# Hot Topics in Adult Infectious Diseases 2014

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# 2014 Adult ID Topic Selection Process

Inclusion Criteria

- Appeared in a high impact medical journal 2013 – 2014
- Likely relevant to ID clinical practice

Exclusion Criteria

- Covered by a  previous years' presenter at this session
- Topic to covered in more detail at this conference:
  - MERS
  - *Various Bird Flus*

*And time constraints…*

## Topics Covered

1. Hepatitis C

2. Two Papers with Direct Application to ID Practice
   a. Penicillin for Recurrent lower extremity Soft Tissue Infection
   b. Predicting who will develop chronic HBV

3. Two Tests that Might Improve Antimicrobial utilization:
   a. MALDI-TOF
   b. Aspergillus Galactomannan /PCR

4. Developments in HIV
   a. New opportunistic pathogen: *Emmonsia pasteuriana*
   b. Dolutegravir
   c. Where is the HIV Field Headed?

# Overview

# Rationale of Antiviral Therapy for HCV

- Prevent hepatic decompensation, HCC, death
- Prevent need for transplantation
- ?Improve histology?

Dig Dis Sci (2011) 56:1853–1861

# Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

*Patrick Marcellin, Edward Gane, Maria Buti, Nezam Afdhal, William Sievert, Ira M Jacobson, Mary Kay Washington, George Germanidis, John F Flaherty, Raul Aguilar Schall, Jeffrey D Bornstein, Kathryn M Kitrinos, G Mani Subramanian, John G McHutchison, E Jenny Heathcote*

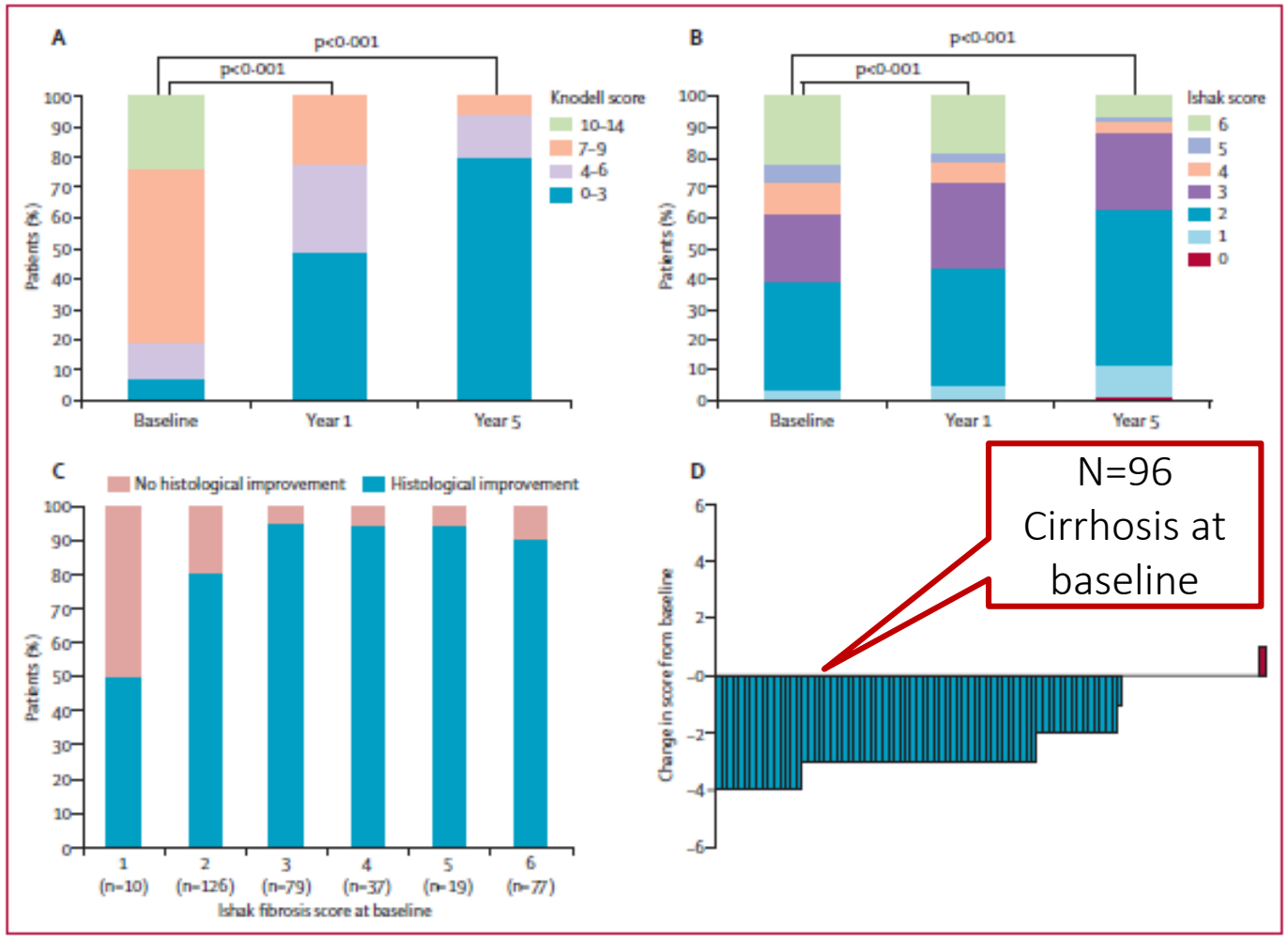


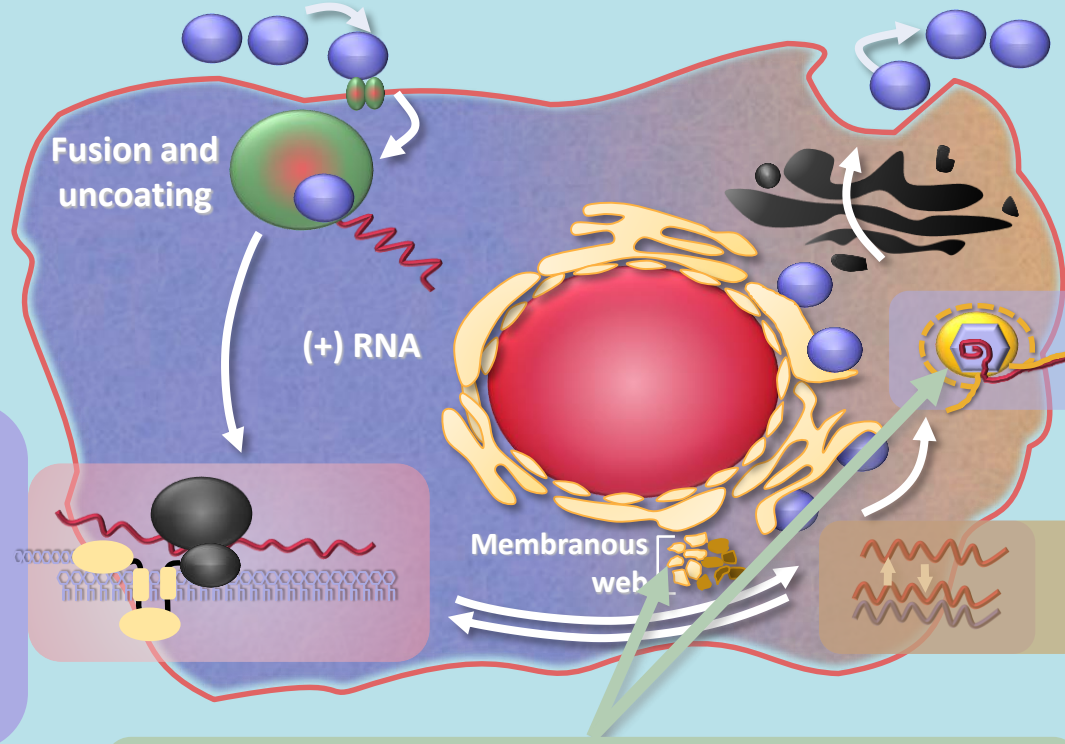

*Figure 2:* Histology results over 5-year treatment phase

# Suppression of HBV DNA Impact on Liver Histology (Same for HCV?)

- Cohort of n=641 patients originally enrolled on tenofovir or adefovir trial for eAg+/- HBV
- After initial 48 weeks, open label ongoing tenofovir for n=348 who agreed to repeat liver biopsy at week 240
- All patients (with or without cirrhosis at baseline) had undetectable HBV DNA at 5 year

