Mycobacterium avium complex

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Last Updated:

Disclosures

Merck: adjudicated cases for a new HIV assay in 2023

Disclaimer

Funding for this presentation was made possible by 1 TR7HA53202-01-00 from the Human Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. *Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.*

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Data Considerations

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.

To Learn More:
https://www.cdc.gov/minorityhealth/racism-disparities

Case Presentation

Case presentation

- A 23 year old man not previously diagnosed with HIV presents with anorexia, dysphagia, a 25# weight loss over 6 months, night sweats, fatigue, and diarrhea.
- On exam he is cachectic and apathetic. Temperature is 38.2, BP 90/60, HR 110, RR 14. He has obvious thrush, seborrheic dermatitis, indurated purple plaques on his face, feet, and hard palate. His liver edge is 2 FB below his R costal margin.
- He tests + for HIV, his CD4 cell count measures 14 cells/uL and a plasma HIV RNA level is 454,000 copies/uL.

Case presentation

- He declines hospitalization but receives several liters of IV fluids, is given fluconazole, TMP/SMX, weekly azithromycin and goes home.
- He returns to clinic 2 weeks later without thrush or dysphagia.
- He claims to be taking TMP/SMX and azithromycin but his diarrhea, fevers, and sweats continue, and he now complains of abdominal fullness and pain.

Case presentation

What conditions might explain his diarrhea, fever, sweats, and abdominal pain?

- Lymphoma
- KS
- Intestinal infections (cryptosporidia, microsporidia, isospora, CMV)
- Disseminated mycobacterial infections (MTB, MAC, *M. bovis*)
- Disseminated fungal infections (Histoplasmosis)

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Case presentation

What diagnostic studies do you want?

- CBC and chemistries: LDH 220, WBC 3.4, Hct 24, Plts 300K, ALT 54, AST 84, AP 650, TB 1.4, TP 9.0, Alb 2.1
- Stool EPP and O&P - negative
- Blood cultures for bacteria, mycobacteria, fungi – negative or pending
- Histoplasma urinary antigen negative
- PPD, IGRA – both negative

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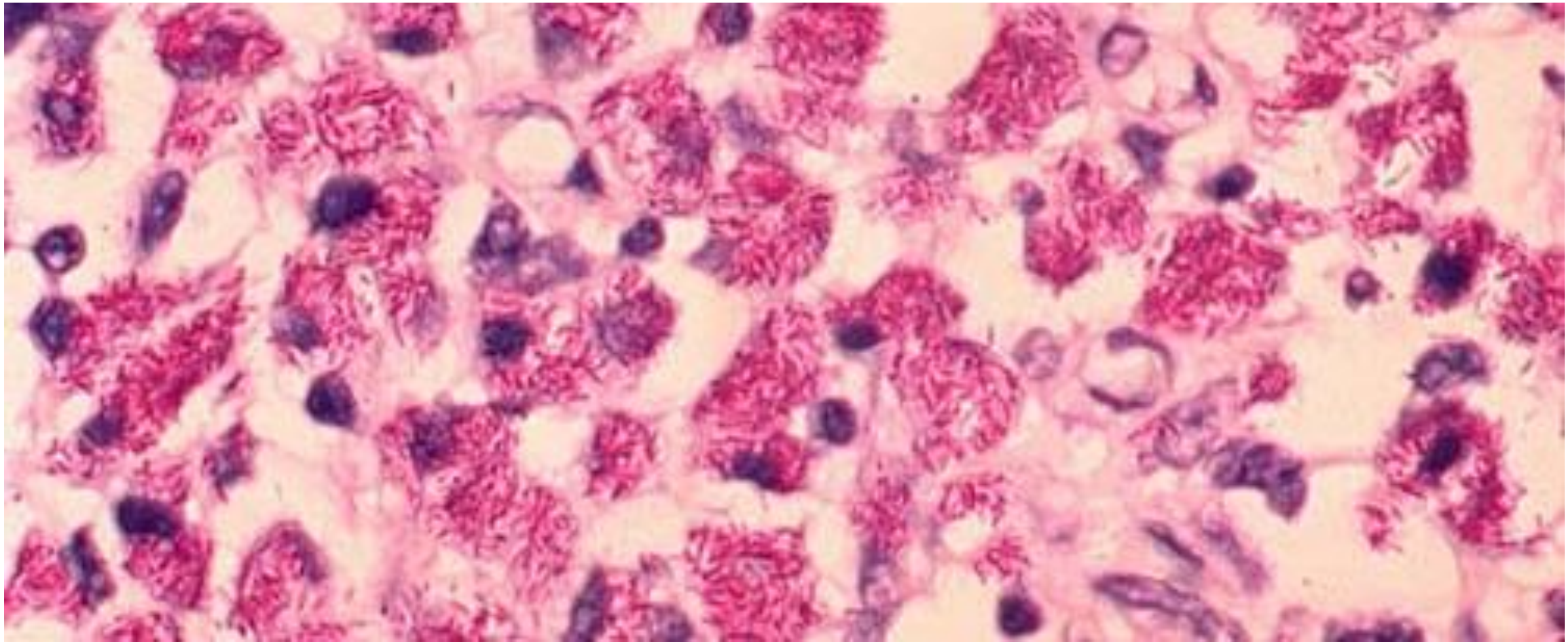
Case presentation

