Chronic Infectious Disease and the Future of Health Care Delivery.

From Pessimism to Optimism
... All five lessons from tuberculosis treatment apply to HIV disease. Many diseases affecting the world’s poor are treatable, including those that are considered untreatable because of delivery, rather than clinical, failures. The belief that it was too costly to treat paralyzed action in Africa for a decade after ART was proved effective....
GENERAL

Management of infections related to totally implantable venous-access ports: challenges and perspectives

Lebeaux D et al.
Doxycycline for Stabilization of Abdominal Aortic Aneurysms: A Randomized Trial
Arnoud Meijer C et al.

Figure 2. Estimated mean growth curves based on linear mixed model analysis for aneurysm growth during 18-mo follow-up.

Bars represent upper and lower limit mean growth; data and P values are presented in Table 2.

Figure 3. Kaplan-Meier estimates for cumulative incidence of elective surgery during 18-mo follow-up.

Among patients randomly assigned to receive either doxycycline or placebo, no benefit with respect to elective surgery or time to repair was found. Twenty-one patients in the doxycycline group had elective surgery vs. 22 in the placebo group. Censored for other reasons for study withdrawal.
Avoidable Antibiotic Exposure for Uncomplicated Skin and Soft Tissue Infections in the Ambulatory Care Setting
Hermione J. Hurley HJ et al
The American Journal of Medicine 2013; 126:1099-1106

Recurrent Urinary Tract Infections Among Women: Comparative Effectiveness of 5 Prevention and Management Strategies Using a Markov Chain Monte Carlo Model
Samantha J. Eells SJ et al.
Clin Infect Dis 2013 58: 147-160 (enlace)

In our Monte Carlo model comparing management strategies for recurrent urinary tract infections in women, we found that nitrofurantoin prophylaxis was most effective, but most expensive to the payer. Other strategies resulted in payer savings but were less efficacious.
Association Between Recent Use of Fluoroquinolones and Rhegmatogenous Retinal Detachment: A Population-Based Cohort Study
Kuo SC et al.
Clin Infect Dis 2013 58: 197-203 (enlace)

An association between use of oral fluoroquinolones and retinal detachment has been described but remains controversial. The current study found that recent use of an oral fluoroquinolone is significantly associated with rhegmatogenous retinal detachment. Hazard ratios differ for specific fluoroquinolones.

Figure 2. Cumulative incidence of rhegmatogenous retinal detachment (RRD) among patients who were prescribed with oral fluoroquinolones or amoxicillin during 90-day follow-up.
BACTERIAS

Invasive Haemophilus influenzae Type b Disease in England and Wales: Who Is at Risk After 2 Decades of Routine Childhood Vaccination?
Collins S, et al.
Clin Infect Dis 2013 57: 1715-1721 (enlace)

In England and Wales, invasive Haemophilus influenzae serotype b(Hib) disease incidence in 2012 was only 0.02/100 000 (14 cases) overall and 0.06/100 000 (2 cases) in <5-year-olds. Most cases now occur in adults with comorbidities who develop pneumonia.
Effects of Immunocompromise and Comorbidities on Pneumococcal Serotypes Causing Invasive Respiratory Infection in Adults: Implications for Vaccine Strategies
Manel Luján M, et al
Clin Infect Dis 2013 57: 1722-1730 (enlace)

There seem to be specific factors mainly related to immunocompromise which determine the appearance of invasive infection by specific pneumococcal serotypes. Although the coverage of serotypes in the 13-valent pneumococcal conjugate vaccine (PCV13) was high in these patients, some non-PCV13 emergent serotypes are more prevalent in immunocompromised patients.

Table 2. Multivariate Model (Multinomial Regression Analysis) of the Conditions Associated With Pneumococcal Infection

<table>
<thead>
<tr>
<th>Condition</th>
<th>PCV13</th>
<th>PPV23 and Non-PCV13</th>
<th>Non-PPV23/Non-PCV13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50 y</td>
<td>1.53</td>
<td>0.94-2.48</td>
<td>1.88</td>
</tr>
<tr>
<td>Tobacco exposure</td>
<td>1.02</td>
<td>0.69-1.50</td>
<td>0.66</td>
</tr>
<tr>
<td>Alcohol exposure</td>
<td>1.03</td>
<td>0.63-1.67</td>
<td>1.07</td>
</tr>
<tr>
<td>Nonimmunocompromising comorbidities</td>
<td>1.06</td>
<td>0.72-1.54</td>
<td>1.72</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1.29</td>
<td>0.82-2.03</td>
<td>1.93</td>
</tr>
<tr>
<td>Lung disease</td>
<td>1.02</td>
<td>0.67-2.53</td>
<td>1.57</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1.45</td>
<td>0.89-2.68</td>
<td>0.97</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>0.97</td>
<td>0.51-1.84</td>
<td>1.53</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0.81</td>
<td>0.46-1.41</td>
<td>1.3</td>
</tr>
<tr>
<td>Immuno compromised</td>
<td>1.24</td>
<td>0.67-1.77</td>
<td>2.01</td>
</tr>
<tr>
<td>HIV infection</td>
<td>2.06</td>
<td>1.14-3.69</td>
<td>2.94</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>1.35</td>
<td>0.78-2.28</td>
<td>1.43</td>
</tr>
<tr>
<td>Hematologic cancer</td>
<td>1.5</td>
<td>0.82-3.74</td>
<td>2.19</td>
</tr>
<tr>
<td>Chronic corticosteroid therapy</td>
<td>0.94</td>
<td>0.57-2.22</td>
<td>1.63</td>
</tr>
<tr>
<td>Nonsteroid immunocompromising therapy</td>
<td>1.04</td>
<td>0.62-2.4</td>
<td>0.82</td>
</tr>
</tbody>
</table>

