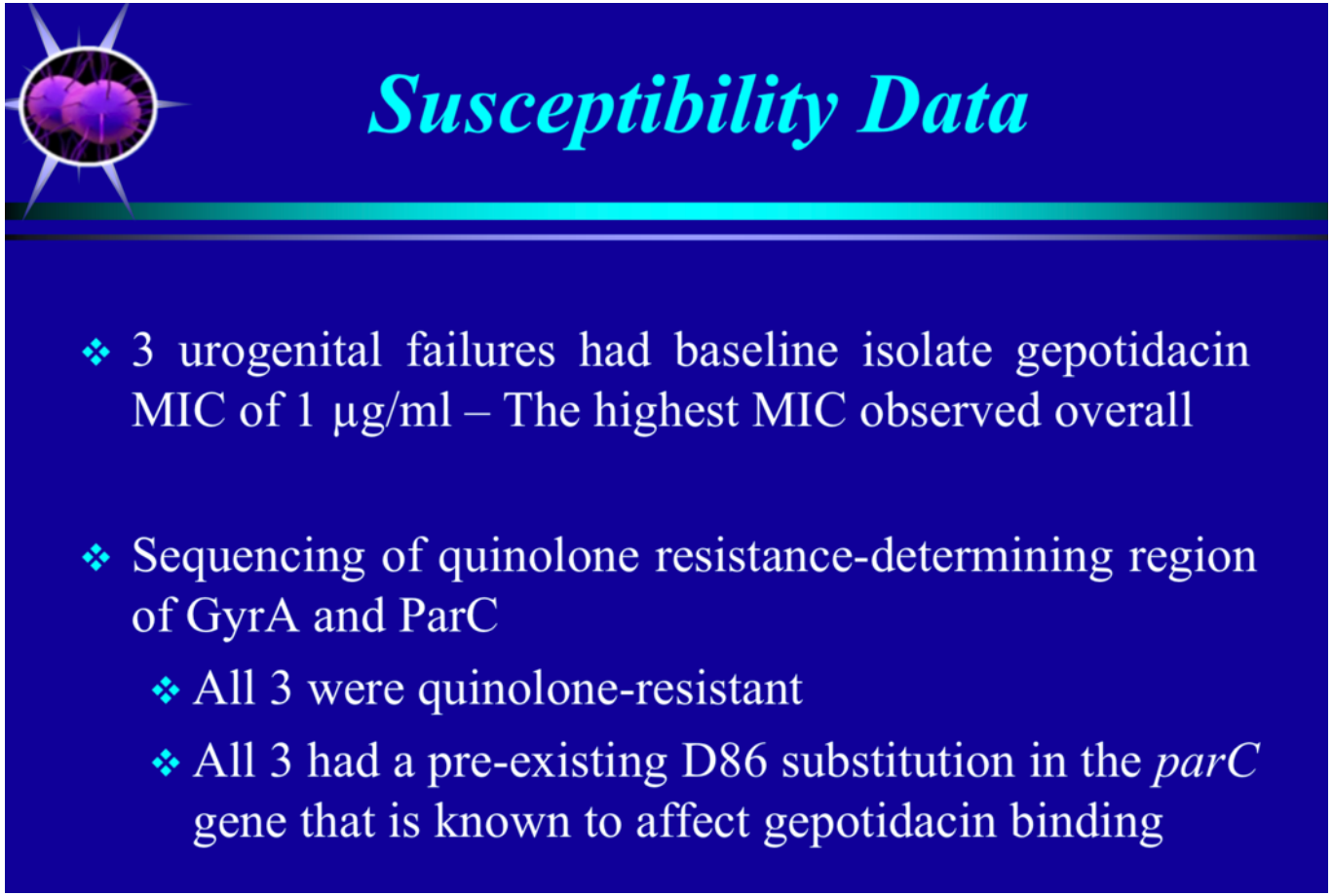
Urogenital infections

Therapy	Confirmed Infections	Cures	Micro. Cure Rate %	Micro. Cure % 95% CI
Gepotidacin 1500 mg	30	29	**97**	85-100
Gepotidacin 3000 mg	39	37	**95**	88-100

Adverse Events

AE Category	Gepotidacin 1500 mg (n = 52)	Gepotidacin 3000 mg (n = 53)	Total
Any AE	27 (52)	34 (64)	61 (58)
Related to study	24 (46)	33 (62)	57 (54)
Common AEs by preferred term			
Diarrhea	9 (17)	19 (36)	28 (27)
Flatulence	14 (27)	10 (19)	24 (23)
Abdominal pain	6 (12)	10 (19)	16 (15)
Nausea	3 (6)	11 (21)	14 (13)
Fatigue	3 (6)	5 (9)	8 (8)
Dizziness	1 (2)	6 (11)	7 (7)
Hyperhidrosis	1 (2)	6 (11)	7 (7)
Abdominal Pain	4 (8)	2 (4)	6 (6)
Eructation	1 (2)	3 (6)	4 (4)
Feces soft	1 (2)	3 (6)	4 (4)

Treatment Failures Explained



Summary

- Both zoliflodacin and gepotidicin are entering phase 3 studies this year and will have roles for drug resistant gonorrhea though they are not a panacea

Extra-Urogenital STIs in Women - 1

Slides from Michaela A. Maynard et al

Methods

Goal: To evaluate prevalence of extragenital chlamydia and gonorrhea infections in cis-gender females

Study Setting: The Rhode Island STI Clinic, provides safety-net STI services to the entire state

Approach: We reviewed all cis-gender females presenting to care from May 2014 to June 2019*

Analyses: We evaluated demographics, behaviors, and laboratory data on urogenital, pharyngeal and rectal CT/GC. Univariate and bivariate analyses were performed to determine the characteristics of demographic and behavioral variables associated with extragenital infection

Results

Total Cohort: 3,183 cis-gender females presented for STI services

Demographics: 43% were 13-24 years of age; 40% White/Caucasian; 23% Black; 30% Hispanic/Latino; 48% uninsured

Behaviors: 88% were FSM only; 8% were FSM/F; 1% were FSF only

76% Condomless oral sex
82% Condomless vaginal/anal sex
18% Sex with an anonymous partner
26% Alcohol/Drugs during sex
8% Ever forced to have sex
32% Ever had an STI
17% Had an STI in the last 12 months

Rationale for Study

- In MSM > 70% of GC and CT infections are missed by screening urogenital site only
- Currently CDC recommends extragenital testing of MSM only at this time
- Less is known about extragenital GC and CT infections in women
- During study period extragenital testing (including pharyngeal and rectal testing) was offered to all women

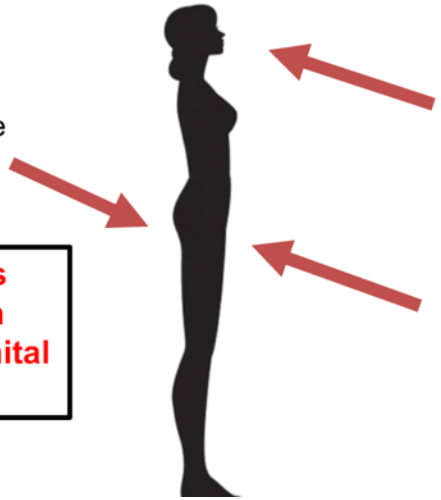
Chlamydia and Gonorrhea by Testing Site (N=3183)				
	Screened (N)	Screened (%)	Positive (N)	Positive* (%)
Urogenital Chlamydia	2960	**93%**	242	**8.2%**
Urogenital Gonorrhea	2992	**94%**	31	**1.0%**
Pharyngeal Chlamydia	2120	**67%**	57	**2.7%**
Pharyngeal Gonorrhea	2125	**67%**	31	**1.5%**
Rectal Chlamydia	551	**17%**	58	**10.5%**
Rectal Gonorrhea	552	**17%**	10	**1.8%**

***Of those screened**

Missed Chlamydia and Gonorrhea Infections

***Total positive at any site (N=332)**

21% Rectal Infection
(8% rectal only, 9% +urogenital, 0.6% +pharyngeal, 3% all three sites)



25% Pharyngeal Infection
(11% pharyngeal only, 11% +urogenital, 0.6% +rectal, 3% all three sites)