What next?

Case presentation

What next?



Mycobacterium avium complex

- Organism
  - Formerly *Mycobacterium avium-intracellulare.* Now *M. avium* sub *hominissuis, M columbiensi.*
  - *M. genevense, M. kansasii, M. simiae, M. micogenicum* were probably included in older cases of disseminated MAC
  - Ubiquitous soil and water organism
- Epidemiology and route of infection
  - Common OI with incidence of 20-40% without prophylaxis or ART. Now < 2 cases as the first OI in 1000 person/yrs (even among those not on ART)
  - Infection initiated by ingestion or inhalation - not reactivation.

Mycobacterium avium complex

Effect of HAART: Less disease and better survival …..but mostly less disease

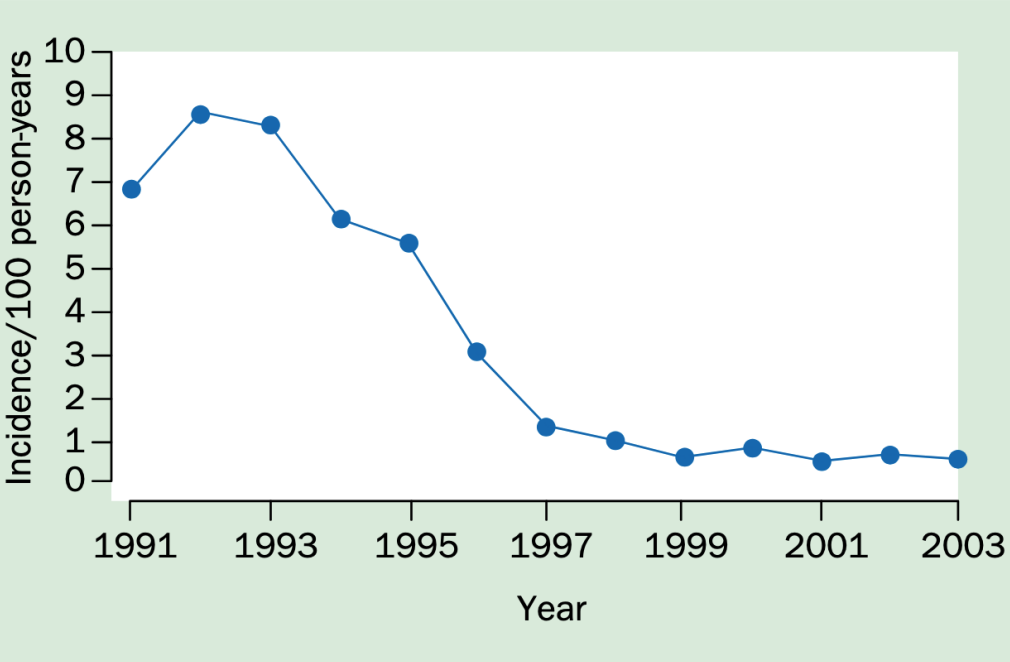


Figure 1. Incidence of MAC infection in patients with a CD4 count <200/μL in the Johns Hopkins HIV clinic cohort, 1991–2003 (methods are described in Moore and Chaisson[12]).

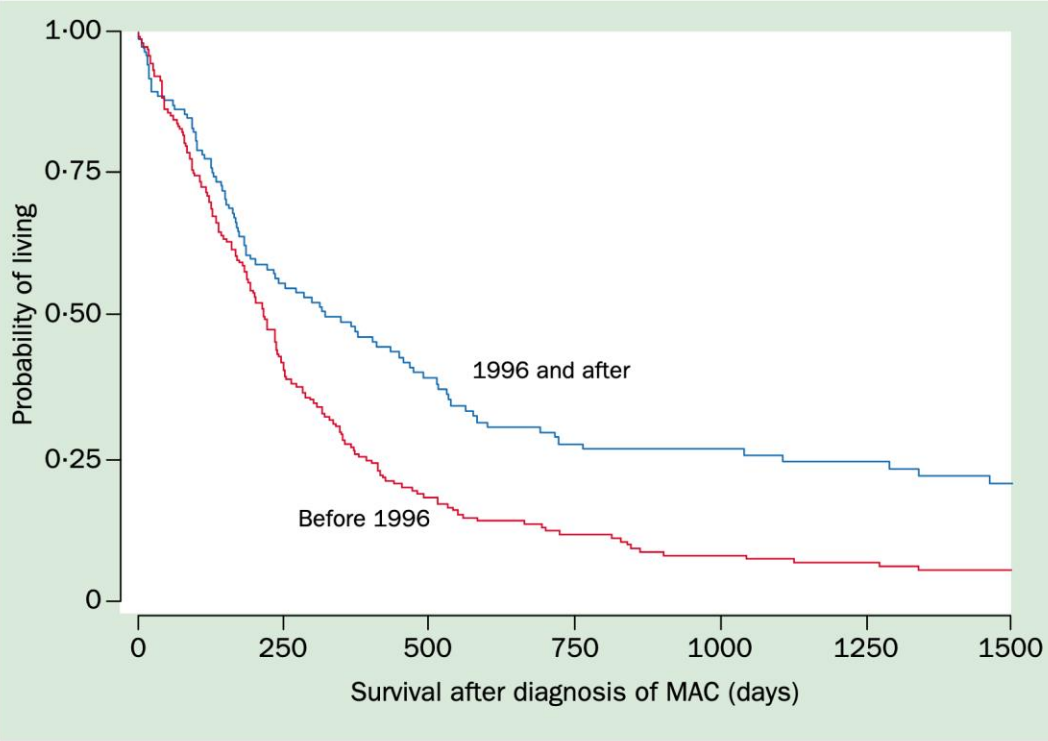


Figure 2. Survival after a diagnosis of MAC in patients in the Johns Hopkins HIV clinic cohort, 1991–1995 versus 1996–2003. Log-rank difference in survival is 0·0002 (methods are described in Moore and Chaisson[12]).

