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CIDS Newsletter

April 2016

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Editor's note

Dear CIDS members

Our senior member Dr PH Chandrasekar has volunteered to contribute periodically to the newsletter, and his first column appears in this issue.

Contributions from others are most welcome!

Sincerely

Ram Gopalakrishnan

Photo quiz

A 37-year gentleman with diabetes mellitus with bilateral polycystic kidney disease was detected to have HIV-1 during evaluation for renal stones. He was asymptomatic and investigations revealed CD4 count of 344 and HIV-1 of VL= 59,92,441 copies/ml. HBsAg, HCV Ab, VDRL and TPHA were all negative.

The patient was started on TDF/FTC/EFV elsewhere and was reportedly fully adherent. Regular follow up revealed virological & immunological failure (see table 1)

Table: 1

	2013	9/2014	1/2015	7/2015
CD4	344	385	233	265
CD4%	-	21%	25%	30%
VL	59,92,441	-	2,51,380	90,506
ART	TDF/FTC/ EFV	TDF/FTC/ EFV	TDF/FTC/ EFV	TDF/FTC/ EFV

HIV Genotypic Resistance Testing revealed HIV Subtype C with the following mutations:

- NRTI- M184V, D67N, K70E
- NNRTI- V-106N, V-179N
- No PI mutations

Which ART regimen should be initiated in this patient?

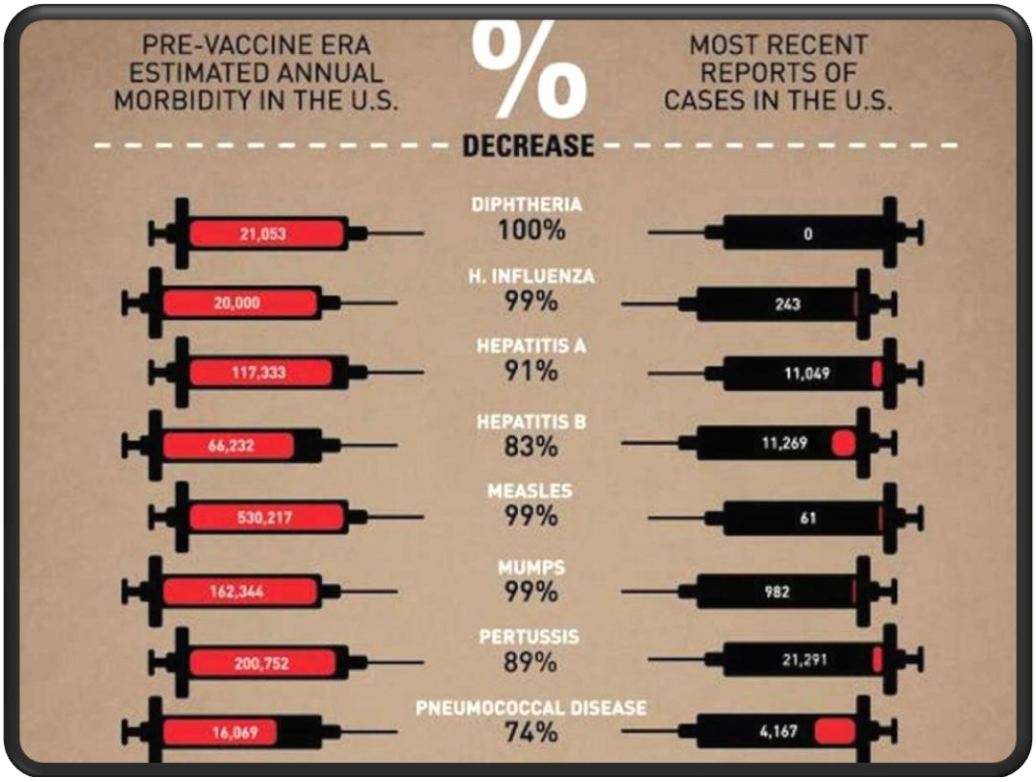
1. TDF+ FTC+ PI/r
2. AZT+3TC + LPV/r
3. RAL + PI/r
4. RAL + PI/r + 3TC
5. ABC + 3TC + ATV/r

News from the ID world

Government introduces rotavirus vaccine

The Government of India has introduced the rotavirus vaccine in four states as part of the universal immunization program through the public healthcare system. Andhra Pradesh, Haryana, Himachal Pradesh and Odisha will be covered first and the program then expanded country-wide. Three doses at 6, 10 and 14 weeks will be administered. The Health Ministry reportedly plans to introduce three more vaccines soon: IPV, measles/rubella and JEV.