Lancet 2013; 381: 468–75


# Canadian Content




**NS3/4 protease Inhibitors (Boceprevir, Telaprevir, Simeprevir, Faldaprevir, ABT-450)**

**NS5B polymerase Inhibitor Chain Terminators Nucleos(t)ide Non-nucleoside (Sofosbuvir, Doleobuvir, ABT-333)**

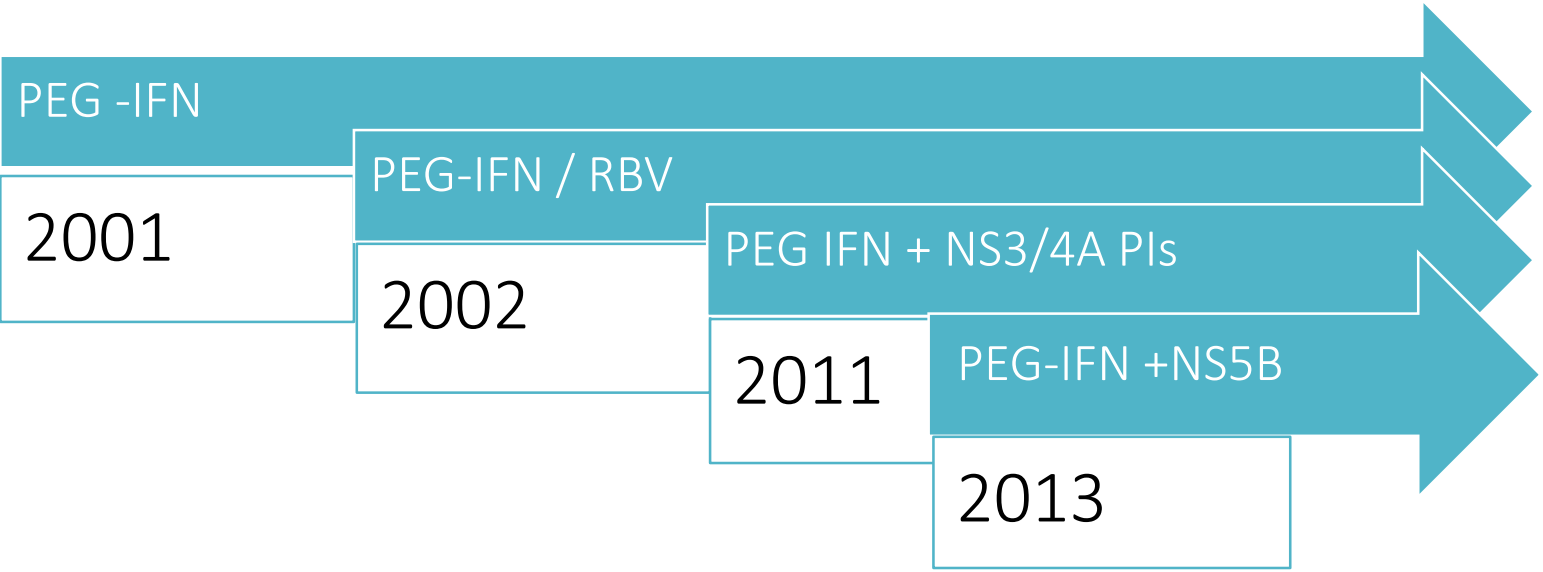
**NS5A inhibitors (Daclatasvir, Ledipasvir)**

**replication and assembly**

Adapted from Manns MP, et al. *Nat Rev Drug Discov*. 2007;6:991-1000.

# Hepatitis C: Direct Acting Antiviral Agents (DAA)

(In Yellow: Agents available for use in Canada)

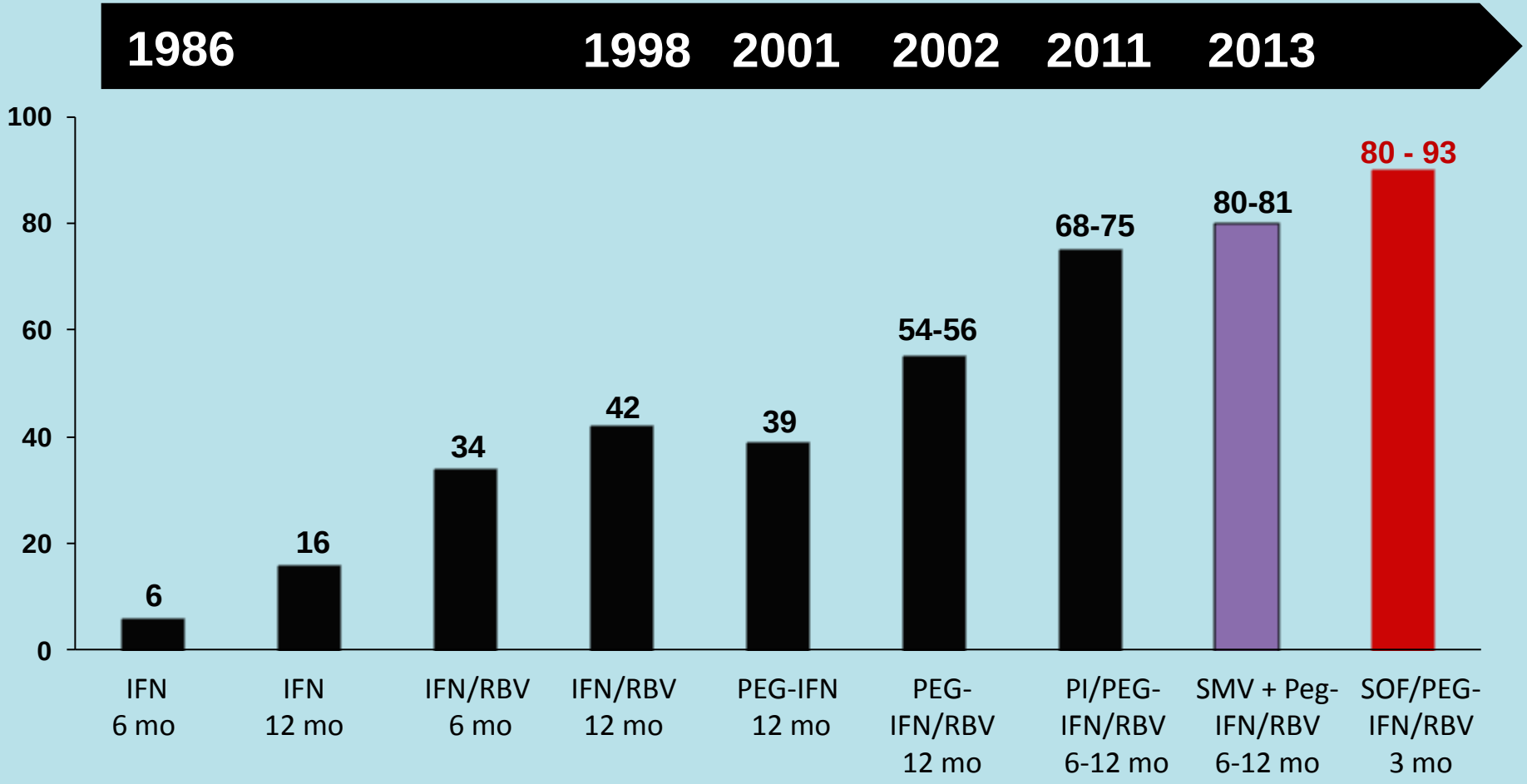



# Evolution of Interferon-Based HCV Therapies 2013 - 2014

- Improving SVR rates
- Decreasing duration of therapy to 12 weeks
- Still use only one DAA

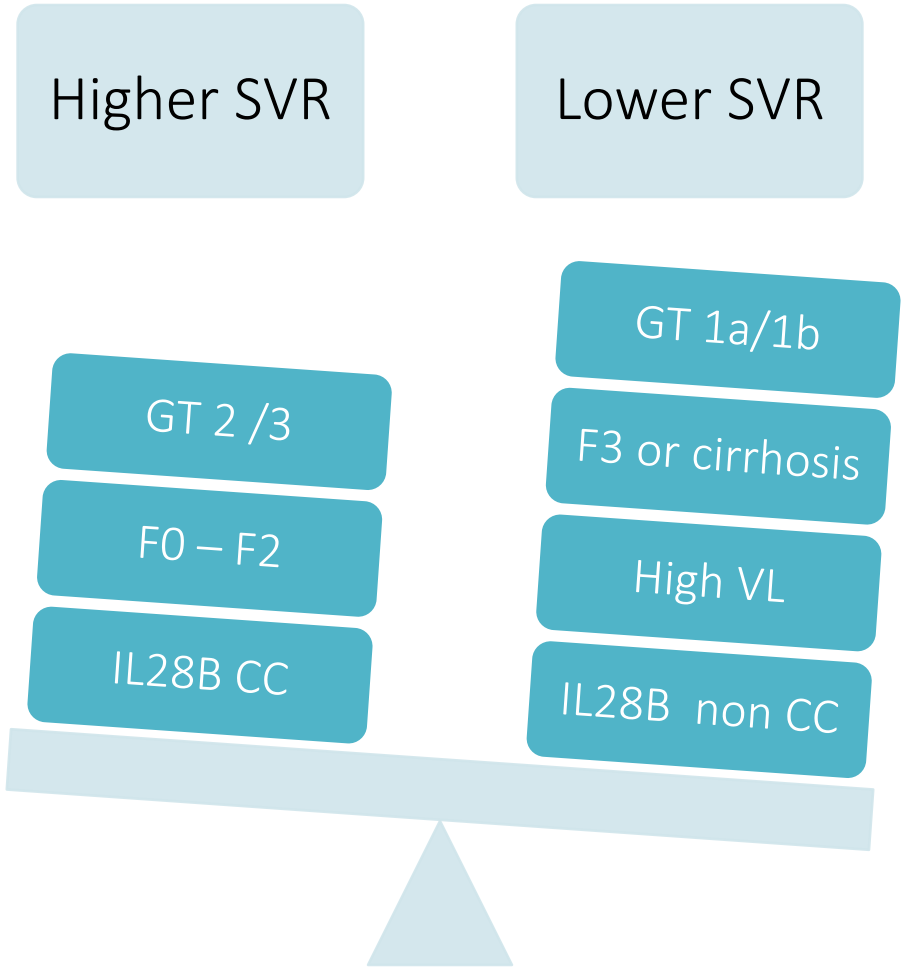
DAA Component

- Increasing potency
- Decreasing pill burden
- Better adverse effect profile
- fewer drug interactions
- More than genotype 1a/1b