(Karakousis, Lancet Infect Dis 2004; 4:557-65)

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- Clinical presentation/syndrome(s)
  - CD4 < 100 (median of 60)
  - Disseminated disease; fever, night sweats, weight loss, abdominal pain, anemia, organomegaly, bacillemia
  - Localized disease; diarrhea (due to small bowel and/or colonic involvement), cholangiopathy, adenitis, endobronchial lesions, pneumonia, cutaneous lesions – more often in patients on ART
- Diagnosis
  - Blood cultures are positive in over 90% (disseminated disease)
  - Isolation from other tissues
  - Only 2/3 of those with MAC cultured from GI or respiratory tract will develop bacillemia

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- Prophylaxis: when CD4 < 50 (hold if occult infection likely or starting ART)
  - Azithromycin or clarithromycin
  - Rifabutin (not if occult TB possible)
  - Can discontinue when CD4 > 100 for 3 months
  - *Primary prophylaxis is not recommended if effective ART is initiated immediately and viral suppression achieved – IAS-USA guidelines 2016*
  - *Not recommended unless people will not be starting ART or who remain viremic on ART – DHHS guidelines 2024*

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Preferred Treatment

- Test for macrolide resistance! Macrolides are the cornerstone of treatment
  - Clarithromycin 500 bid + ethambutol (15 mg/kg/d) OR
  - Azithromycin 500-600 qd + ethambutol (15 mg/kg/d)

  - *Consider* adding rifabutin (300 qd) in patients with severe disease
  - *Consider* adding a 4th drug in patients with severe disease, those with high bacterial loads, if drug resistance is likely (e.g. failed prophylaxis) and if ART is not being used: levofloxacin, moxifloxacin, amikacin > bedaquiline, linezolid, omadacycline
  - Duration is for 12 months – but can consider shorter duration with excellent immune reconstitution. CD4 counts should be > 100 for at least 6 months

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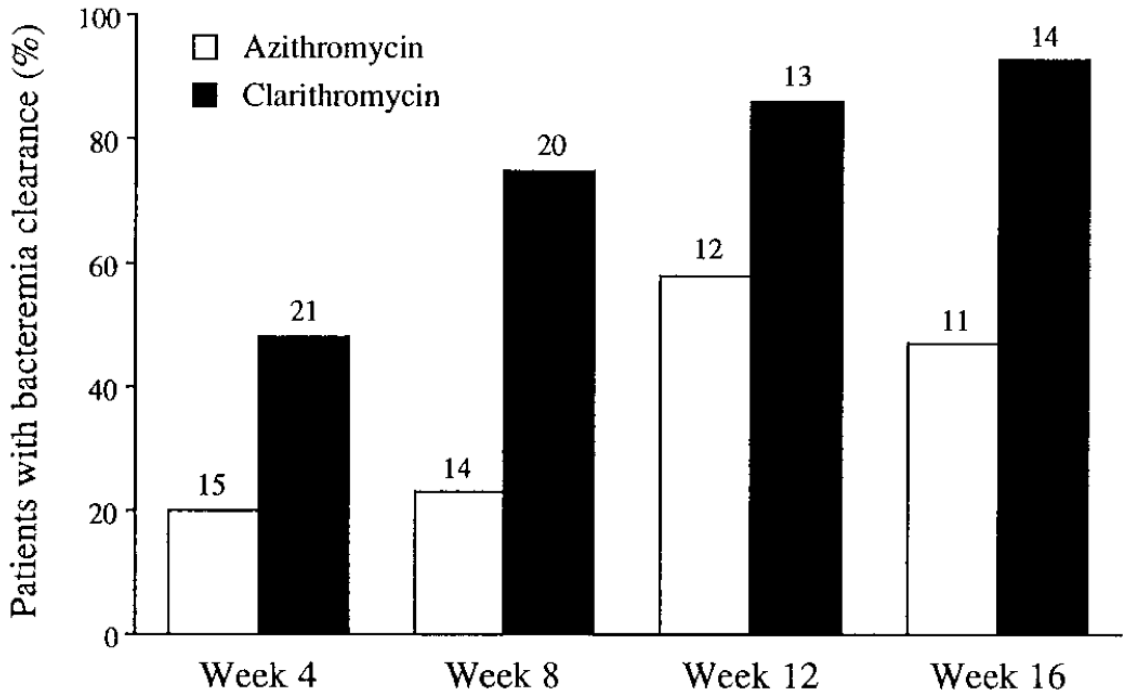
Clarithromycin Vs Azithromycin?