Pneumococcal conjugate, influenza, typhoid conjugate, HPV and hepatitis A vaccines are also needed in the future. These vaccines are already available and used in the private sector.



WHO recommends dengue vaccine

The World Health Organisation's Strategic Advisory Group of Experts on Immunization (SAGE) has recommended the use of dengue vaccine to control spread of disease. The WHO has set objectives to reduce dengue morbidity by 25 percent and mortality by 50 percent by 2020.The vaccine has been approved in four countries already, including Mexico and Brazil, which have regulatory authorities recognised by the WHO.

Snippets from the literature

Arterolane Maleate–Piperaquine Phosphate vs Artemether–Lumefantrine for Falciparum Malaria

Clin Infect Dis. (2016) 62 (8):964-971.

In this multicenter, randomized, double-blind, comparative, parallel-group trial, 1072 patients aged 12–65 years with *P. falciparum* mono-infection from India and Africa received either AM–PQP (714 patients) once daily or artemether–lumefantrine (A–L; 358 patients) twice daily for 3 days. In both groups, the polymerase chain reaction corrected adequate clinical and parasitological response (PCR–corrected ACPR) on day 28 in intent-to-treat (ITT) and per-protocol (PP) populations was 92.86% and 92.46% and 99.25% and 99.07%, respectively.

AM–PQP showed comparable efficacy and safety to A–L in the treatment of uncomplicated *P. falciparum* malaria in adolescent and adult patients. AM–PQP demonstrated high clinical and parasitological response rates as well as rapid parasite clearance. The drug has been available in India for the last few years.

False positive Xpert MTB/RIF Results in Patients with Previous Tuberculosis

Clin Infect Dis. (2016) 62 (8):995-1001.

Pretreatment patients (n = 2889) with symptoms of tuberculosis from Cape Town, South Africa, underwent a sputum-based liquid culture and Xpert. One in 7 Xpert-positive retreatment patients were culture negative and potentially false positive. False positivity was associated with recent previous tuberculosis, high C_T, and a chest radiograph not suggestive of active tuberculosis. Xpert detected nonviable, nonintact bacilli without a change in C_T vs controls.

Clinicians may consider awaiting confirmatory testing in retreatment patients with suspected relapse of TB, especially those with $C_T > 30$ and a history of recent tuberculosis treatment, rather than re-treating based on Xpert.

GeneXpert MTB/Rif to Diagnose Tuberculous Meningitis: Perhaps the First Test but not the Last

(courtesy Dr Ashwini Tayade)

http://m.cid.oxfordjournals.org/content/early/2016/03/09/cid.ciw083.full.pdf

This viewpoint article by a group of "TBM experts" discussed the 2014 World Health Organization strong recommendation favoring the use of Xpert "in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid (CSF) if the sample volume is low or if additional specimens cannot be obtained to make a quick diagnosis." The authors were concerned that the limitations of Xpert testing for TBM are not emphasized. Clear guidance is needed for the investigational pathway for TBM, including recommendations on the diagnostic package of investigations, which does not stop with Xpert testing. Second, emphasis on the large CSF volumes (ideally 8–10 mL) needed for Xpert testing is required. Guidelines should also emphasize that TBM is a medical emergency and early treatment reduces mortality.