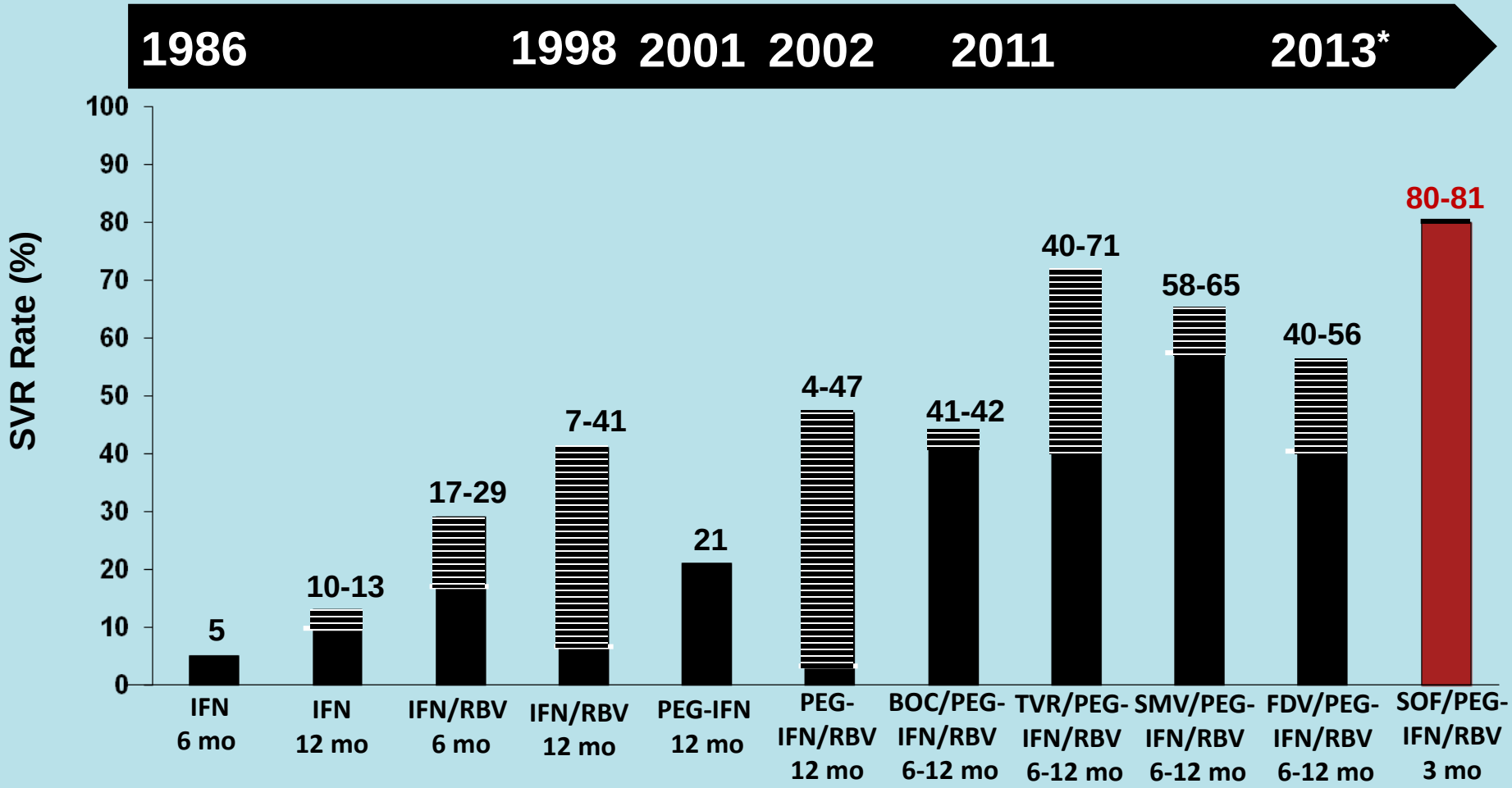

# Peg-IFN Based Regimens Available for GT1 - Overall SVR Rates

*Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02*




# Historic Predictors of SVR with PEG –IFN Based Regimens

- Treatment-experienced partial /null responders have lower SVR than treatment-naïve patients
- Lower SVR rates for HIV/HCV coinfection
- These predictors will be increasingly obsolete in the era of DAAs




# Improving SVR for F3/F4 with PEG-IFN Based Regimens for Patients

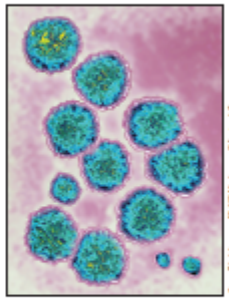
Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. McHutchison J, et al. *NEJM* 1998; 339: 1485-92; Poynard T, et al. *Lancet* 1998: 352: 1426-32; Manns M, et al. *Lancet* 2001; 358: 958-65; Fried M, et al. *NEJM* 2002; 347: 975-82; Hadziyannis S, et al. Ann Intern Med 2004; 140: 346-55; McHutchison J, et al. *NEJM* 2009; 361: 580-93. PEGASYS [PI]. Hoffmann-La Roche Inc; 2013. PEGINTRON [PI]. Whitehouse Station, NJ: Merck & Co; 2013. Jacobson I, et al. *EASL* 2013; Manns M, et al. *EASL* 2013; Ferenci P, et al. *EASL* 2013; Fontaine H, et al. EASL 2013. Amsterdam, The Netherlands. #60; Lawitz E, et al. EASL 2013. Amsterdam, The Netherlands. Oral #1411; Lawitz E, et al. *N Engl J Med.* 2013 May 16.

## Interferon-free hepatitis C treatment: one pill to fit all?

Hepatitis C virus (HCV) treatment is evolving rapidly. Less than 10 years ago, few individuals could be successfully treated. Now, more than two-thirds of eligible treatment-naive patients are effectively cured with a combination of pegylated interferon and ribavirin, and addition of a first-generation protease inhibitor for those with HCV genotype 1 infection.[1,2] Yet all licensed regimens involve weekly injections and a high pill burden; adverse effects are common and include substantial mental illness and cytopenias.[3] Patients with advanced liver disease or those who have had previously unsuccessful treatment have more severe side-effects and a lower chance of cure. Consequently, many individuals are deemed ineligible

generation protease inhibitor with pegylated interferon plus ribavirin (cohort B, n=40). 22 (55%) of the 40 participants in cohort B had compensated cirrhosis. Treatment-naive individuals were randomly allocated to receive sofosbuvir plus ledipasvir alone for 8 weeks (n=20) or 12 weeks (n=19), or sofosbuvir plus ledipasvir plus ribavirin for 8 weeks (n=21). Treatment-experienced patients received either 12 weeks of sofosbuvir plus ledipasvir alone (n=19) or with ribavirin added (n=21).

A sustained virological response (SVR) at weeks 12 and 24 was achieved in 97 (97%) of 100 participants, with an SVR at 12 weeks of at least 95% (95% CI 74–100) in patients in each treatment group. One person was lost



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See Articles page 515

IFN-Free, Maintain RBV

Abbvie Trials with ABT-450/r and ABT-333 and/or ABT 267

IFN-Free, RBV Free

SOF/Ledipasvir +/- RBV
LONESTAR Trial

SOF/Daclatasvir +/- RBV
A1444040 Trial

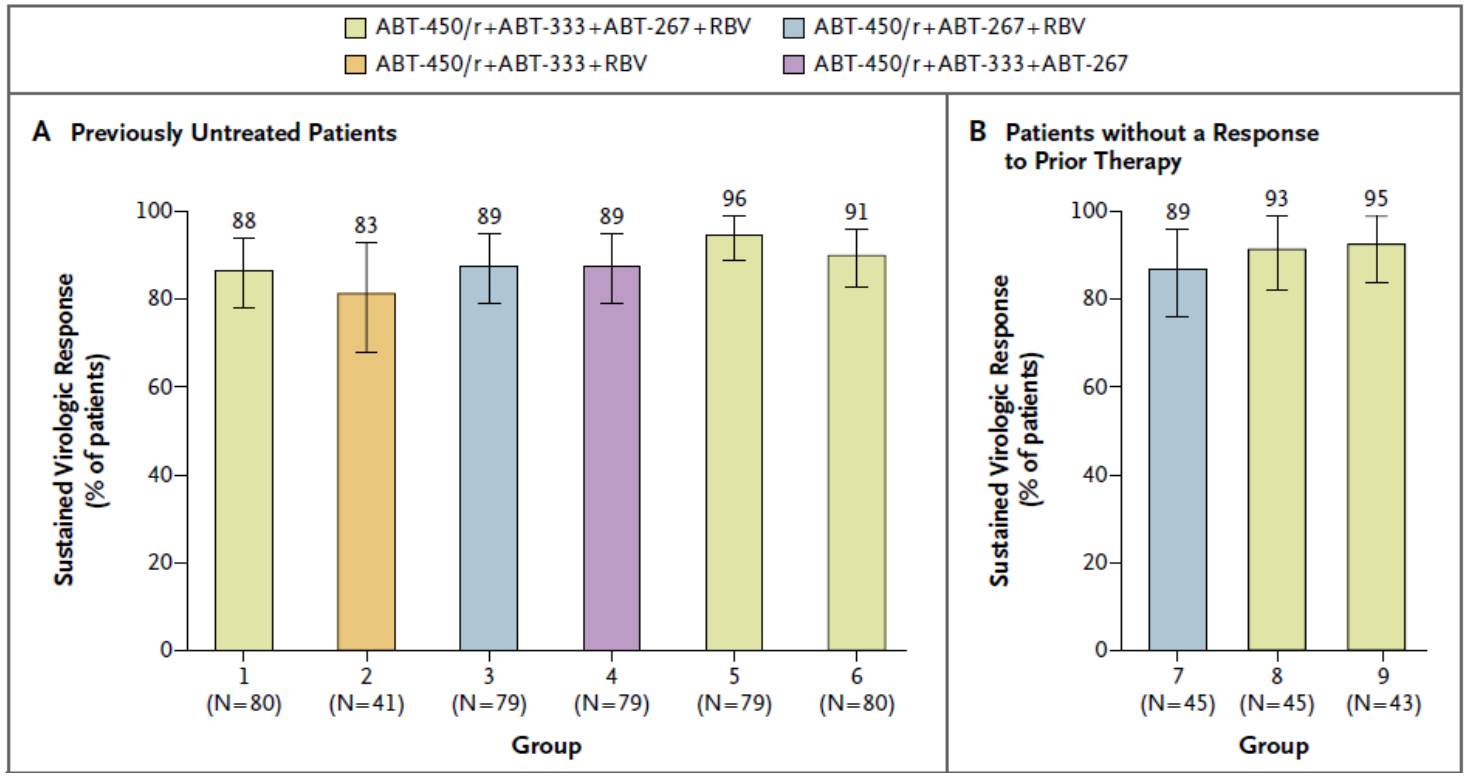
Faldaprevir/Doleobuvir +/- RBV

# Evolution to All-Oral HCV Therapies

- Timing of drug approvals uncertain
- Cost and reimbursement will be key considerations