- P, R study of 59 VA patients with HIV and dMAC
- Compared Clarithromycin + Ethambutol to Azithromycin + Ethambutol
- Performed between 1991-1994 (pre-HAART)
- Outcome: clearance of bacteremia - out to 16 weeks

Clearance of Bacteremia



Ward CID 1998

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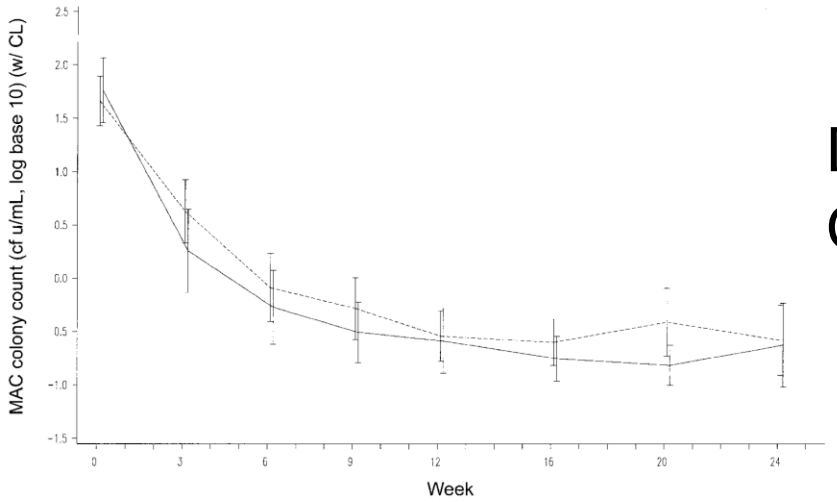
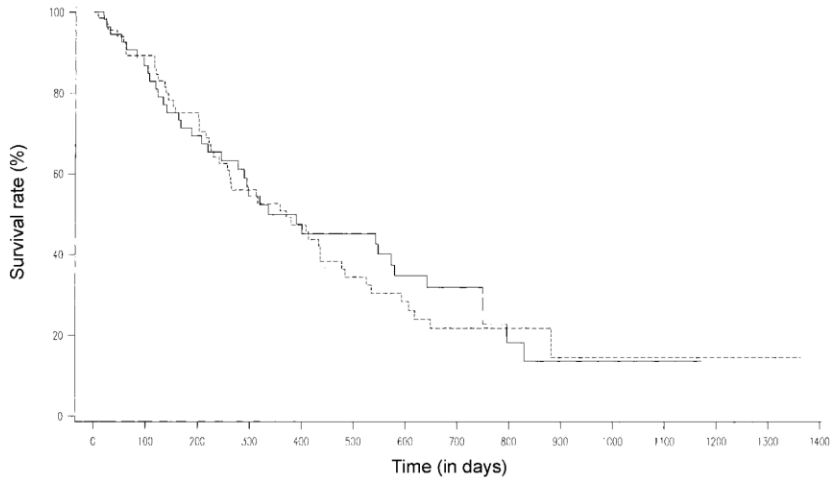
Clarithromycin Vs Azithromycin?

- P, R, DB study of 246 patients in US, Brazil, Argentina, Chile and The Netherlands between 1994-1998.
- Compared Clarithromycin + Ethambutol to Azithromycin (2 doses) + Ethambutol
- Only 28/246 on ART including a PI
- No difference in clearance of bacteremia or survival
- Relapse rate: 39% (A) and 27% (C) – not significant



Drop in Colony counts



Survival

Dante CID 2000

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Clarithromycin Vs Azithromycin?