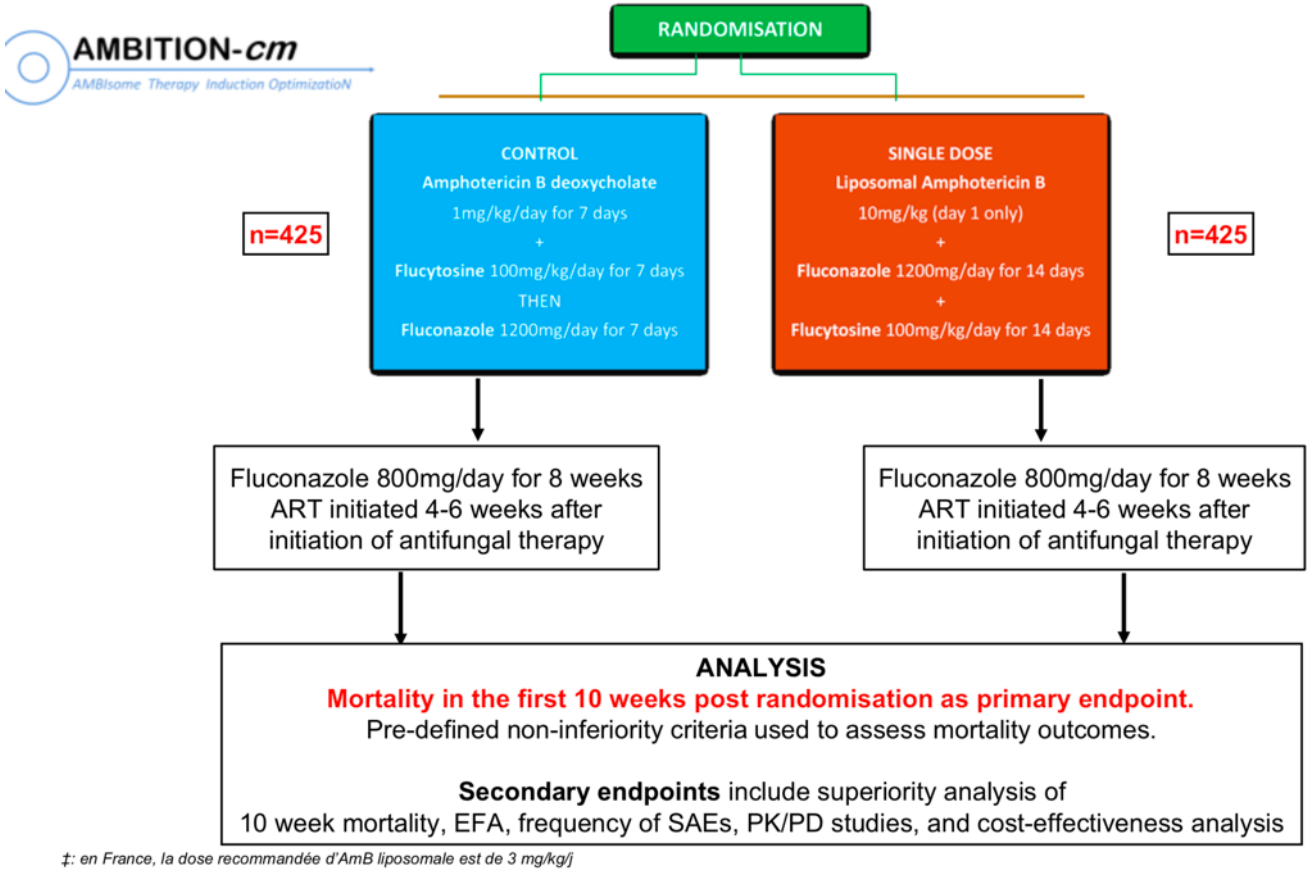
81% Urogenital Infection
(57% urogenital only, 11% +pharyngeal, 9% +rectal, 3% all three sites)

19% of infections would have been missed with urogenital screening only

Extragenital Infections by Age Category			
	13-24 years (N=1357)	25+ years (N=1826)	p-value
Urogenital Chlamydia	176 (**13.0%**)	66 (3.6%)	p<0.01
Pharyngeal Chlamydia	42 (**3.1%**)	15 (0.8%)	p<0.01
Rectal Chlamydia	30 (**2.2%**)	28 (1.5%)	p<0.01
Urogenital Gonorrhea	19 (**1.4%**)	12 (0.7%)	p<0.01
Pharyngeal Gonorrhea	15 (**1.1%**)	16 (0.9%)	p<0.01
Rectal Gonorrhea	2 (0.1%)	8 (**0.4%**)	p=0.01

Updates in Crypto-Meningitis - 1

Slides by Dr. Olivier Lortholary

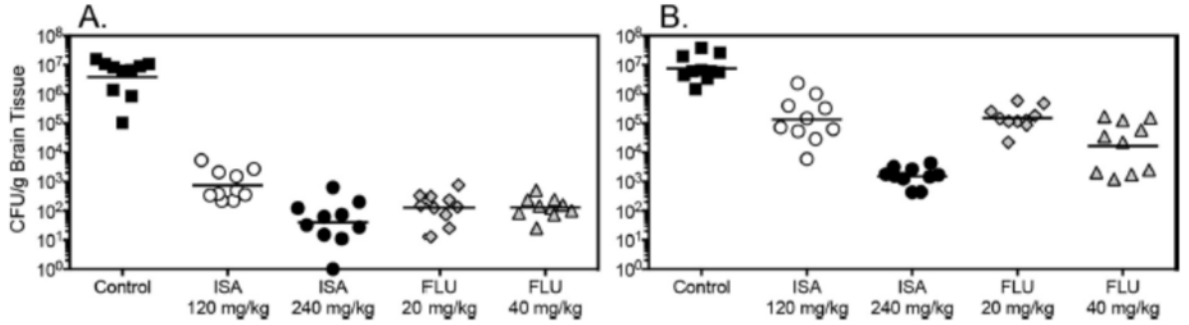


Updates in Crypto-Meningitis - 2

Isavuconazole

Murine model of CM, 2 isolates, fungal burden & survival
Similar efficacy than FCZ; dose effect of ISA

Wiederhold, AAC 2016



Rabbit model of CM, 1 isolate
Similar efficacy than FCZ, lack of dose effect of ISA

Kovanda AAC Sept 2019

Parameter	Mean ± SD value at the following dose:	
	83.8 mg/kg	111.8 mg/kg
Brain isavuconazole concn (mg/liter)	1.15 ± 1.5	1.31 ± 0.96
CSF isavuconazole concn (mg/liter)	0.08 ± 0.049	0.05 ± 0.028
Ratio of brain-to-plasma concn	0.69 ± 0.69	0.42 ± 0.27
Ratio of CSF-to-plasma concn	0.044 ± 0.044	0.019 ± 0.006

Higher ISA conc in infected vs. normal human brain
Rouzaud AAC Sept 2019

HIV Highlights

Raj Gandhi, MD
Massachusetts General Hospital
Harvard Medical School

Disclosures: Scientific advisory board: Merck. Educational grants to MGH from Gilead, Viiv, Janssen, Theratechnologies

Thanks to Delaney Taylor for help with slides

HIV Highlights

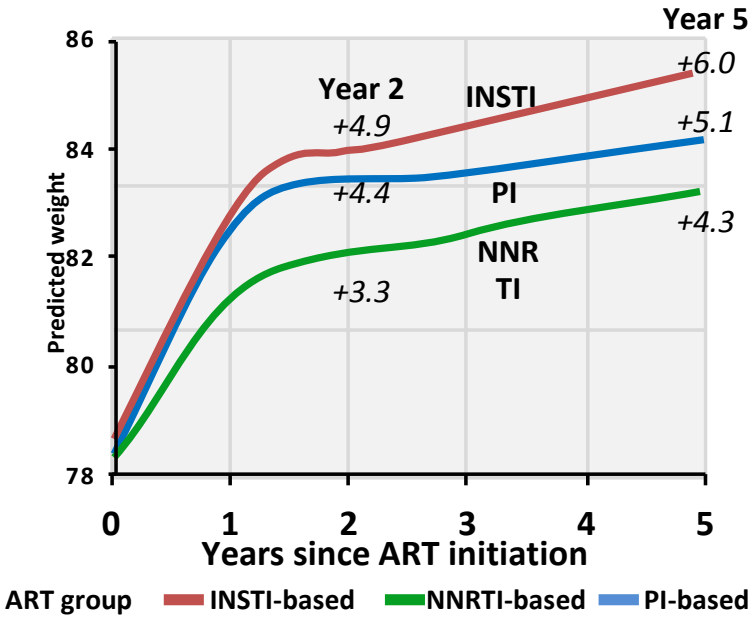
- Weight gain and metabolic changes
- New long-acting drugs on the horizon
- PrEP