# Phase 2b Trial of Interferon-free Therapy for Hepatitis C Virus Genotype 1

Kris V. Kowdley, M.D., Eric Lawitz, M.D., Fred Poordad, M.D., Daniel E. Cohen, M.D., David R. Nelson, M.D., Stefan Zeuzem, M.D., Gregory T. Everson, M.D., Paul Kwo, M.D., Graham R. Foster, F.C.R.P., Mark S. Sulkowski, M.D., Wangang Xie, Ph.D., Tami Pilot-Matias, Ph.D., George Liossis, B.A., Lois Larsen, Ph.D., Amit Khatri, Ph.D., Thomas Podsadecki, M.D., and Barry Bernstein, M.D.




## All Oral, IFN-free GT1

- Phase 2b trial – small numbers in each group
- Few treatment-naïve patients with advanced fibrosis
- All received RBV
- Various combinations of ABT-450/r (PI) with either or both of ABT 267 (NS5A) , ABT-333 (NS5B)
- Treatment duration 8, 12 or 24 weeks
- Previously treated patients did better with at least 12 weeks of treatment

N ENGL J MED 370;3 NEJM.ORG JANUARY 16, 2014

# Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial

*Eric Lawitz, Fred F Poordad, Phillip S Pang, Robert H Hyland, Xiao Ding, Hongmei Mo, William T Symonds, John G McHutchison, Fernando E Membreno*

| | Cohort A: treatment-naive patients | | | Cohort B: patients previously treated with protease inhibitors | |
|---|---|---|---|---|---|
| | Sofosbuvir plus ledipasvir for 8 weeks (n=20) | Sofosbuvir plus ledipasvir with ribavirin for 8 weeks (n=21) | Sofosbuvir plus ledipasvir for 12 weeks (n=19) | Sofosbuvir plus ledipasvir for 12 weeks (n=19) | Sofosbuvir plus ledipasvir with ribavirin for 12 weeks (n=21) |
| Treatment week 4 | 20 (100%; 83–100) | 21 (100%; 84–100) | 19 (100%; 82–100) | 18 (95%; 74–100) | 21 (100%; 84–100) |
| End of treatment | 20 (100%; 83–100) | 21 (100%; 84–100) | 19 (100%; 82–100) | 19 (100%; 82–100) | 21 (100%; 84–100) |
| SVR4 | 20 (100%; 83–100) | 21 (100%; 84–100) | 19 (100%; 82–100) | 18 (95%; 74–100) | 21 (100%; 84–100) |
| SVR12 | 19 (95%; 75–100) | 21 (100%; 84–100) | 18* (95%; 74–100) | 18 (95%; 74–100) | 21 (100%; 84–100) |
| Virological failure | | | | | |
| During treatment† | 0 | 0 | 0 | 0 | 0 |
| Relapse | 1 (5%) | 0 | 0 | 1 (5%) | 0 |

Data are n (%; 95% CI) or number (%). SVR4=sustained virological response at week 4 after treatment. SVR12=sustained virological response at week 12 after treatment. *One patient in this group was lost to follow-up after achieving SVR at week 8 of treatment. †Includes virological breakthrough, rebound, and non-response.

*Table 2:* Response during and after treatment

# All-oral, IFN-free, GT1

- Open-label phase 2 trial, single tablet SOF/LDP pill
- Randomization 1:1:1 of 60 Rx-naïve non-cirrhotic patients to:
  a. 8 weeks SOF/LDP (NS5B + NS5A)
  b. 12 weeks SOF/LDP
  c. 8 weeks SOF/LDP/RBV
- Randomization 1:1 of 40 prior PI failures to:
  a. 12 weeks of SOF/LDP vs SOF/LDP/RBV
- Few AEs, mainly due to RBV
- Limitation of this study: n=100, and even fewer (n=20) with cirrhosis

# Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection

Mark S. Sulkowski, M.D., David F. Gardiner, M.D., Maribel Rodriguez-Torres, M.D., K. Rajender Reddy, M.D., Tarek Hassanein, M.D., Ira Jacobson, M.D., Eric Lawitz, M.D., Anna S. Lok, M.D., Federico Hinestrosa, M.D., Paul J. Thuluvath, M.D., Howard Schwartz, M.D., David R. Nelson, M.D., Gregory T. Everson, M.D., Timothy Eley, Ph.D., Megan Wind-Rotolo, Ph.D., Shu-Pang Huang, Ph.D., Min Gao, Ph.D., Dennis Hernandez, Ph.D., Fiona McPhee, Ph.D., Diane Sherman, M.S., Robert Hindes, M.D., William Symonds, Pharm.D., Claudio Pasquinelli, M.D., Ph.D., and Dennis M. Grasela, Pharm.D., Ph.D., for the AI444040 Study Group

**RESULTS**

Overall, 211 patients received treatment. Among patients with genotype 1 infection, 98% of 126 previously untreated patients and 98% of 41 patients who did not have a sustained virologic response with HCV protease inhibitors had a sustained virologic response at week 12 after the end of therapy. A total of 92% of 26 patients with geno-

# All Oral, Interferon-free, GT1 – 3

- Open label study of n=167 GT1 patients with few cirrhosis cases
- Initial protocol with 1 weeks lead-in SOF removed subsequently
- Included n=44 prior virologic failures with telaprevir or boceprevir regimens
- Randomization to DCL/SOF +/- RBV for 24 weeks

N ENGL J MED 370;3 NEJM.ORG JANUARY 16, 2014

# Faldaprevir and Deleobuvir for HCV Genotype 1 Infection

Stefan Zeuzem, M.D., Vincent Soriano, M.D., Ph.D., Tarik Asselah, M.D., Ph.D., Jean-Pierre Bronowicki, M.D., Ph.D., Ansgar W. Lohse, M.D., Beat Müllhaupt, M.D., Marcus Schuchmann, M.D., Marc Bourlière, M.D., Maria Buti, M.D., Stuart K. Roberts, M.D., Ed J. Gane, M.D., Jerry O. Stern, M.D., Richard Vinisko, M.A., George Kukolj, Ph.D., John-Paul Gallivan, Ph.D., Wulf-Otto Böcher, M.D., and Federico J. Mensa, M.D.

**Table 2. Virologic Response during and after the Treatment Period.***

| Variable | TID16W (N=81) | TID28W (N=80) | TID40W (N=77) | BID28W (N=78) | TID28W-NR (N=46) |
|---|---|---|---|---|---|
| | *number/total number (percent)* | | | | |
| Undetectable HCV RNA 12 wk after completion of therapy: sustained virologic response | | | | | |
| All patients | 48/81 (59) | 47/80 (59) | 40/77 (52) | 54/78 (69) | 18/46 (39) |
| Patients with genotype 1a | 13/34 (38) | 14/32 (44) | 16/34 (47) | 13/30 (43) | 2/18 (11) |
| Patients with genotype 1b | 35/47 (74) | 33/48 (69) | 24/43 (56) | 41/48 (85) | 16/28 (57) |
| Patients with *IL28B* CC | 14/21 (67) | 14/21 (67) | 12/19 (63) | 16/19 (84) | 7/12 (58) |
| Patients with *IL28B* non-CC | 34/60 (57) | 32/58 (55) | 28/58 (48) | 38/59 (64) | 11/33 (33) |

## All Oral, Interferon-free, GT1 Treatment- Naïve

- Phase 2b open label trial, n=362
- Approximately 10% with cirrhosis
- Multiple (5) arms with once daily FDV (PI) and varying deleobuvir (NS5B) and RBV doses
- Less impressive SVR than NS5B / NS5A combinations

N ENGL J MED 369;7 NEJM.ORG AUGUST 15, 2013

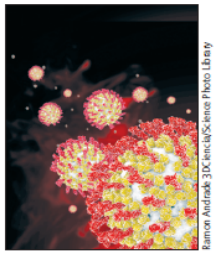
Over the past few years, new medicines for HCV infection have begun to transform the treatment landscape, and, just in the past few months alone, the development of new regimens has been so successful that disease experts are heralding an era where all patients can be cured, even debating whether eradication is possible.