In the first model, nonimmunocompromising comorbidities and immunocompromise were analyzed together. In the second model, both conditions were analyzed by subgroup.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.
**VIRUS**

**HIV-1 Vpr Induces Adipose Dysfunction in Vivo Through Reciprocal Effects on PPAR/GR Co-Regulation.**

Agarwal N, et al.

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**Table 3.** Associations Between Individual Serotypes With >10 Isolates and Subgroups of Immunocompromised Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Associated Serotypes</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic cancer</td>
<td>6A</td>
<td>64.47 (10.4–396)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>10A</td>
<td>14.62 (3.06–69.84)</td>
</tr>
<tr>
<td></td>
<td>23F</td>
<td>15.04 (3–75.24)</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>11A</td>
<td>11.16 (2.56–48.65)</td>
</tr>
<tr>
<td></td>
<td>23F</td>
<td>7.09 (1.52–32.94)</td>
</tr>
<tr>
<td></td>
<td>33F</td>
<td>9.55 (2.01–45.39)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

*Adjusted for age, smoking, alcohol abuse, and nonimmunocompromising comorbidities.*

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**Fig. 1.** Vpr in HIV patients and mouse models. (A) Box-and-whisker plots of serum Vpr concentrations in HIV-negative persons and four HIVinfected groups: ART-naïve, on NRTI only, on cART, and on cART with undetectable VL. Median Vpr concentrations in patients: ART-naïve = 7.0 pg/ml; NRTI only = 32.0 pg/ml; cART = 3.9 pg/ml; cART with undetectable VL = 4.2 pg/ml. Whiskers indicate minimum and maximum of all data. Dashed line indicates cutoff between false- and true-positive values. False-positive rate = 3% ART-naïve HIV, 0% HIV on NRTI, 6% HIV on cART, and 4% HIV on cART with undetectable VL.
Fig. 8. **Vpr-mediated pathogenesis of HIV-associated metabolic defects.** HIV persisting in tissue macrophages or sequestered T cells after ART releases Vpr that transduces and affects preadipocytes, adipocytes, and hepatocytes. (A) In preadipocytes, Vpr blocks the cell cycle at G2-M, blunting turnover and differentiation into adipocytes. (B) In mature adipocytes, Vpr co-represses PPARγ-regulated genes and coactivates GR-regulated genes, leading to lipolysis, defective fatty acid storage and metabolism, and diminished secretion of adiponectin. (C) In hepatocytes, Vpr co-represses PPARα, leading to defective fat oxidation and blunted VLDL-triglyceride packaging and export. Hepatic consequences secondary to Vpr’s adipocyte effects include increased fatty acid flux and blunted activation of AMPK because of decreased adiponectin, leading to diminished PGC1α expression. Collectively, the direct and secondary hepatic effects lead to fatty liver.
**Conclusions**

RAL-FTC-TDF is well tolerated as NPEP, results in high levels of adherence and avoids potential drug–drug interactions. Patients and clinicians should be aware of the potential for acute muscle toxicity when RAL is used as NPEP.

Fig. 1
Mean (standard deviation) plasma concentration–time curves for total darunavir (a), unbound darunavir (b) and total ritonavir (c) after administration of darunavir/ritonavir 600/100 mg twice daily (bid), during the second and third trimesters and postpartum
Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine
Hammer SM, et al.