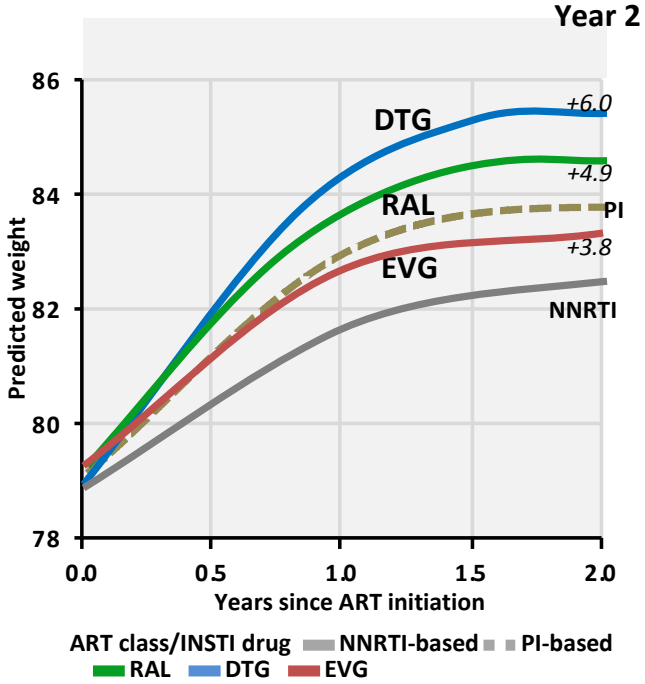
Sax P et al, CID, 2019

Weight Gain and Metabolic Changes

NA-ACCORD: Weight Gain after Starting ART

- NA-ACCORD: observational study of 24,001 participants initiating ART
  - INSTIs and PIs associated with greater increase in weight than NNRTI
  - DTG and RAL associated with greater weight gain than EVG



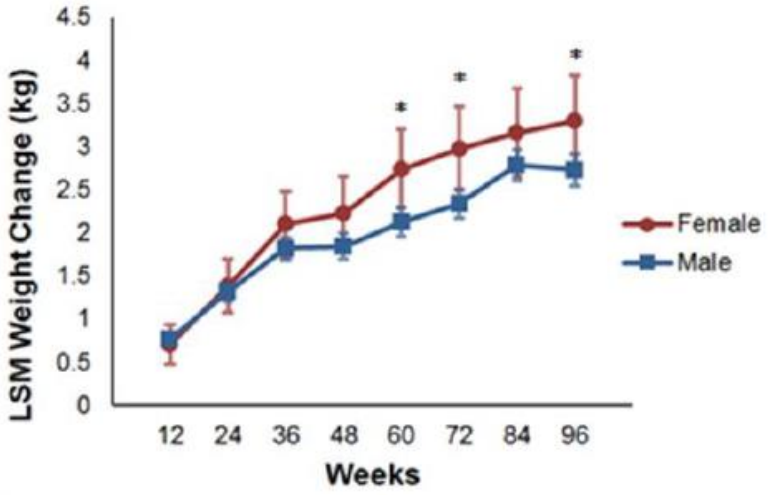


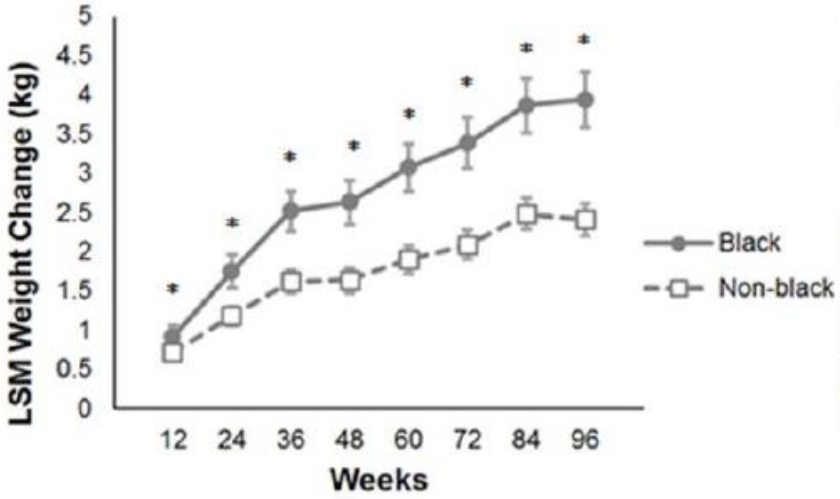
Weight Gain after Initiation of ART: Randomized Trials

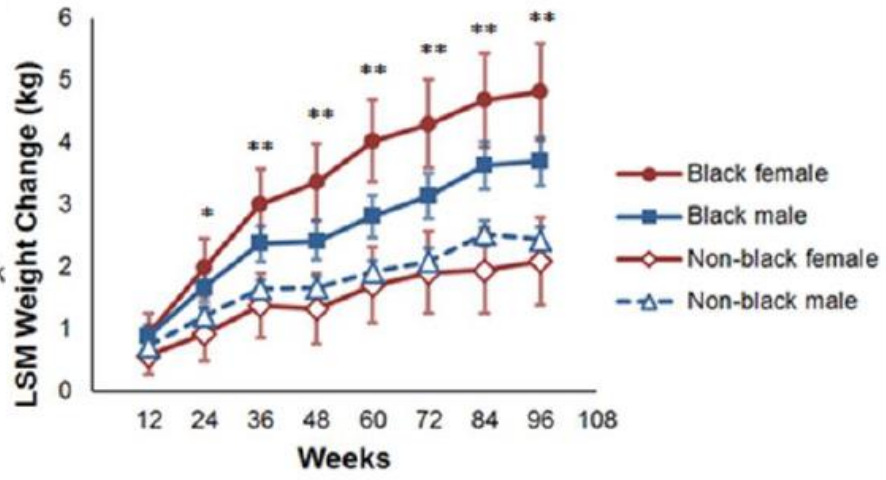
- Pooled analysis of 8 Gilead-sponsored randomized clinical trials of treatment-naïve people initiating ART between 2003-2015
- N=5680 participants
- 96-week median weight gain: 2.0 kg
- 17% of participants had >10% weight increase from baseline (30% lost weight)
- Risk factors for weight gain in multivariate models:
  - Baseline CD4 count <200 gained on average 2.97 kg more than those with bCD4 >200
  - HIV RNA >100K
  - Black race: about 1 kg greater weight gain than non-black participants
  - Female sex