Faropenem: the value of a seductive name

Clin Infect Dis. 2016;62:1050-1052

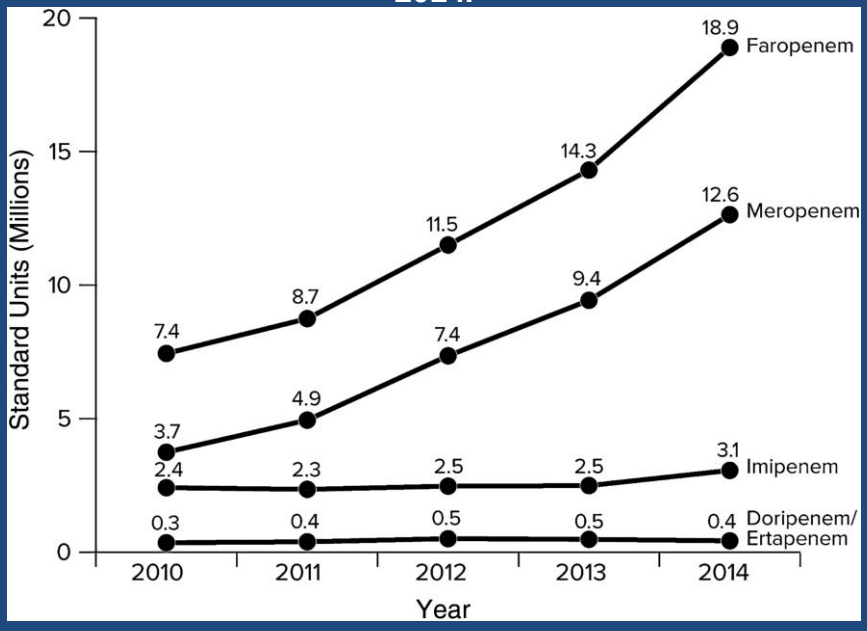
Faropenem consumption in India increased by 154% since it was approved in 2010. Salient features of faropenem are as follows:

- Oral agent active against aerobic gram-positive, gram-negative, and anaerobic bacteria, and is also resistant to TEM-, SHV-, and CTX-M–type ESBLs
- In India, faropenem is approved for the treatment of respiratory tract, urinary tract, skin, soft-tissue, and gynecological infections
- It is often used to treat invasive ESBL-producing Enterobacteriaceae infections even though its efficacy in these cases is not clinically proved.

- Susceptibility testing against faropenem is not routinely performed
- Recent in vitro studies have shown that faropenem could be a screening indicator of carbapenemase activity in an organism
- More than 99% of carbapenemase producers tested show growth up to the edge of a faropenem disk (in contrast to carbapenems te-
-sted, which showed inhibition zones)
- This feature makes it a convenient antibiotic to screen for carbapenemase producers, but it may be indicative of a lower activity of faropenem against such strains or of a higher induction of the carbapenemase by faropenem

The authors warn of potential loss of the carbapenem class due to abuse of faropenem.

Trends in faropenem and carbapenem consumption in India, 2010–2014.



Sumanth Gandra et al. Clin Infect Dis. 2016;62:1050-1052

Clinical Infectious Diseases

Cellulitis = Streptococcus

Open Forum Infect Dis (Winter 2016) 3 (1):doi: 10.1093/ofid/ofv181

The authors prospectively enrolled 216 patients hospitalized with cellulitis. Clinical details were registered. Bacterial culture was performed from blood, cutaneous or subcutaneous tissue, and/or swabs from skin lesions. Paired serum samples were analyzed for anti-streptolysin O and anti-deoxyribonuclease B antibodies. Serology or blood or tissue culture confirmed β-hemolytic streptococcal (BHS) etiology in 72% (146 of 203) of cases. An additional 13% (27 of 203) of cases had probable BHS infection, indicated by penicillin response or BHS cultured from skin swabs. β-hemolytic streptococcal etiology was predominant in all clinical subgroups, including patients without sharply demarcated erythema. β-hemolytic group C or G streptococci (GCS/GGS) were more commonly isolated than GAS (36 vs 22 cases). *Staphylococcus aureus* was cultured from swabs as a single pathogen in 24 cases, 14 (64%) of which had confirmed BHS etiology.

It appears we can treat most episodes of cellulitis as Streptococcal with a narrow spectrum drug such as penicillin, even if a superficial swab shows Staph.

Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis

Lancet ID 2016; March 9

In this open-label dose-finding study, the authors recruited HIV-infected individuals with cryptococcal meningitis in Kampala, Uganda. To assess safety and tolerability, the first 60 participants were given sertraline at escalating doses of 100 mg/day, 200 mg/day, 300 mg/day, or 400 mg/day as induction therapy for 2 weeks, followed by consolidation therapy with 200 mg/day for an additional 8 weeks. Participants receiving sertraline had faster cryptococcal CSF clearance and a lower incidence of immune reconstitution inflammatory syndrome and relapse than that reported in the past.
This inexpensive and off-patent oral medication is a promising adjunctive antifungal therapy.

Long-term Immune Response to Hepatitis B Virus Vaccination Regimens in Adults with HIV

(courtesy Dr A Murali)

JAMA Intern Med. Published online April 11, 2016. doi:10.1001/jamainternmed.2016.074

The phase 3, open-label, multicenter parallel-group (1:1:1 allocation ratio) randomized clinical trial was conducted from June 28, 2007, to October 23, 2008, at 33 centers in France. Participants included 437 HBV-seronegative adults with HIV-1 and CD4 cell counts of more than 200/μL. Patients were randomly assigned to receive 3 intramuscular standard-dose (20-μg) injections of recombinant HBV vaccine at weeks 0, 4, and 24 (IM20 × 3 group) (145 participants), 4 intramuscular double-dose (40-μg) injections at weeks 0, 4, 8, and 24 (IM40 × 4 group) (148 participants), or 4 intradermal low-dose (4-μg) injections at weeks 0, 4, 8, and 24 (ID4 × 4 group) (144 participants). The percentage of responders at month 42 was 41% in the IM20 × 3 group, 71% in the IM40 × 4 group ($P < .001$ vs the IM20 × 3 group), and 44% in the ID4 × 4 group ($P = .64$ vs IM20 × 3 group).

IM40 x 4 seems the best option for HBV vaccination in HIV patients.

Booster doses unnecessary for HBV vaccine

(courtesy Dr Ashwini Tayade)

J Infect Dis. 2016 Jan;

In 1981, the authors immunized a cohort of 1578 Alaska Native adults and children from 15 Alaska communities aged≥6 months using 3 doses of plasma-derived hepatitis B vaccine. Persons were tested for antibody to hepatitis B surface antigen (anti-HBs) levels 30 years after receiving the primary series. Those with levels<10 mIU/mL received 1 booster dose of recombinant hepatitis B vaccine 2-4 weeks later and were then evaluated on the basis of anti-HBs measurements 30 days after the booster. Among 243 persons (56%) who responded to the original primary series but received no subsequent doses during the 30-year period, 125 (51%) had an anti-HBs level≥10 mIU/mL. 88 percent of those without protective levels mounted an anamnestic response.
Based on anti-HBs level≥10 mIU/mL at 30 years and an 88% booster dose response, the authors estimate that≥90% of participants had evidence of protection 30 years later. Booster doses are not needed.

Guideline watch

Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care from the American College of Physicians and the Centers for Disease Control and Prevention

Ann Intern Med. 2016;164(6):425-434. doi:10.7326/M15-1840

High-Value Care Advice 1: Clinicians should not perform testing or initiate antibiotic therapy in patients with bronchitis unless pneumonia is suspected.

High-Value Care Advice 2: Clinicians should test patients with symptoms suggestive of group A streptococcal pharyngitis (for example, persistent fevers, anterior cervical adenitis, and tonsillopharyngeal exudates or other appropriate combination of symptoms) by rapid antigen detection test and/or culture for group A Streptococcus. Clinicians should treat patients with antibiotics only if they have confirmed streptococcal pharyngitis.

High-Value Care Advice 3: Clinicians should reserve antibiotic treatment for acute rhinosinusitis for patients with persistent symptoms for more than 10 days, onset of severe symptoms or signs of high fever (>39 °C) and purulent nasal discharge or facial pain lasting for at least 3 consecutive days, or onset of worsening symptoms following a typical viral illness that lasted 5 days that was initially improving (double sickening).

High-Value Care Advice 4: Clinicians should not prescribe antibiotics for patients with the common cold.

IDSA/SHEA guidelines on Antimicrobial Stewardship

(courtesy Dr Ashwini Tayade and Dr Neha Gupta)

Refer www.idsociety.org for complete details

Chandra's Corner

Notes from the United States

My dad died, prematurely in my opinion, after serving as a newspaper Editor for several decades in Srilanka and India.