Conclusions

The DNA/rAd5 vaccine regimen did not reduce either the rate of HIV-1 acquisition or the viral-load set point in the population studied. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00865566.)
Noticia de agencias

**New HIV Cure Research Findings-Radioimmunotherapy Therapy (RIT):**
Radiological Society of North America (RSNA) 99th Scientific Assembly and Annual Meeting: Abstract SSK12

"*We found that radioimmunotherapy could kill HIV-infected cells both in blood samples that received antiretroviral treatment and within the central nervous system, demonstrating RIT offers real potential for being developed into an HIV cure, to kill HIV-infected lymphocytes previously treated with HAART, reducing the HIV infection in the blood samples to undetectable levels*". Reported at the Radiological Society of North America 99th Scientific Assembly and Annual Meeting

The researchers previously used gp41 radioimmunotherapy in mice with severe combined immunodeficiency that were injected with infected human cells (*PLoS One*. 2012;7:e31866). "We are basically able to eliminate the HIV-infected cells in those mice," Dr. Dadachova said enthusiastically. More important, they were able to eliminate HIV-infected cells in the brains of the mice.

**Safety of Tenofovir During Pregnancy for the Mother and Fetus: A Systematic Review**
Wang L, et al
Clin Infect Dis 2013 57: 1773-1781 ([enlace](#))

Based on limited evidence, tenofovir appears to be safe in pregnancy. No increased risk of poor growth or bone abnormalities was observed among infants with maternal tenofovir exposure; only 1 study showed slightly lower height at 1 year of age.
HIV Re-emerges in Boston Bone Marrow Transplant Patients

Two bone marrow stem cell recipients who had undetectable HIV according to the most sensitive tests for months after an experimental antiretroviral therapy (ART) interruption have experienced viral rebound and had to restart treatment, frustrating hopes for a functional cure, according to a report at the 6th International Workshop on HIV Persistence during Therapy last week in Miami.

Timothy Henrich and Daniel Kuritzkes from Brigham and Women’s Hospital first reported at the 2012 International AIDS Conference that 2 Boston men with HIV who had received donor stem cell transplants to treat lymphoma had no detectable traces of the virus.

Unlike the Berlin Patient, Timothy Brown, these patients received donor stem cells that were susceptible to HIV infection. Brown’s donor had a double CCR5-delta-32 mutation, meaning those stem cells did not express the CCR5 co-receptor that most strains of HIV use to enter cells.

At the International AIDS Society this past summer, Henrich reported that the men continued to have undetectable plasma HIV RNA as well as undetectable integrated HIV DNA in peripheral blood mononuclear cells after 7 and 15 weeks off treatment. This finding raised hopes that some aspect of the stem cell transplant process -- other than resistant donor cells, which is difficult to replicate -- might lead to a functional cure, or the ability to maintain viral suppression without disease progression in the absence of ART (enlace prensa).

Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection

Doitsh G, et al
Nature(2013)doi:10.1038/nature12940

a, b, VX-765 efficiently blocks CD4 T-cell death in HIV-infected tonsillar and splenic lymphoid tissues. No toxicity was observed at any of these drug concentrations. Error bars represent s.e.m. from three independent experiments using tonsil or spleen cells from three different donors. c, Pyroptosis in HIV-infected lymphoid tissues may establish a chronic cycle of CD4 T-cell death and inflammation, which attracts new CD4 T cells and ultimately contributes to disease progression and tissue damage. Inhibitors of caspase 1 such as VX-765 may inhibit pyroptosis in a manner that both preserves CD4 T cells and reduces inflammation.
Five-Year Safety Evaluation of Maraviroc in HIV-1–Infected Treatment-Experienced Patients
Gulick RM, et al
J Acquir Immune Defic Syndr 2014;65:78–81

**TABLE 1. Incidence of 5-Year Death and Selected Clinical Events in 938 Subjects Receiving Maraviroc (Total Exposure 2639 Patient-Years)**

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. (% Study Subjects)</th>
<th>No. Events</th>
<th>Raw Event Rate (Events Per 100 Patient-Years)*</th>
<th>Incidence Rate (Events Per 100 Patient-Years)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>46 (5%)</td>
<td>46</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>AIDS event</td>
<td>78 (8%)</td>
<td>98</td>
<td>3.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>5 (0.5%)</td>
<td>5</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Infection judged to be a serious adverse event</td>
<td>114 (12%)</td>
<td>163</td>
<td>6.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Malignancy</td>
<td>61 (6%)</td>
<td>79</td>
<td>3.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Myocardial infarction or cardiac ischemia</td>
<td>26 (3%)</td>
<td>30</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>5 (0.5%)</td>
<td>5</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* (Total number of events per total patient-years of exposure) ×100.
† Based on time-to-first event.
Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada - pdf attached article below
Samji H, et al
PLOS one 2013; 8:e81355

"Based on current patterns of ART use among participants observed from 2000 to 2007 in the NA-ACCORD, a 20-year-old individual on ART today in the U.S. or Canada would expect to live into their early 70s, a life expectancy that approaches that of a 20-year-old person in the general population [12]. Life expectancy estimates for the general population at age 20 years in 2009 were 59.7 and 57.0 years for men and 63.9 and 61.7 years for women, in Canada and the U.S., respectively [12]. Indeed, given that many individuals living with HIV have demographic, clinical, and behavioral characteristics associated with greater morbidity and mortality than the general population [20], [21], the gap in life expectancy may be attributable to other lifestyle factors and not just HIV infection."
Cellular HIV reservoir replenishment is not affected by blip or intermittent viremia episodes during darunavir/ritonavir monotherapy
Torres-Cornejo, A, et al
AIDS 2014; 28:201-208 (enlace)

Conclusion: Blip episodes and intermittent viremia did not affect the cellular HIV reservoir dynamic during MtDRV/rtv. Higher adherence and an HIV-DNA levels less than 2 log10 copies/106 PBMCs at baseline were associated with a lower risk of virological failure.