Sax P et al, CID, 2019

Weight Gain after Initiation of ART: Race and Sex

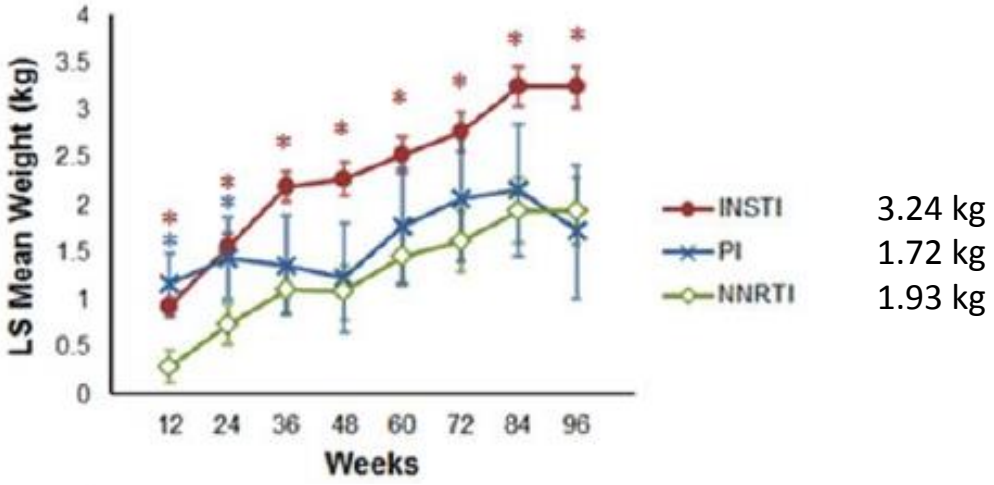




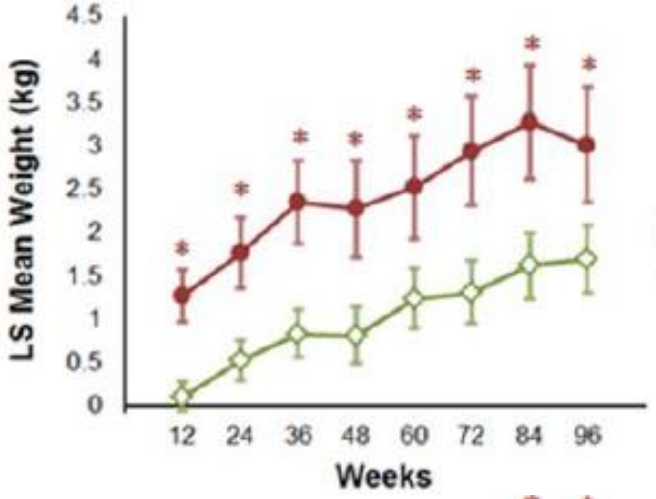


Sax P et al, CID, 2019

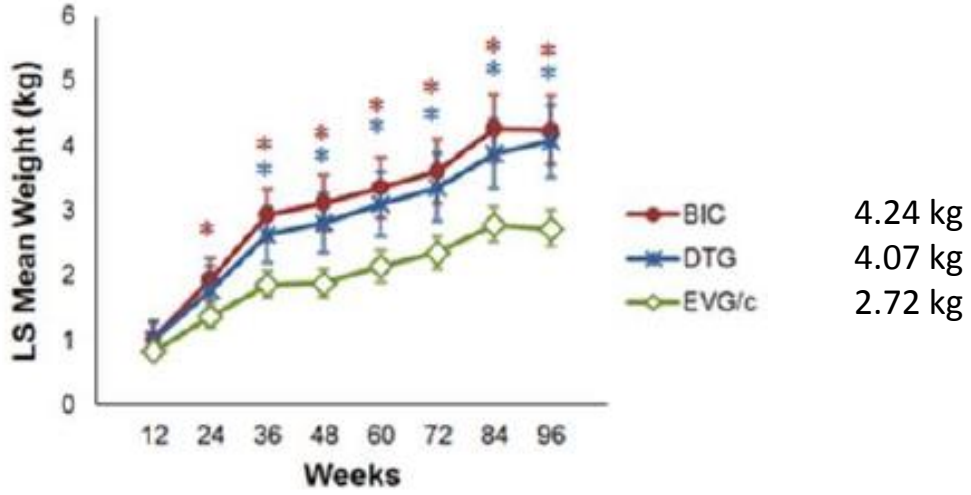
Weight Gain after Initiation of ART: Effect of ART



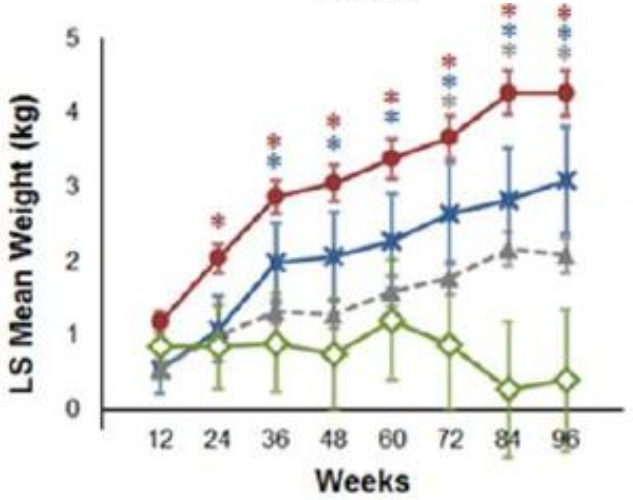
3.24 kg
1.72 kg
1.93 kg



3.01 kg
1.7 kg



4.24 kg
4.07 kg
2.72 kg



4.25 kg
3.08 kg
2.07 kg
0.39 kg

Sax P et al, CID, 2019

Weight Gain after Initiation of ART: Randomized Trials

- Risk factors for weight gain >10% from baseline over 48 wks (12.8% of participants)
  - Lower CD4 cell count, higher HIV RNA
  - Female sex
  - Black race
  - Compared to EFV, initiation of BIC or DTG (OR 1.82), EVG/c (OR 1.36), RPV (OR 1.51)
  - Among the NRTI, compared to AZT, initiation of TAF (OR 1.75) but not ABC or TDF

Sax P et al, CID, 2019

My Take on Weight Gain

- Accumulating data that INSTI-based regimens are associated with greater weight gain than some other regimens, especially in African or African-American women
  - Weight gain with bictegravir and dolutegravir are similar, and greater than with elvitegravir/cobicistat
  - Weight gain greater with tenofovir alafenamide than with abacavir, tenofovir disoproxil fumarate, or zidovudine
- Mechanism of weight gain and distribution of fat should be evaluated
- In patients with significant weight gain, the impact of changing to another INSTI or to a non-INSTI based regimen needs to be studied