I think I may have the same genetic predisposition for journalism. Through this column, with your permission, I hope to capture and report some of the current events in the medical field, particularly in Infectious Diseases, from the U.S. perspective. I thank you for your indulgence. Given my seniority, this column may appear periodically rather than on a regular basis.

What is hot and current in the U.S. today? It certainly is the U.S. election. This is driving most people insane. I have had enough of the finger pointing politicians, lies and mudslinging and the numerous TV ads. All this is happening several months before the election and I dread to think of the days as we get closer. From the ID perspective, everyone's attention has been drawn by the Zika virus. Zika virus from South America, the epicenter being Brazil, has steadily marched northwards as far as the mosquito vector, Aedes aegypti could thrive. The mosquito does not survive very well in the temperate climate, and so it is unlikely it will reach as north as Michigan. Meanwhile, Zika virus has invaded Puerto Rico and Florida where the mosquito is in abundance. Scores of patients have been affected, mostly asymptomatically. Serious neurological manifestations such as Guillain-Barre and microcephaly in the newborn are the complications of major concern. U.S. Centers for Disease Control, on a regular basis, is publishing travel advisories and management algorithms for infected or exposed men and women. Updates are coming out every few weeks, fast and furious. Possible sexual transmission of the virus is making the recommendations even more complex. The eco-

-nomy of Brazil has been significantly impacted; interesting to watch how the summer Olympics are going to be handled.

Zika virus joins two other common viruses namely Dengue and Chikungunya transmitted through mosquito bites. These three illnesses constitute the differential diagnoses for febrile illnesses in patients hailing from Zika-endemic regions. Ocular manifestations and diffuse maculopapular skin rashes appear to predominate in Zika infection as compared to others. Zika and Dengue are flaviviruses. Dengue virus researchers from the National Institutes of Health, U.S. have announced the plausibility of a Zika vaccine.

As you may know, IDSA and ICAAC are separate events this year, the former in October with the latter earlier in June. Many of you may already have your abstracts accepted. Congratulations. Whichever meeting you decide to attend, you can be certain that you will get an earful on Zika.

Best wishes,

C.

Answer to photo quiz

Answer: 3 or 4. RAL + PI/r with or without 3TC

Rationale:

1. TDF+ FTC+ PI/r (No K65R but 2 TAMS; weak NRTI backbone)
   -Subtype C virus- If TAMS already exist exposure to TDF increases the selection of TAMS
2. And 5. AZT or ABC/3TC + LPV/r or ATV/r (2 TAMS - weak NRTI backbone)
3. RAL + PI/r (RAL has low genetic barrier to mutation)
4. RAL + PI/r + 3TC (M184V also makes the virus less fit for replication)

Table 2: Significance of NNRTI mutations

ART Class	Mutations	Significance
NNRTI	K103 N	High- Level Resistance
	V-106N	High- Level Resistance
	V-179 N	Reduced susceptibility in combination with other NNRTI-resistance mutations but high-level resistance to Rilpivirine
	Y 188 L	High- Level Resistance

Table 3: Significance of the NRTI mutation

Mutation	Selected by	Effects on other NRTIs
M184V	3TC, FTC	Loss of susceptibility to 3TC, FTC ↓ susceptibility to ABC, ddI (clinically insignificant) Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF
TAMs	AZT, d4T	↓ susceptibility to all NRTIs based on number of TAMs More resistance with 41/210/215 than 67/70/219 pathway
151M, 69ins	AZT/ddI, ddI/d4T	Resistance to all NRTIs T69ins: TDF resistance
K65R	TDF, ABC, ddI	Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC) ↑ susceptibility to AZT
L74V	ABC, ddI	↓ susceptibility to ABC, ddI ↑ susceptibility to AZT, TDF

(case provided by Dr Neha Gupta).

CIDSCON - 2016

6th Annual Conference of Clinical Infectious Diseases Society, India

Venue : Banaras Hindu University, Varanasi, Uttar Pardesh

Block your Dates

26th, 27th, 28th, August 2016

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