The Natural History of Influenza Infection in the Severely Immunocompromised vs Nonimmunocompromised Hosts
Matthew J. Memoli MJ, et al
Clin Infect Dis 2013 58: 214-224 (enlace)

Severely immunocompromised individuals infected with influenza are different from the influenza infected that are nonimmunocompromised. Issues to consider during medical management include asymptomatic shedding, development of multi-drug resistance during prolonged antiviral therapy, and the potential high risk of pulmonary involvement.
Renal Impairment Is Frequent in Chronic Hepatitis C Patients Under Triple Therapy With Telaprevir or Boceprevir
Mauss S, et al
Hepatology 2014;59: 46-48

Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: A multicenter experience
Audrey Coilly A, et al
Journal of Hepatology 2014 vol. 60:78–86
**HONGOS**

**A Multistep Voriconazole-Related Phototoxic Pathway May Lead to Skin Carcinoma: Results From a French Nationwide Study**

Olivier Epaulard O, et al

Clin Infect Dis 2013 57: e182-e188 ([enlace](#))

A call for notification led to the identification of 19 patients with skin carcinoma(s) during/after voriconazole therapy. Likelihood of voriconazole involvement in the carcinoma onset was “high” in 15 cases. A multistep sequence (phototoxicity, keratosis, carcinoma) was observed in 14 patients.
PARASITOS

Successful treatment with fumagillin of the first pediatric case of digestive microsporidiosis in a liver-kidney transplant.

G. Desoubeaux G, et al
Transpl Infect Dis 2013: 15: E250–E259. All rights reserved

...the first successful use, ... of fumagillin alone in a pediatric patient to cure intestinal microsporidiosis in a liver-kidney transplanted child. Detection of Enterocytozoon bieneusi in stool became negative from the first posttherapeutic control, while digestive symptoms disappeared in 4 days. During a 9-month follow-up, polymerase chain reaction and direct examinations remained negative for microsporidia in her feces. No major undesirable effects were noted during the antimicrosporidial therapy.
Toxoplasma gondii Serostatus Is Not Associated With Impaired Long-Term Survival after Heart Transplantation
van Hellemont JJ et al
Transplantation 2013;96: 1052Y1058

TABLE 2. Causes of death in all patients

<table>
<thead>
<tr>
<th>Recipient Toxoplasma serostatus</th>
<th>Negative</th>
<th>Positive</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>258</td>
<td>324</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>117 (45)</td>
<td>219 (67)</td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early cardiac</td>
<td>11 (9)</td>
<td>22 (10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>8 (7)</td>
<td>9 (4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Infection</td>
<td>10 (9)</td>
<td>19 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Malignancy</td>
<td>20 (17)</td>
<td>40 (18)</td>
<td>0.88</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>9 (8)</td>
<td>28 (13)</td>
<td>0.20</td>
</tr>
<tr>
<td>Late cardiac</td>
<td>33 (28)</td>
<td>53 (24)</td>
<td>0.43</td>
</tr>
<tr>
<td>Other</td>
<td>26 (22)</td>
<td>48 (22)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Survival of all recipients according to Toxoplasma serostatus

- Recipient Toxo pos
- Recipient Toxo neg

p = 0.003
EVENTOS RECENTES

6th Intl Workshop on HIV Persistance during Therapy (enlace)
Highlights on HIV eradication in 2013 - (enlace)

Report Summary Report by David Margolis MD, UNC Chapel Hill and the Collaboratory of AIDS Researchers for Eradication (CARE)

HEPDART 2013:
Frontiers in Drug Development for Viral Hepatitis
December 8-12, 2013
Big Island, Hawaii

NOTA IMPORTANTE
Se recuerda a los socios que los artículos incluidos en el boletín son seleccionados por los miembros de la Junta directiva entre las publicaciones que “medianamente” controlan. Muchas publicaciones de interés no están recogidas. Solicitamos la colaboración de todos los socios (y cualquier otro colega) para recoger el máximo de las publicaciones de impacto de Enfermedades Infecciosas. Hacednos llegar la referencia y nosotros localizaremos el original e incluiremos la figura, tabla o frase “impactante”.

Podéis enviar la referencia a secretariaSEICV@gmail.com