Editorial

## Only just the beginning of the end of hepatitis C

2014 marks the 25th anniversary of the identification of the hepatitis C virus (HCV). HCV infection continues to be a major global health problem. Unlike many chronic diseases, hepatitis C can be cured, but it is difficult to treat, not all patients are responsive, side-effects can be severe, and progression to end-stage liver disease and liver cancer is common. Over the past few years, new medicines for HCV infection have begun to transform the treatment landscape, and, just in the past few months alone, the development of new regimens has been so successful that disease experts are heralding an era where all patients can be cured, even debating whether eradication is possible.

The main drawback of these new agents is the huge price tag, which will make treatment out of reach for people in the developed and developing world. Indeed, current treatment uptake is also impeded by cost. One 12 week course of sofosbuvir will cost US$84 000, even though the scientist involved in formulating sofosbuvir, Raymond Schinazi, estimates costs at just $1400. An even lower price was shown by Andrew Hill and colleagues in a recent study. Based on the fact that the new hepatitis C treatments are comparable in molecular structure and chemistry to HIV antiretrovirals, the authors used the same market dynamics to determine



Ramon Andrade 3DCiencia/Science Photo Library

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# Can We Cure All Hepatitis C Patients?

- Need more subgroup data (post-Tx, cirrhosis, HIV-HCV coinfection, different genotype, Black ancestry)
- Will likely have many different ways to achieve virologic suppression in next five years
- For developing countries, will we see activism movements regarding access?

# Penicillin to Prevent Recurrent Leg Cellulitis

Kim S. Thomas, Ph.D., Angela M. Crook, Ph.D., Andrew J. Nunn, M.Sc., Katharine A. Foster, Ph.D., James M. Mason, D.Phil., Joanne R. Chalmers, Ph.D., Ibrahim S. Nasr, M.Sc., Richard J. Brindle, D.M., John English, M.B., B.S., Sarah K. Meredith, F.F.P.H., Nicholas J. Reynolds, M.D., F.R.C.P., David de Berker, M.D., F.R.C.P., Peter S. Mortimer, M.D., F.R.C.P., and Hywel C. Williams, Ph.D., F.R.C.P., for the U.K. Dermatology Clinical Trials Network's PATCH I Trial Team*

- Direct advertising – hospital recruitment; dermatologist investigators
- Episode of cellulitis in the preceding six months were eligible with a prior episode in the last three years
- Randomized (DB) to penicillin 250mg po BID vs. placebo (n=136 vs. 138)
- Treatment adherence monitored by self-reporting an follow-up phone calls

## Clinical Situation

47F, above ideal body weight, right leg cellulitis

- Last episode in 2011 in the same lower extremity
- No other underlying diseases
- No hardware, laceration or trauma preceding the cellulitis
- Responding to IV Cefazolin and ready for discharge

Should long term "suppressive" antibiotics be prescribed?

N ENGL J MED 368;18 NEJM.ORG MAY 2, 2013

**Table 1. Baseline Characteristics of the Study Participants.***

| Characteristic | Penicillin (N=136) | Placebo (N=138) |
|---|---|---|
| Preexisting leg edema or ulceration associated with cellulitis — no. of patients (%) | | |
| Neither | 45 (33) | 44 (32) |
| Edema | 81 (60) | 82 (59) |
| Ulceration | 1 (1) | 2 (1) |
| Both | 9 (7) | 10 (7) |
| Age — yr | | |
| Mean | 58.1±12.6 | 57.4±14.4 |
| Median (interquartile range) | 59 (50–65) | 58 (46–69) |
| Female sex — no. of patients (%) | 83 (61) | 82 (59) |
| White race and British nationality — no. of patients (%) | 115 (85) | 121 (88) |
| No. of previous cellulitis episodes | | |
| Mean | 3.7±4.3 | 3.8±4.8 |
| Median (interquartile range) | 2 (1–5) | 2 (1–4) |
| Local warmth, tenderness, or acute pain — no. of patients (%) | 136 (100) | 138 (100) |
| Erythema at the affected site — no. of patients (%) | 135 (99) | 136 (99) |
| Edema at the affected site — no. of patients (%) | 135 (99) | 138 (100) |
| BMI | | |
| Mean | 35.1±9.4 | 35.2±9.5 |
| Median (interquartile range) | 33.7 (27.7–38.9) | 32.5 (27.8–40.7) |
| Chronic edema — no. of patients (%)† | | |
| Asymmetric | 64 (47) | 64 (46) |
| Symmetric | 28 (21) | 28 (20) |
| Venous insufficiency — no. of patients (%) | 36 (26) | 34 (25) |
| Leg ulceration subsequent to cellulitis — no. of patients (%)† | 13 (10) | 12 (9) |
| Tinea pedis or toe-web maceration — no. of patients (%) | 52 (38) | 48 (35) |
| Surgery >2 wk before the index cellulitis episode — no. of patients (%) | 22 (16) | 18 (13) |
| Blunt injury — no. of patients (%) | 6 (4) | 11 (8) |
| Definite or possible onychomycosis — no. of patients (%) | 30 (22) | 39 (28) |
| Inpatient admission for index episode of cellulitis at baseline — no. of patients (%) | 65 (48) | 59 (43) |
| Duration of hospital stay for hospitalized participants — days | 7.7±5.7 | 5.7±4.3 |

* Plus–minus values are means ±SD. No significant between-group differences were observed at baseline. BMI denotes body-mass index, calculated as the weight in kilograms divided by the square of the height in meters.
† The values for chronic edema and leg ulceration at baseline vary slightly from the values for the stratification variables (preexisting leg edema or ulceration associated with cellulitis) as a result of the different data-collection methods used.

# Baseline Characteristics

N ENGL J MED 368;18 NEJM.ORG MAY 2, 2013

**Table 2. Hazard Ratios for Confirmed Recurrence of Cellulitis in the Penicillin Group as Compared with the Placebo Group.**

| Variable | Recurrence of Cellulitis | Percentage-Point Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of events/total no. of patients (%)** | | | |
| Primary analysis: prophylaxis phase, year 1 | | | | |
| Penicillin | 30/136 (22) | −15 (−26 to −4) | 0.55 (0.35 to 0.86) | 0.01 |
| Placebo | 51/138 (37) | | | |
| Secondary analysis: follow-up phase, years 2 and 3† | | | | |
| Penicillin | 26/97 (27) | 0 (−14 to 12) | 1.08 (0.61 to 1.93) | 0.78 |
| Placebo | 22/81 (27) | | | |

* The proportion of patients with a recurrence of cellulitis was a prespecified secondary end point. Proportions are presented as percentages, not person-time event rates.
† The secondary analysis for years 2 and 3 was postrandomization. As a result, the groups may not have been balanced at the start of this period.

# Results

Risk factors for prophylaxis failure during Year 1:

- BMI > 33
- Three or more prior episodes
- ?presence of edema

# High Levels of Hepatitis B Virus After the Onset of Disease Lead to Chronic Infection in Patients With Acute Hepatitis B

**Hiroshi Yotsuyanagi,[1,a] Kiyoaki Ito,[2,5,a] Norie Yamada,[1,3,4] Hideaki Takahashi,[3] Chiaki Okuse,[3] Kiyomi Yasuda,[4] Michihiro Suzuki,[3] Kyoji Moriya,[1] Masashi Mizokami,[2] Yuzo Miyakawa,[6] and Kazuhiko Koike[1]**

[1]Department of Internal Medicine, Graduate School of Medicine, University of Tokyo, Bunkyo; [2]The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa; [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, St Marianna University School of Medicine, Kawasaki; and [4]Department of Internal Medicine, Center for Liver Diseases, Kiyokawa Hospital, Suginami, [5]Department of Microbiology and Immunology, Aichi Medical University School of Medicine, and [6]Miyakawa Memorial Research Foundation, Minato, Tokyo, Japan

- 159 /215 Japanese patients with acute HBV between 1994 to 2010 followed for clinical outcomes (retrospective)
- no patients received antiviral therapy
- Quantitative HBsAg, HBV DNA, and genotype available on all
- Duration of HBsAg divided into:
  a. Group 1 (<3 mo)
  b. Group 2 (3 – 6 mo)
  c. Group 3 (6 – 12 mo)
  d. Group 4 (>12 mo)

## Clinical Situation: 42M, MSM with an acute febrile icteric due to acute HBV

Peak AST 400, ALT 700

Initial HBV DNA 2.81 E+9 IU/mL (1IU = 5.82 c/mL)