New Long-acting Drugs on the Horizon

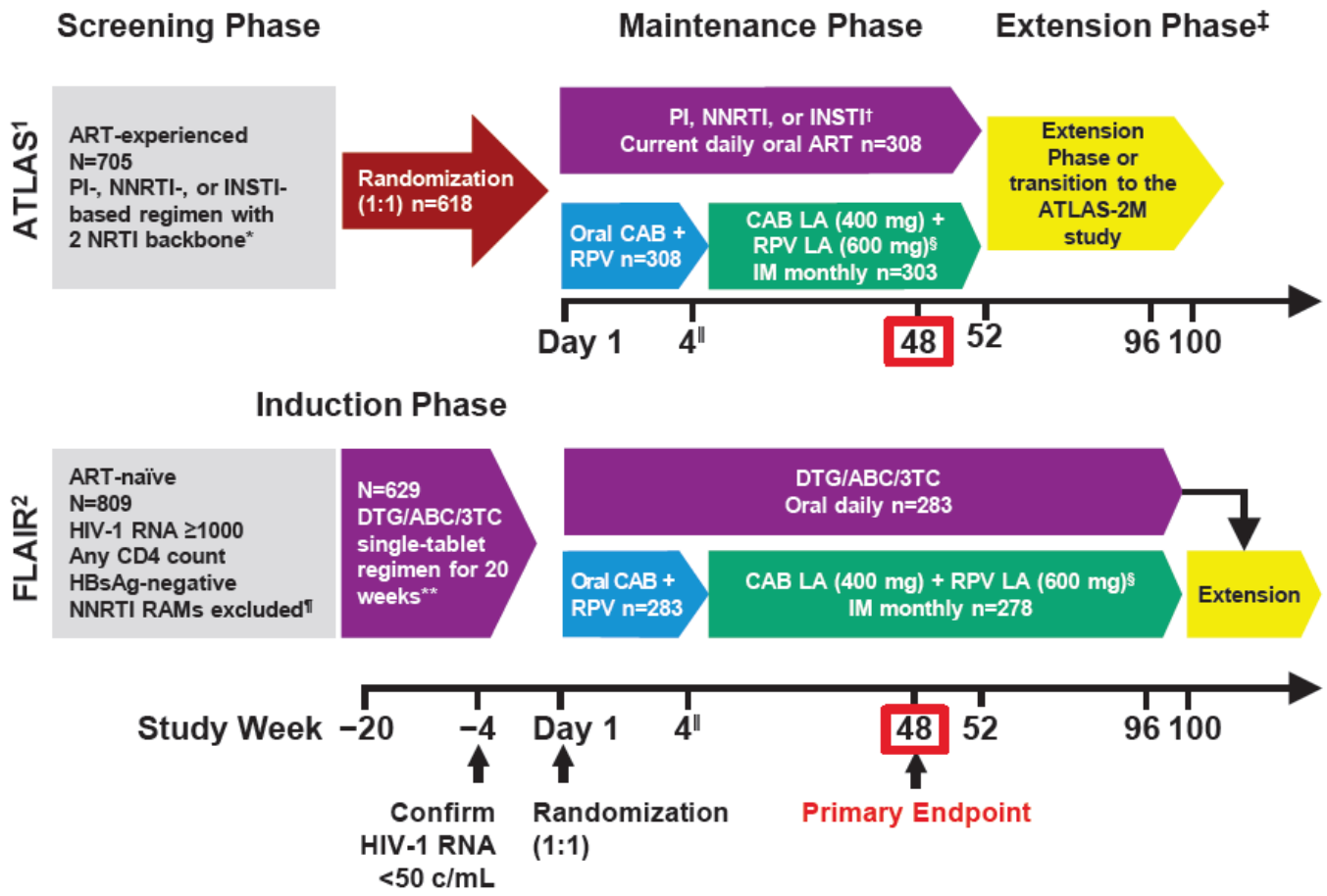
Long-acting cabotegravir/rilpivirine

- Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, available in long-acting nanosuspension formulations; half-lives of months

Shamsuddin H et al, IDWeek 2019, Abstract 886.

Phase 3 Clinical Trials: ATLAS/FLAIR Week 48

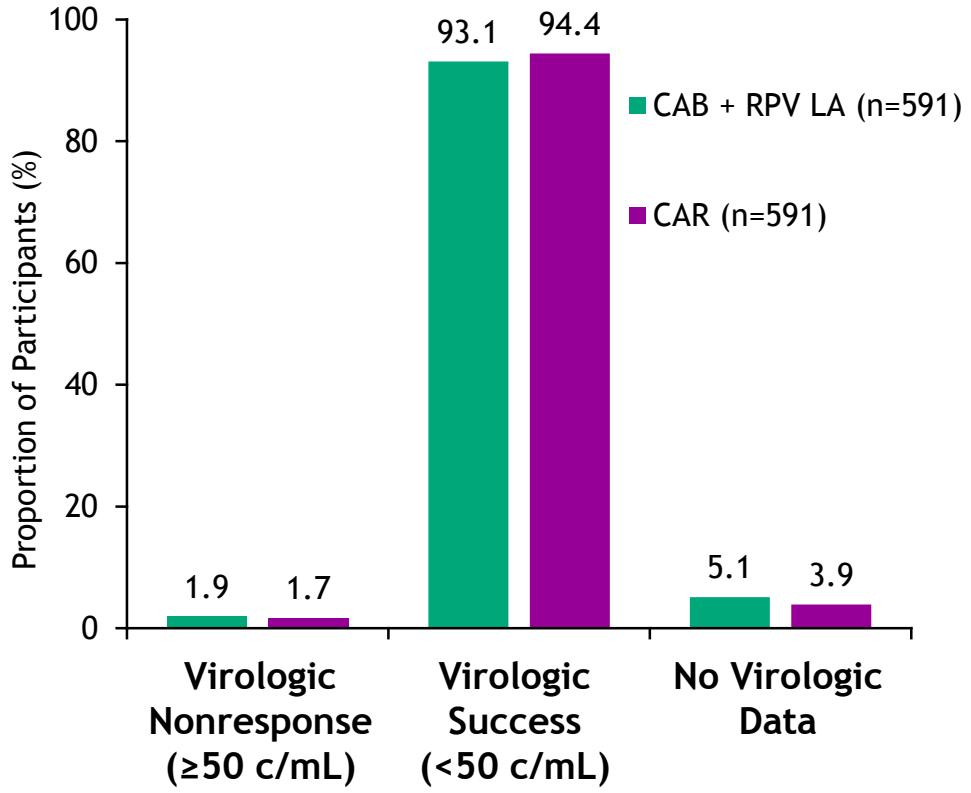
- ATLAS: virologically suppressed; switch to monthly IM LA CAB/RPV vs. continue oral ART
- FLAIR: Treatment naïve; suppress with oral ART; switch to monthly IM LA CAB/RPV vs. continue oral ART



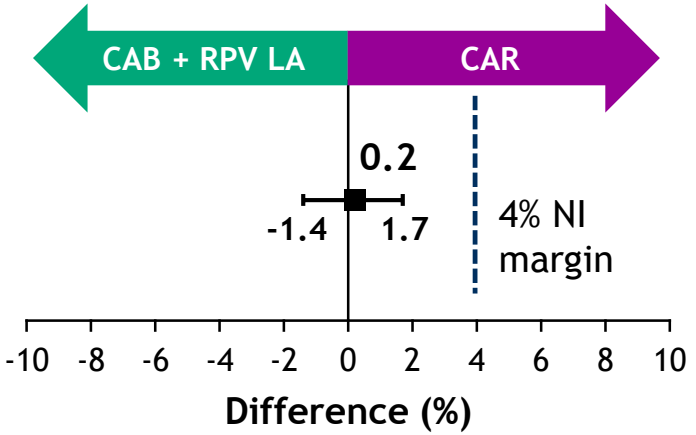
Overton E IAS 2019 MOPEB257; Swindells S, et al. CROI 2019; #139; Orkin C, et al. CROI 2019; #140.

ATLAS/FLAIR Week 48 Pooled Results

Virologic outcomes

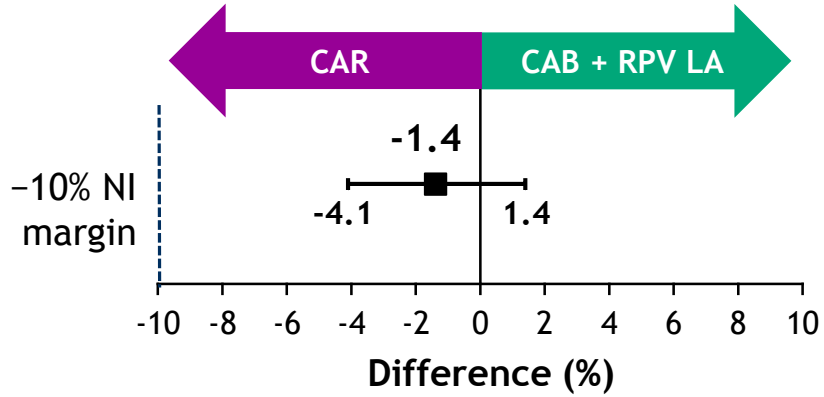


Adjusted treatment difference (95% CI)*



Primary Endpoint:

LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48



Key Secondary Endpoint:

LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

Overton E, IAS 2019 MOPEB257 Swindells S, CROI 2019; #139
Orkin C, CROI 2019; #140.

LA CAB/RPV: Questions

- Is the oral lead-in needed? What about direct to inject?
- What about the long tail in people who stop the drugs? CAB detectable up to 48 wks after single injection, longer in women
- Will the drugs be useful in people who have difficulty adhering to oral ART?
- Can LA CAB/RPV be used in someone who is viremic?
  - Case: person with bowel resection; not able to absorb oral ART; suppressed on IM CAB/RPV
- What will the cost of the drugs be? Will the cost of the administration be reimbursed?