- P, R study of 85 patient with HIV and dMAC
- Clarithromycin (2 doses: 1000 mg bid or 500 mg bid) + ethambutol + [clofazimine or rifabutin]
- Higher death rate in those treated with clarithromycin at 1000 mg bid (43%) Vs those treated with 500 mg bid (22%)
- High concentrations of clarithromycin associated with:
  - Inhibition T-cell proliferation (in vitro)
  - Suppression of IL-6 and other cytokines

Clarithromycin is a potent inhibitor of P450-3A4 and P-glycoprotein

Drug	Effect	Recommendation
Rifabutin	Increased Rif and decreased Clari	Use caution
Rifampin	Increased Rif and decreased Clari	No
Rifapentine	Increased Rif and decreased Clari	Daily Rifapentine - No
Atazanavir	Increased ATZ and increased Clari	Consider alternative
Darunavir	Increased DRV and increased Clari	Consider alternative
Doravirine	Increased DOR	Monitor
Etravirine	Increased ETR and decreased Clari	Alternative macrolide
Rilpivirine	Increased RLP	Alternative macrolide
Elvitegravir	Increased cobi and increased Clari	Decrease Clari 50%

Cohn CID 1999

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Does Adding Rifabutin Help ?

- P, R, PC study of 198 patient with HIV and dMAC – conducted 1993-1996
- Clarithromycin + ethambutol + [rifabutin or placebo]
- At 16 weeks
  - No difference in bacteriologic response (clearance or 2-log drop in CFU) 61% (placebo) Vs 63% (rifabutin)
  - No differences in clinical responses or survival

Gordin CID 1999

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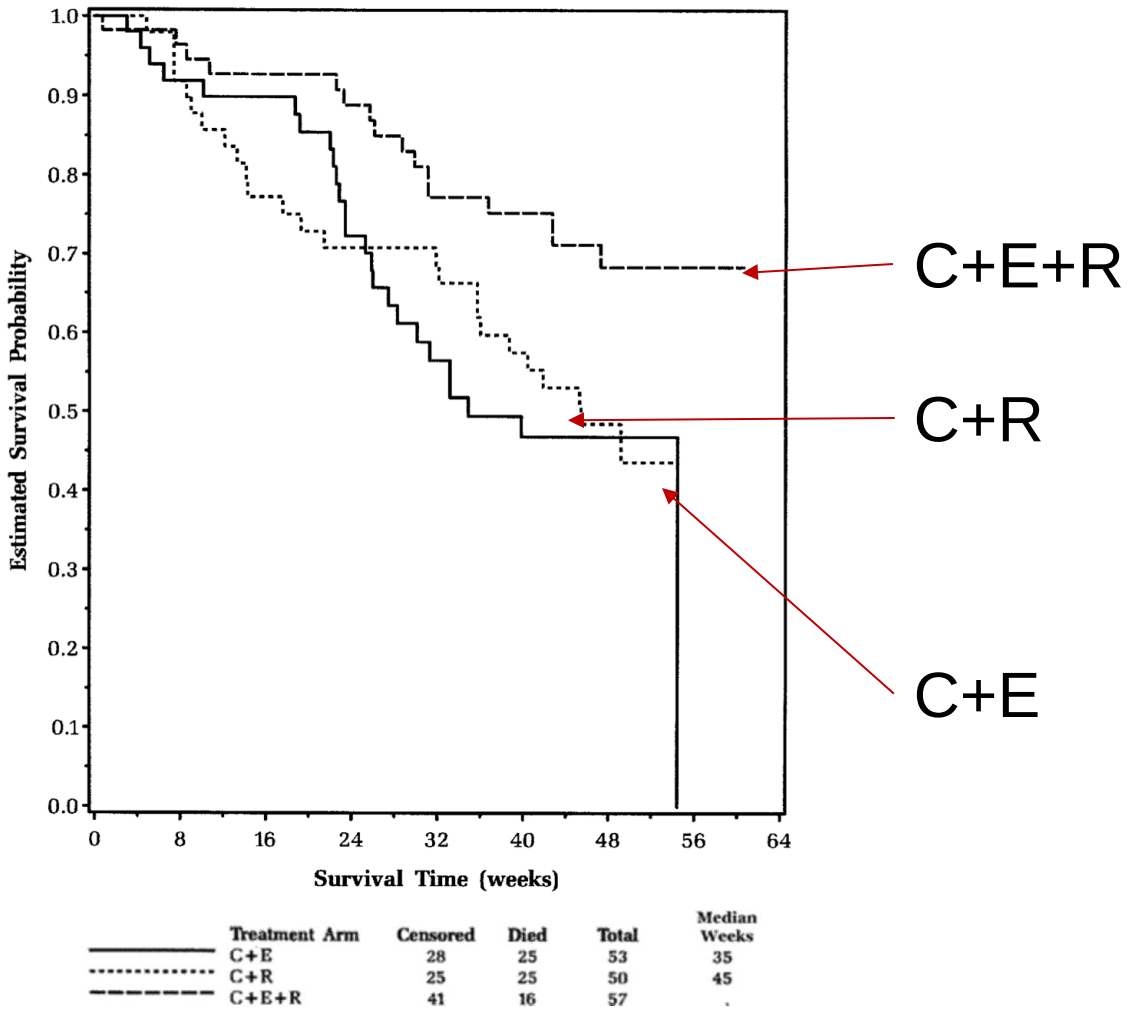
Does Adding Rifabutin Help ?