## Will he develop Chronic Hepatitis B?

Clinical Infectious Diseases 2013;57(7):935–42

**Table 2. Baseline Characteristics and the Duration of Hepatitis B Surface Antigen in Patients With Acute Hepatitis B Virus With Different Hepatitis B Virus Genotypes**

| | HBV Genotypes | | | | | |
|---|---|---|---|---|---|---|
| Features | A (n = 113) | B (n = 26) | C (n = 73) | D (n = 1) | E (n = 1) | F (n = 1) |
| Age, y | 30.8 ± 9.5 | 32.3 ± 9.5 | 33.3 ± 10.9 | 27 | 26 | 58 |
| Male | 106 (93.8%)[a] | 21 (80.7%)[b] | 29 (39.7%)[a,b] | 0 | 0 | 1 (100%) |
| Transmission routes Identified | 102 (90.2%) | 21 (80.8%) | 53 (72.6%) | 1 (100%) | 1 (100%) | 1 (100%) |
| Heterosexual | 70 (68.6%) | 19 (90.4%) | 47 (88.7%) | 1 (100%) | 1 (100%) | 1 (100%) |
| MSM | 32 (31.4%)[c,d] | 1 (4.8%)[c] | 6 (11.3%)[d] | 0 | 0 | 0 |
| ALT, IU/L | 2126 ± 938[e,*] | 2394 ± 820 | 2857 ± 1668[e] | 4180 | 1175 | 1533 |
| Bilirubin, mg/dL | 7.1 ± 6.4[f*] | 4.8 ± 3.3[f,g] | 9.0 ± 7.5[g] | 6.8 | 3.9 | 3.5 |
| HBV DNA, log copies/mL | 6.3 ± 1.7[h,*] | 5.5 ± 2.3 | 4.9 ± 1.5[h] | 5.2 | 7.4 | 4.8 |
| HBeAg | 95/121 (77.3%)[i,*] | 24/28 (88.5%) | 37/58 (65.5%)[i] | 1/1 (100%) | 1/1 (100%) | 1/1 (100%) |
| Anti-HIV | 7/72 (9.7%) | 0/7 (0%) | 0/23 (0%) | Not tested | 0/1 (0%) | Not tested |
| Duration of HBsAg* | | | | | | |
| Group (mo) | | | | | | |
| 1 (<3) | 35 (42.2%) | 16 (64.0%) | 31 (64.6%) | 0 | 1 | 1 |
| 2 (3–6) | 34 (41.0%) | 8 (32.0%) | 11 (22.9%) | 1 | 0 | 0 |
| 3 (>6–12) | 9 (10.8%) | 0 | 6 (12.5%) | 0 | 0 | 0 |
| 4 (>12) | 5 (6.0%) | 1 (4.0%) | 0 | 0 | 0 | 0 |

Abbreviations: ALT, alanine aminotransferase; anti-HIV, antibody to human immunodeficiency virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MSM, men who have sex with men.

# Clinical Situation: 42M, MSM with an acute febrile icteric due to acute HBV

Peak AST 400, ALT 700

Initial HBV DNA 2.81 E+9 IU/mL (1IU = 5.82 c/mL)

# Will he develop Chronic Hepatitis B?

Clinical Infectious Diseases 2013;57(7):935–42

# High Levels of Hepatitis B Virus After the Onset of Disease Lead to Chronic Infection in Patients With Acute Hepatitis B

**Hiroshi Yotsuyanagi,[1,a] Kiyoaki Ito,[2,5,a] Norie Yamada,[1,3,4] Hideaki Takahashi,[3] Chiaki Okuse,[3] Kiyomi Yasuda,[4] Michihiro Suzuki,[3] Kyoji Moriya,[1] Masashi Mizokami,[2] Yuzo Miyakawa,[6] and Kazuhiko Koike[1]**

[1]Department of Internal Medicine, Graduate School of Medicine, University of Tokyo, Bunkyo; [2]The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa; [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, St Marianna University School of Medicine, Kawasaki; and [4]Department of Internal Medicine, Center for Liver Diseases, Kiyokawa Hospital, Suginami, [5]Department of Microbiology and Immunology, Aichi Medical University School of Medicine, and [6]Miyakawa Memorial Research Foundation, Minato, Tokyo, Japan

## Duration of HBsAg divided into:

a. Group 1 (<3 mo)
b. Group 2 (3 – 6 mo)
c. Group 3 (6 – 12 mo)
d. Group 4 (>12 mo)

## Results

- 6% cleared HBsAg between six and twelve months (Group 3)
- 8 week HBV DNA >10E+6IU/mL at week 8 predictive of chronic (>12mo) infection
- 12 week quantitative HBsAg >1,000IU/mL (readily available in Canada?) predictive

Clinical Infectious Diseases 2013;57(7):935–42

# Impact of Rapid Organism Identification via Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Combined With Antimicrobial Stewardship Team Intervention in Adult Patients With Bacteremia and Candidemia

**Angela M. Huang,[1,2] Duane Newton,[5,6] Anjly Kunapuli,[1,2] Tejal N. Gandhi,[3] Laraine L. Washer,[3,4] Jacqueline Isip,[1,2] Curtis D. Collins,[1,2] and Jerod L. Nagel[1,2]**

Departments of [1]Pharmacy Services and [2]Clinical Sciences, University of Michigan Health System and College of Pharmacy, [3]Division of Infectious Diseases, Department of Internal Medicine, [4]Department of Infection Control and Epidemiology, [5]Clinical Microbiology Laboratories, and [6]Department of Pathology, University of Michigan Health System and Medical School, Ann Arbor

- Antibiotic Stewardship Team (AST): 2 IDs, 3 ID Pharms, 1 ID Pharm Resident
- 24/7 email notification to AST of +BC, updated ID, susceptibilities

## Preintervention:

- No real time BC intervention except yeast on Gram Mo – Fri
- Restricted antimicrobial reviewed

## Intervention:

- Real time BC inteventions based on Gram, ID and susceptibilities using institution / evidence-based guidelines
- ?7d / week

# Will MALDI-TOF Improve BSI Outcomes?

- Single centre pre –post intervention period during same three month calendar interval (Sept – Nov)
- Patients with BSI identified at admission / in-hospital
- During MALDI-TOF period, no direct testing on blood cultures
- Lab work hours 0600 – 2330h
- Multiple primary and secondary endpoints

**Clinical Infectious Diseases 2013;57(9):1237–45**

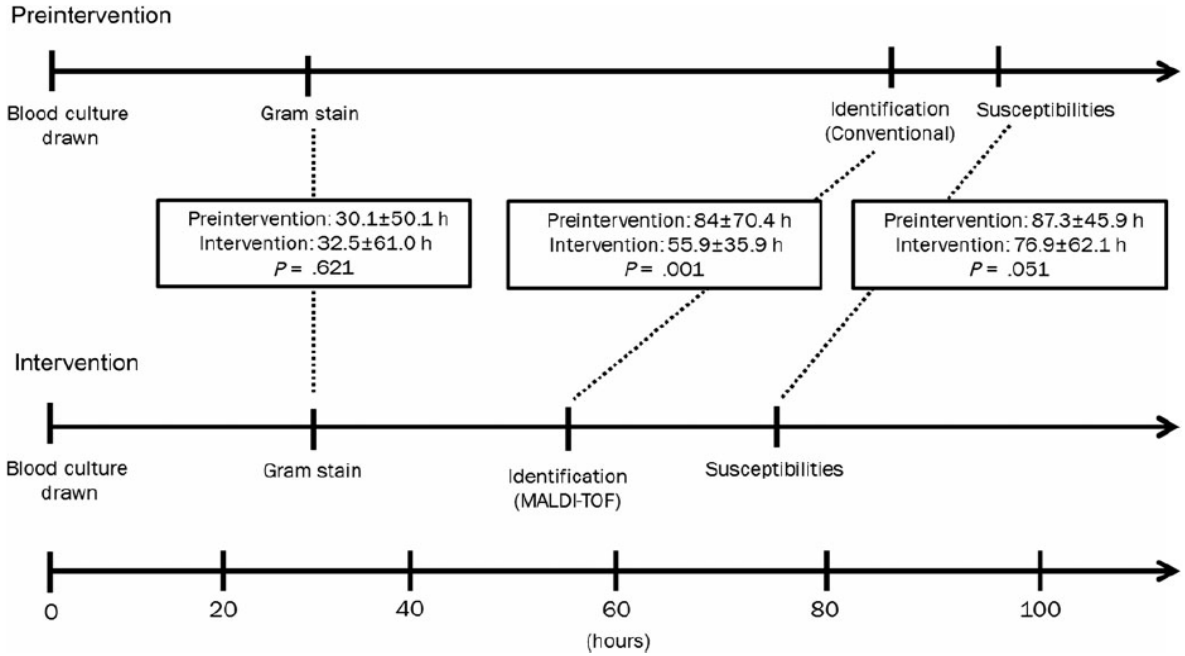


**Table 4. Antimicrobial Stewardship Team Interventions**

| Intervention | Timing of Intervention Recommendation: Gram Stain | Organism Identification | Antimicrobial Susceptibility | Total (%) |
|---|---|---|---|---|
| Narrowed coverage to target the isolated organism | 2 | 22 | 48 | 72 (34.3) |
| Discontinued therapy targeting organisms not isolated | 5 | 44 | 19 | 68 (32.4) |
| Initiated or broadened coverage | 39 | 5 | 9 | 53 (25.2) |
| Other | 8 | 4 | 5 | 17 (8.1) |
| Total (%) | 54 (25.7) | 75 (35.7) | 81 (38.6) | 210 (100) |
| Interventions accepted (%) | 49 (90.7) | 62 (82.7) | 78 (96.3) | 189 (90.0) |

# Combined MALDI-TOF and AST Intervention: Results

- Outcome analysis on pre-intervention (n=256) and intervention period (n=245)
- Shorter time to effective therapy (30.1h vs. 20.4h)
- Shorter time to optimal therapy (90.3 vs. 47.3h)
- Significant de-escalation and discontinuation at time of organism identification

Clinical Infectious Diseases 2013;57(9):1237–45

**Table 3. Clinical and Treatment-Related Outcomes**

| Outcome | Total | | |
|---|---|---|---|
| | Preintervention (n = 256) | Intervention (n = 245) | *P* Value |
| Clinical outcomes | | | |
| 30-day all-cause mortality | 52 (20.3) | 31 (12.7) | .021 |
| Time to microbiological clearance, d | 3.3 ± 4.8 | 3.3 ± 5.7 | .928 |
| Length of hospitalization, d[a] | 14.2 ± 20.6 | 11.4 ± 12.9 | .066 |
| Length of ICU stay, d[a] | 14.9 ± 24.2 | 8.3 ± 9.0 | .014 |
| Recurrence of same BSI | 15 (5.9) | 5 (2.0) | .038 |
| 30-day readmission with same BSI | 9 (3.5) | 4 (1.6) | .262 |
| Treatment-related outcomes | | | |
| Time to effective therapy, h | 30.1 ± 67.7 | 20.4 ± 20.7 | .021 |
| Time to optimal therapy, h | 90.3 ± 75.4 | 47.3 ± 121.5 | <.001 |

Data are No. (%) or mean ± standard deviation.