Orkin C, IAS 2019 TUSY0403; Landovitz, R, HIV R4P, Madrid, 2018. Abstract #OA15.06LB; Saman R, EACS 2019

Ongoing CAB/RPV Studies

- **2 monthly IM: ATLAS 2M** (n=1049)
  - Phase 3 open-label 48 wk results in persons suppressed on oral ART or on every 4 wk CAB/RPV LA
  - Randomized 1:1 to CAB/RPV LA every 4 weeks

    or every 8 weeks
  - Every 8 wk therapy was non-inferior

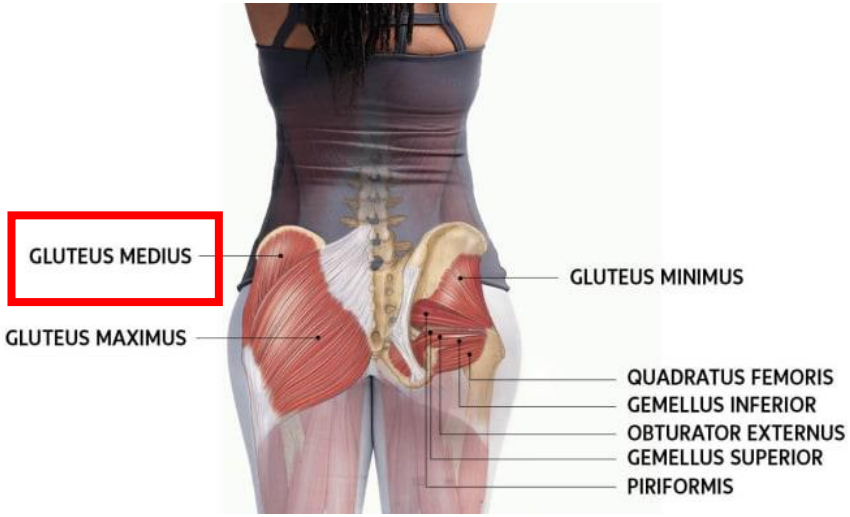
22 August 2019

ViiV Healthcare reports positive phase III study results of investigational, long-acting, injectable HIV-treatment regimen administered every two months

ATLAS-2M study met its primary endpoint, showing similar efficacy of cabotegravir and rilpivirine administered every eight weeks compared to four-week administration.

Practical Aspects of Using CAB/RPV

- Loading dose: CAB LA 600 mg (one 3-mL injection) and RPV LA 900 mg (one 3-mL injection)
- Monthly maintenance: CAB LA 400 mg (one 2-mL injection) and RPV LA 600 mg (one 2-mL injection)
- RPV LA requires cold chain
- Injection into gluteus medius (upper outer quad
  - Need a private place for injections
  - What about people with buttock implants?



Orkin C, et al. IAS 2019 TUSY0403; Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB; Saman R et al, EACS 2019

Practical Aspects of Using CAB/RPV: Continued

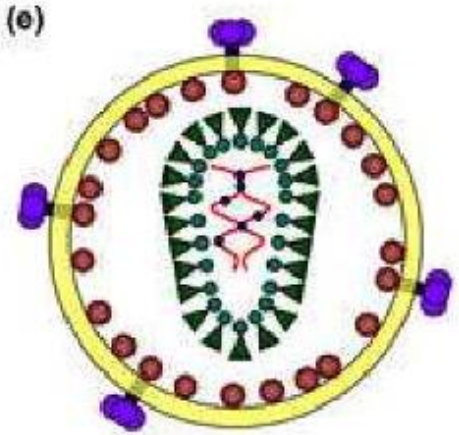
- Staffing and physical space to deliver injections
  - In 3000 patient clinic, if 10% want injections: 15 visits/day, 30 injections/day (if monthly)
- Are there alternative places to deliver injections? Pharmacies? Home healthcare? Infusion centers?
- How will people remember to come in for visits? How will we remind people to come in for visits?
- If people are late in coming in, will need oral ARV bridging

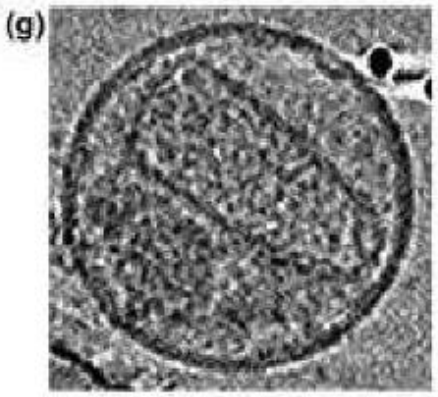
Orkin C, et al. IAS 2019 TUSY0403; Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB; Saman R et al, EACS 2019

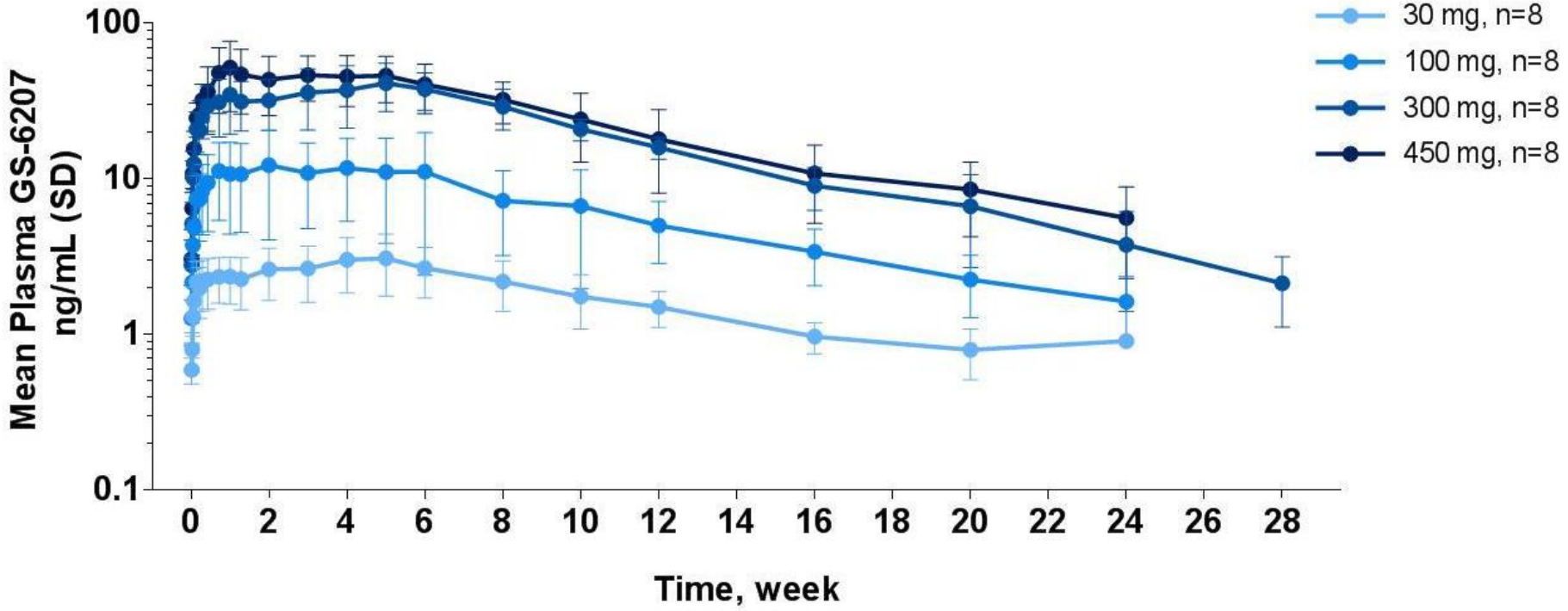
My take on LA Cabotegravir/Rilpivirine

- For most people, oral daily ART will remain effective and convenient option
- LA CAB/RPV may be good option for people who struggle with taking daily oral regimen (e.g., swallowing difficulties, stigma – external or internal)
- In people who struggle with adherence with oral ART, LA CAB/RPV may be helpful as long as the person comes back for appointments
- Combining visits with other appointments may be helpful, e.g. when picking up methadone refills, psychiatrist/psychologist/support group visits
- Every 8 wk dosing (if safe and effective) will make LA CAB/RPV more attractive but adherence, long pharmacokinetic tail, oral bridging for missed injections, reminders, administration logistics, and cost will still be important considerations

HIV Capsid Inhibitor: Sustained levels for >24 weeks after single subcutaneous injection