- P, R, PC study of 160 patient with HIV and dMAC – conducted 1993-1996
  - Clarithromycin + ethambutol (C+E)
  - Clarithromycin + rifabutin(C+R)
  - Clarithromycin + ethambutol + rifabutin (C+E+R)
  - Only 12-16% on ART (including a PI)
- Relapse on therapy: C+R 23%, C+E 7%, C+E+R 6%
- Death: C+R 25, C+E 25, C+E+R 16
  - HRs: 0.44-0.49
  - HRs, adjusted for PI use: 0.35 (c/w C+E) and 0.44 (c/w C+R)



Benson CID 2003

Treatment Conclusions

- Treat dMAC with a macrolide and ethambutol.
- Clarithromycin is more active against MAC than azithromycin and clears bacteremia faster but probably does not enhance survival and is associated with more adverse effects and more drug interactions.
- Furthermore, clarithromycin at doses of 1000 mg bid is associated with higher death rates.
- The addition of rifabutin to a macrolide and ethambutol enhances survival in those not on HAART but is of limited value in those on HAART. Exceptions might be those with severe disease, extremely high levels of mycobacteria or macrolide drug resistance.

Other Treatment Considerations

- Those not responding to treatment should have repeat blood cultures obtained 4-8 weeks into treatment
- Treatment of those who relapse should be with a new regimen containing at least 2 new drugs to which the organism is susceptible
- If macrolide drug resistance is demonstrated – stop the macrolide!
- Clarithromycin should be avoided in pregnancy (based on animal studies)

Case presentation

- Azithromycin and ethambutol result in a gradual reduction in temperature, sweats, and diarrhea over the next weeks.
- He is then started on ART (dolutegravir-TDF-FTC) and 3 weeks later presents with recurrent fever, abdominal pain, and a L sided abdominal mass
- Imaging reveals……..

Case presentation

Diagnosis?

MAC IRIS

- Clinical presentation: fever, sweats, adenitis (cervical, inguinal, thoracic, abd/retroperitoneal)
  - Low CD4 (< 50): more severe illness; fevers, weight loss, leukocytosis, positive blood cultures
  - High CD4 (> 100-150): fewer systemic symptoms, more localized suppurative disease
- Treatment:
  - Continue ART
  - Continue MAC therapy
  - NSAIDS
  - Steroids (prednisone 20-40 mg per day)

Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of award 1 TR7HA53202-01-00 totaling $2,982,063 with 0% financed with non-governmental sources.

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