Abbreviations: BSI, bloodstream infection; ICU, intensive care unit.

[a] Length of hospitalization and ICU stay were defined as time from blood culture positivity to discharge.

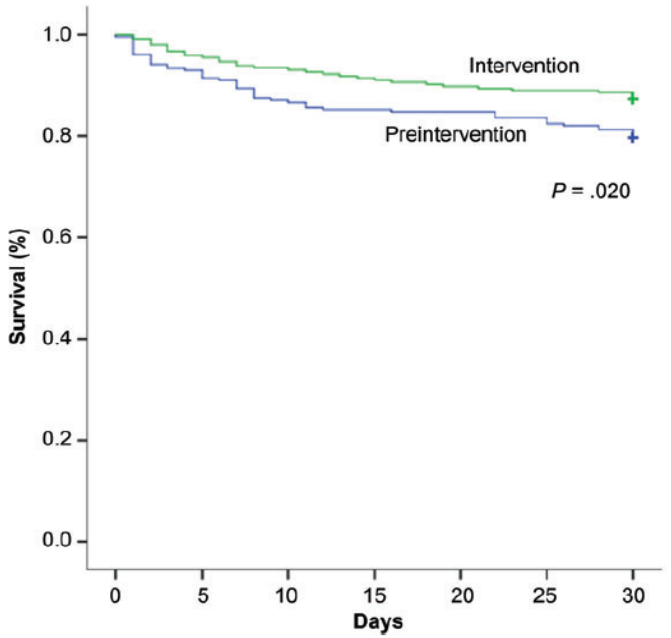


**Figure 3.** Kaplan-Meier survival analysis: overall survival in both study groups, censored for patients discharged prior to 30 days.

# Impact of AST Intervention

Limitations:

- Improved time to effective therapy was mainly in response to the Gram stain, rather than organism ID
- Would real-time +BC ASP interventions achieve the same mortality endpoint
- Long term sustainability of ASP interventions?

Clinical Infectious Diseases 2013;57(9):1237–45

## Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial

C Orla Morrissey, Sharon C-A Chen, Tania C Sorrell, Samuel Milliken, Peter G Bardy, Kenneth F Bradstock, Jeffrey Szer, Catriona L Halliday, Nicole M Gilroy, John Moore, Anthony P Schwarer, Stephen Guy, Ashish Bajel, Adrian R Tramontana, Timothy Spelman, Monica A Slavin, for the Australasian Leukaemia Lymphoma Group and the Australia and New Zealand Mycology Interest Group

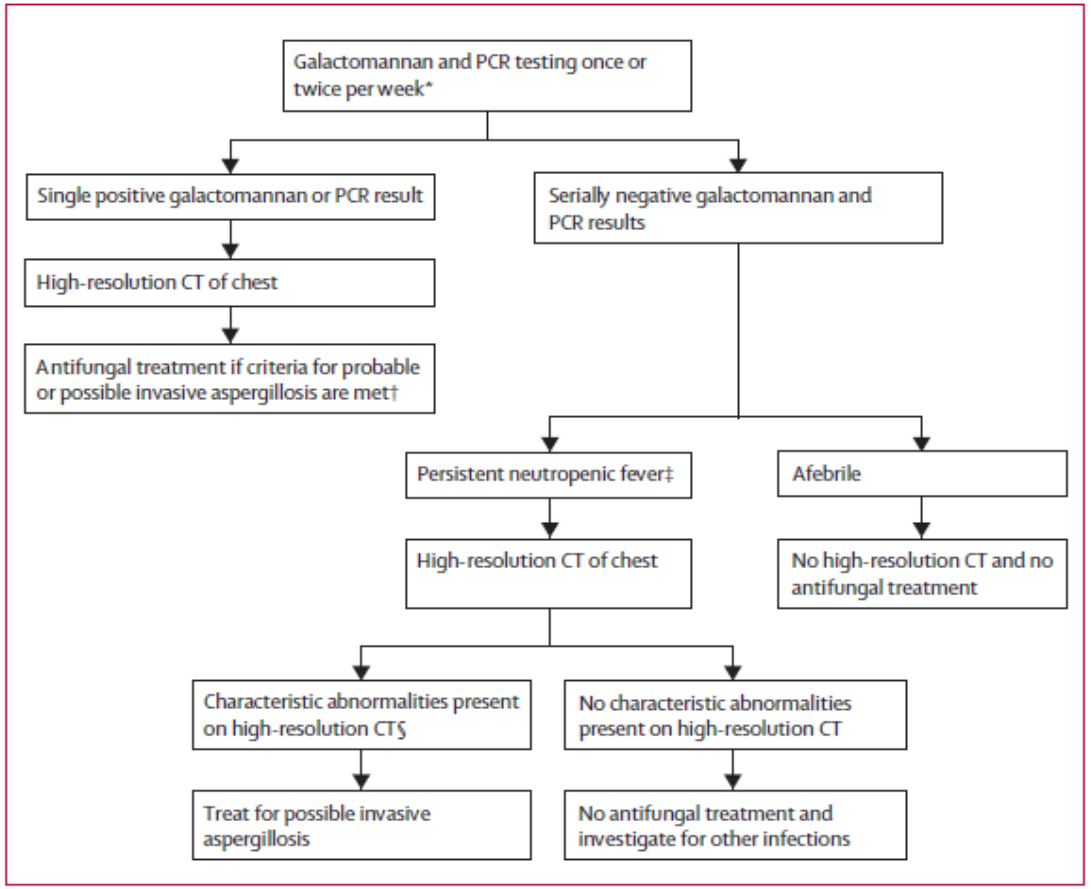


***Figure 1:*** **Diagnostic and treatment algorithm for the biomarker-based diagnostic strategy**
*Frequency of testing depended on whether the patient was treated as an inpatient or an outpatient. †Irrespective of persistent neutropenic fever. ‡Despite use of broad-spectrum antibiotics and with no other cause identified. §Defined as dense, well-circumscribed lesion or lesions (larger than 1 cm diameter) with or without a halo sign, air-crescent sign, or cavity.[16]

# Stewardship for Antifungal Therapy?

- High risk patient population undergoing chemotherapy: allogeneic BMT, acute leukemia
- Open-label, multicentre RCT of standard diagnostic strategy (n=122) vs. galactomannan / PCR (n=118)
- Weekly (OPD) or Biweekly (Inpatient) biomarker testing for 26 weeks
- Biomarker results not released to standard arm physicians

Primary endpoint: Proportion of patients receiving empiric antifungal therapy

Secondary Endpoints: Death (all cause, IA IFI), etc.

Lancet Infect Dis 2013; 13: 519–28

| | Standard diagnosis group (n=122) | Biomarker diagnosis group (n=118) | % difference between groups (95% CI) | p value |
|---|---|---|---|---|
| Received empirical treatment with antifungal drugs | 39 (32%) | 18 (15%) | 17% (4 to 26) | 0·002 |
| Mortality | | | | |
| All-cause | 18 (15%) | 12 (10%) | 5% (−4 to 14) | 0·31 |
| Invasive aspergillosis-related | 6 (5%) | 3 (3%) | 2% (−2·5 to 7·3) | 0·5 |
| Other invasive fungal disease-related* | 0 | 2 (2%) | .. | 0·24 |
| Incidence of invasive aspergillosis | | | | |
| Proven | 1 (1%) | 1 (1%) | .. | 1·0 |
| Probable | 0 | 16 (14%) | −14% (−20 to −7) | <0·0001 |
| Possible | 0 | 6 (5%) | −5% (−9 to −1) | 0·013 |
| Incidence of other invasive fungal disease† | | | | |
| Proven | 4 (3%) | 5 (4%) | .. | 0·75 |
| Probable | 0 | 1 (1%) | .. | 0·49 |

Data are n (%). Results for possible other invasive fungal disease are not shown because cases were not individually identified by microscopic or culture methods. *_Scedosporium prolificans_ fungaemia (n=1), disseminated mucormycosis (_Rhizopus_ sp; n=1). †_Candida guilliermondii_ (n=1), _Candida glabrata_ (n=3), _Candida krusei_ (n=1), _Candida parapsilosis_ (n=1), _Rhizopus_ sp (n=1), _Rhizopus microsporus_ (n=1), _S prolificans_ (n=1), _Exserohilum_ sp (n=1).