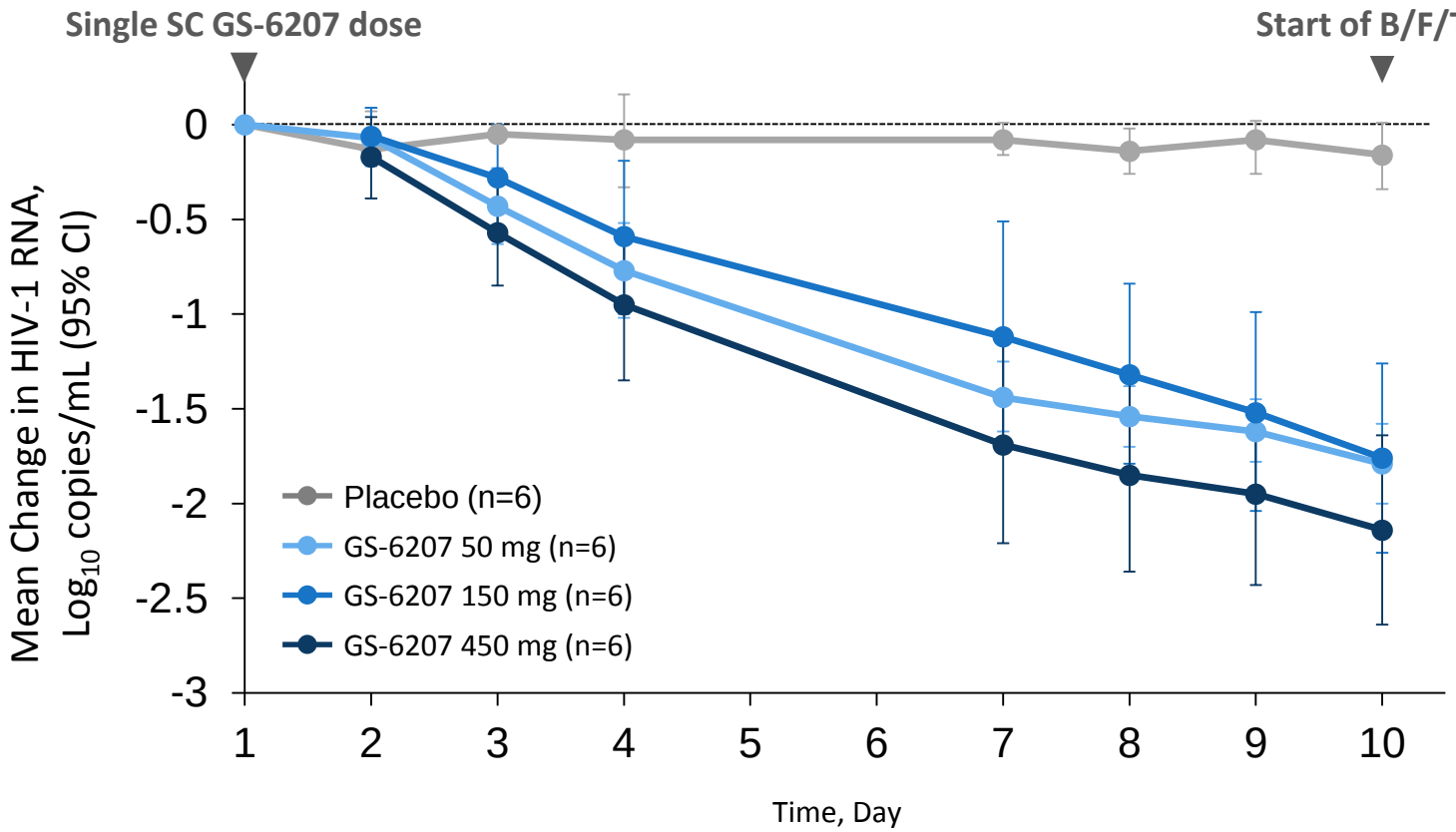






Ganser-Pornillos BK, Yeager M, Sundquist WI, Curr Opin Struct Biol, 2008
Sager et al CROI 2019 abstract 141

HIV Capsid Inhibitor: Antiviral activity after single subcutaneous dose in people with HIV



Mean reduction of HIV RNA:
-1.4 to 2.2 log_{10} c/mL over 10 days

Recently announced[2]:

- Phase 2/3 study in treatment experienced/multi-drug resistant HIV
- Phase 2 trial in treatment naïve
- Capsid inhibitor: two-week oral lead-in followed by subcutaneous injection every 6 mo.

[1]Daar E IAS 2019 LBPEB13; Daar E EACS 2019 PE3/17
[2]clinical trials.gov: NCT04150068; NCT04143594

PrEP

DISCOVER Trial: Daily Emtricitabine/Tenofovir AF or Emtricitabine/Tenofovir DF for HIV PrEP

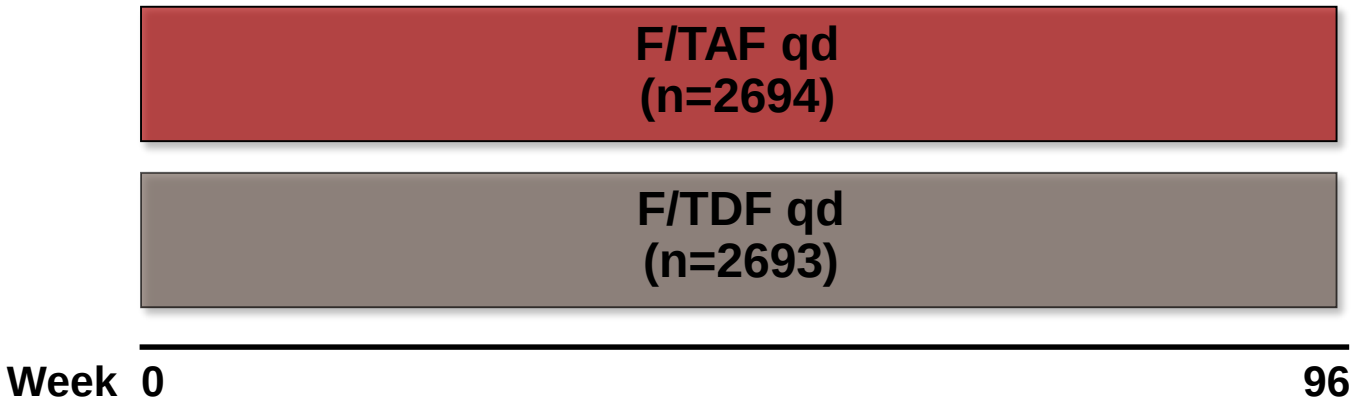
Phase 3, non-inferiority study

Gilead funded

Double-blind

HIV negative MSM and transgender women at risk for HIV

eGFR: ≥60 mL/min

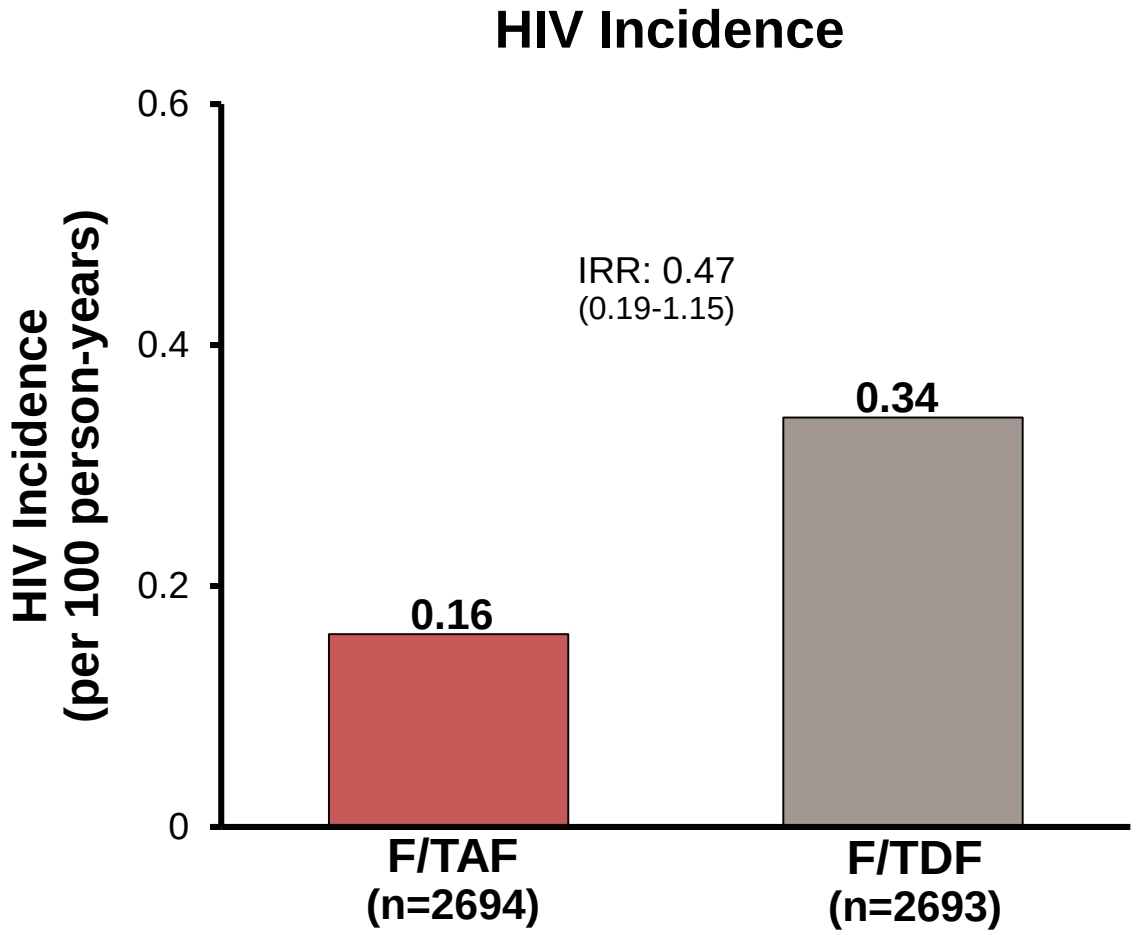


Primary analysis:
HIV incidence/100 person-years when 100% complete week 48 and 50% complete week 96.

HIV risk factors (%):
≥2 condomless anal sex (receptive) past 12 weeks: 59%.
Rectal gonorrhea/chlamydia past 24 weeks: 10%/13%.
Syphilis past 24 weeks: 10%.
Recreational drug use past 12 weeks: 67%.
Binge drinking: 23%.
Taking F/TDF for PrEP at baseline: 17%.

DISCOVER Trial: HIV Incidence Outcomes

- F/TAF was non-inferior to F/TDF for HIV prevention
- 22 HIV infections over 8856 person-years of follow-up
  - F/TAF (n=7)
  - F/TDF (n=15)



IRR: incidence rate ratio.

Mills A, et al. IDWeek, Washington, DC 2019. Abstract 1962.

FDA NEWS RELEASE

FDA approves second drug to prevent HIV infection as part of ongoing efforts to end the HIV epidemic

For Immediate Release: October 03, 2019

The U.S. Food and Drug Administration today approved Descovy in at-risk adults and adolescents for PrEP to reduce the risk of HIV-1 infection from sex, excluding those who have receptive vaginal sex.

Descovy is not indicated in individuals at risk of HIV-1 infection from receptive vaginal sex because the effectiveness in this population has not been evaluated.

Factors Associated With HIV Seroconversion Among Women Attending an Urban Health Clinic in the South

- Matched case-control cohort (2011-2016)
  - Women with clinician-assisted visit in downtown Atlanta (with and without HIV)
  - Controls matched for race, age, and date of first clinician-assisted visit
- Outcome: HIV seroconversion
- Factors most strongly associated with HIV
  - Syphilis (OR: 4.2)
  - Anal sex (OR: 3.0)
  - IDU/crack cocaine use (OR: 23.7)
  - Exchange sex (OR: 2.2)

Women who had a history of syphilis, reported anal sex, and used injection drugs and/or crack were 6 times more likely to acquire HIV than age and race matched women who did not have those risk factors.

Onwubiko U, et al. IDWeek, Washington, DC 2019. Abstract 1964.

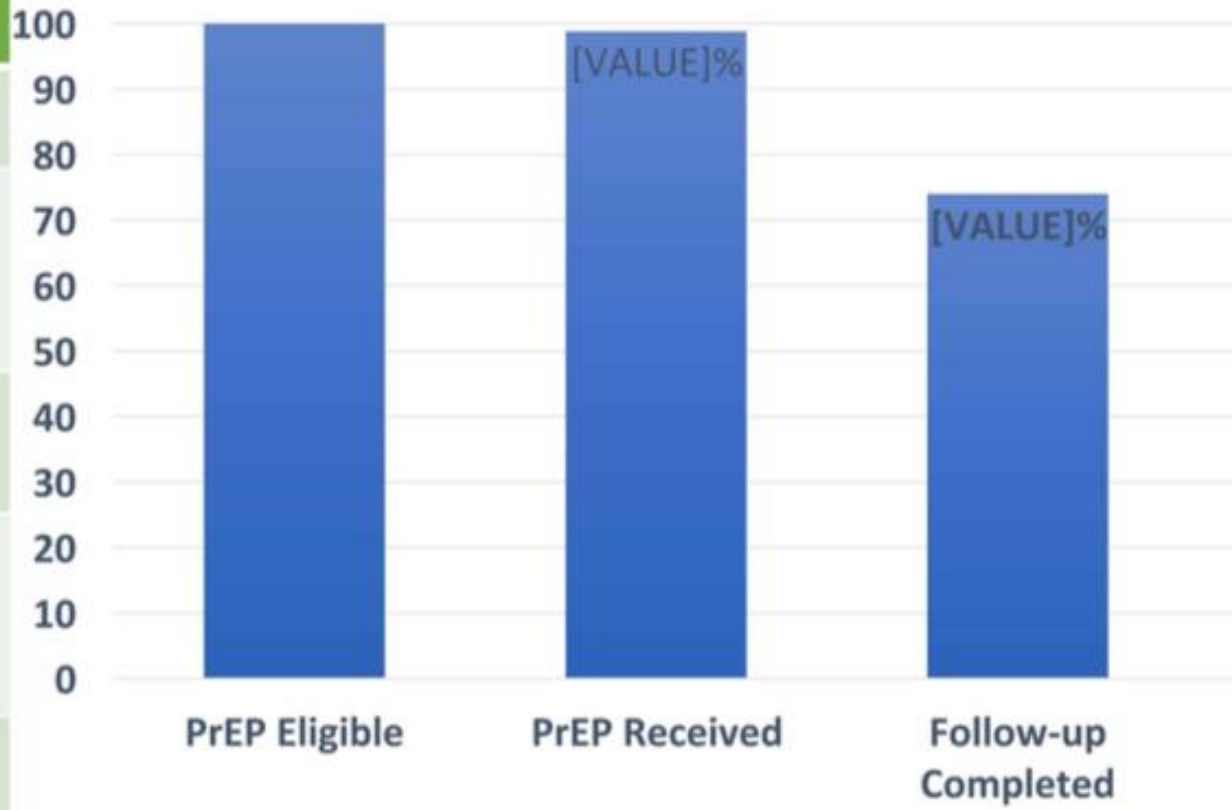
PrEP on the Go

- Delivery of PrEP on a mobile van in Miami
- PrEP Counselor/Navigator
- Medical Provider (MD/APRN)
- Rapid HIV test, HCV test
- 3-site GC/CT testing, U/A, Upreg
- Phlebotomy for HIV, syphilis, Cr, HBV test
- E-Prescription for PrEP (3 mo) routed by pharmacist to ensure fill
- Patient Assistance Program paperwork
- Intense navigation and follow-up

Doblecki-Lewis S et al, IDWeek 2019, Abstract 1965.

PrEP Receipt and Early Follow-up

Mobile Clinic Outcomes Oct 2018 – April 2019	
PrEP-Eligible Clients	168
HIV Baseline Reactive	6 (3.5%) 2 acute/early infections
Received PrEP meds (of eligible)	166 (98.8%)
Completed follow-up (of clients enrolled >3 mo ; n=77)	55 (71.4%)
New Bacterial STI Diagnoses Baseline Follow-up (n=77)	 45 (26.6%) 9 (16.3%)



Extra slide

Role of NRTIs in Weight Gain: Randomized Trials

- ADVANCE: greater weight gain when DTG combined with TAF than when DTG was combined with TDF, especially in women
- DISCOVER (TAF/FTC vs. TDF/FTC for PrEP): greater weight gain (1 kg) in men/transgender women who received TAF vs. those who received TDF[1]
- In GEMINI: mean weight gain of 3.1 kg in DTG/3TC group and 2.1 kg in DTG/FTC/TDF group
- In TANGO, the group that stayed on TAF-containing therapy had a similar weight gain (0.8 kg) as the group that switched to DTG/3TC

Spinner CD et al, IAS 2019, TUAC0403LB