***Table 2:*** **Empirical treatment with antifungal drugs, mortality, and incidence of invasive fungal infections through 26 weeks of follow-up**

# Results

- Less empiric antifungal use in the biomarker group, applied to those on fluconazole prophylaxis
- If biomarkers had been available in the standard group, earlier IA diagnosis by a median of 7 days
- 64% in standard diagnosis group would had negative biomarkers
- Biomarker strategy low yield on patients receiving voriconazole or itraconazole

Lancet Infect Dis 2013; 13: 519–28

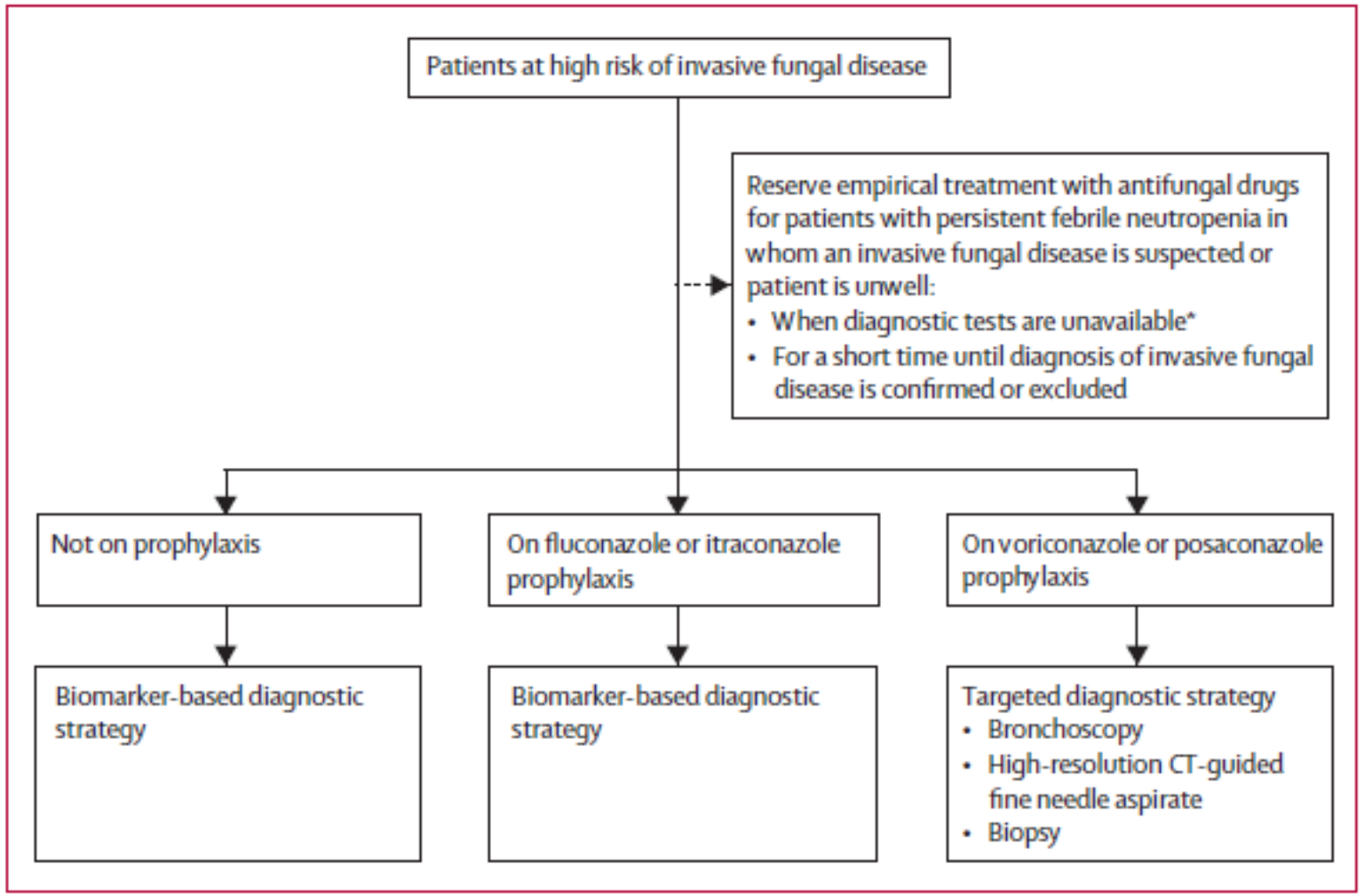


***Figure 3*: Integrated antifungal strategies for patients at risk of invasive fungal disease**
Patients at high risk of invasive fungal infection are listed in the appendix. High-risk patients for whom a biomarker-based diagnostic strategy combined with fluconazole, itraconazole, or no prophylaxis is a suitable alternative to voriconazole or posaconazole prophylaxis are also listed in the appendix. In the targeted diagnostic strategy, appropriate investigations are determined by clinical symptoms and signs, and by abnormalities seen on high-resolution CT of the chest—these investigations are outlined in full in the appendix.[16,31] *On-site access to galactomannan or fungal PCR assays is not available, and high-resolution CT or bronchoscopy with lavage are not readily accessible or available.

# Results

- Biomarker strategy may provide alternative to broad spectrum antifungal prophylaxis

Lancet Infect Dis 2013; 13: 519–28

A Dimorphic Fungus Causing Disseminated Infection in South Africa

Chris Kenyon, M.D., Ph.D., Kim Bonorchis, M.Med., Craig Corcoran, F.C.Path., Graeme Meintjes, M.D., Ph.D., Michael Locketz, M.Med.Path., Rannakoe Lehloenya, F.C.Derm., Hester F. Vismer, Ph.D., Preneshni Naicker, M.D., Hans Prozesky, M.Med., Marelize van Wyk, Ph.D., Colleen Bamford, M.Med., Moira du Plooy, Gail Imrie, Sipho Dlamini, M.D., Andrew M. Borman, Ph.D., Robert Colebunders, M.D., Ph.D., Cedric P. Yansouni, M.D., Marc Mendelson, M.D., Ph.D., and Nelesh P. Govender, M.D.

- 13 cases identified with an average CD4 was 16
- Skin lesions in all cases; positive blood cultures in approx. 50%
- Dramatic response to antifungal therapy (itraconazole , AmB x 14 d)
- 3/13 died soon after presentation

# A New HIV Opportunistic Infection: *Emmonsia pasteuriana*

- Enhanced molecular diagnostic capabilities for identification of systemic dimorphic fungal infections 2008 – 2011
- Retrospective review of skin biopsy tissue from March 2003 – 2011
- 10/24 cases originally called histoplasmosis were actually due to *Emmonsia sp.*
- 3 more cases found prospectively

N Engl J Med 2013;369:1416-24.

# A Dimorphic Fungus Causing Disseminated Infection in South Africa

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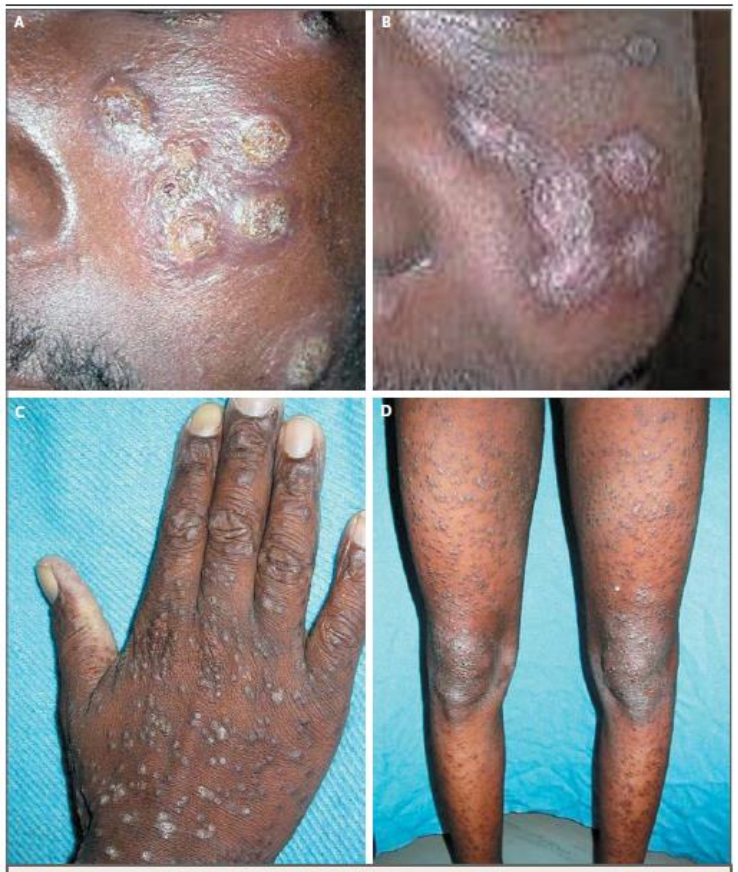



Figure 1. **Clinical Features of Emmonsia Species Infection.**
Shown are crusted, boggy facial plaques and nodules on one patient before treatment (Panel A) and 1 month after the start of treatment (Panel B). Another patient presented with generalized scaly and erythematous papules a few millimeters in diameter (Panels C and D).

# A New HIV Opportunistic Infection: *Emmonsia pasteuriana*

- Median age 34
- All patients anemic
- Presented as IRIS in some
- Occasional mucosal ulceration

N Engl J Med 2013;369:1416-24.

# Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection

Sharon L. Walmsley, M.D., Antonio Antela, M.D., Ph.D., Nathan Clumeck, M.D., Dan Duiculescu, M.D., Andrea Eberhard, M.D., Felix Gutiérrez, M.D., Laurent Hocqueloux, M.D., Franco Maggiolo, M.D., Uriel Sandkovsky, M.D., Catherine Granier, D.E.S.S., Keith Pappa, Pharm.D., Brian Wynne, M.D., Sherene Min, M.D., and Garrett Nichols, M.D., for the SINGLE Investigators*

# Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study

*Pedro Cahn, Anton L Pozniak, Horacio Mingrone, Andrey Shuldyakov, Carlos Brites, Jaime F Andrade-Villanueva, Gary Richmond, Carlos Beltran Buendia, Jan Fourie, Mati Ramgopal, Debbie Hagins, Franco Felizarta, Jose Madruga, Tania Reuter, Tamara Newman, Catherine B Small, John Lombaard, Beatriz Grinsztejn, David Dorey, Mark Underwood, Sandy Griffith, Sherene Min, on behalf of the extended SAILING Study Team*

## Dolutegravir: Integrase Inhibitor

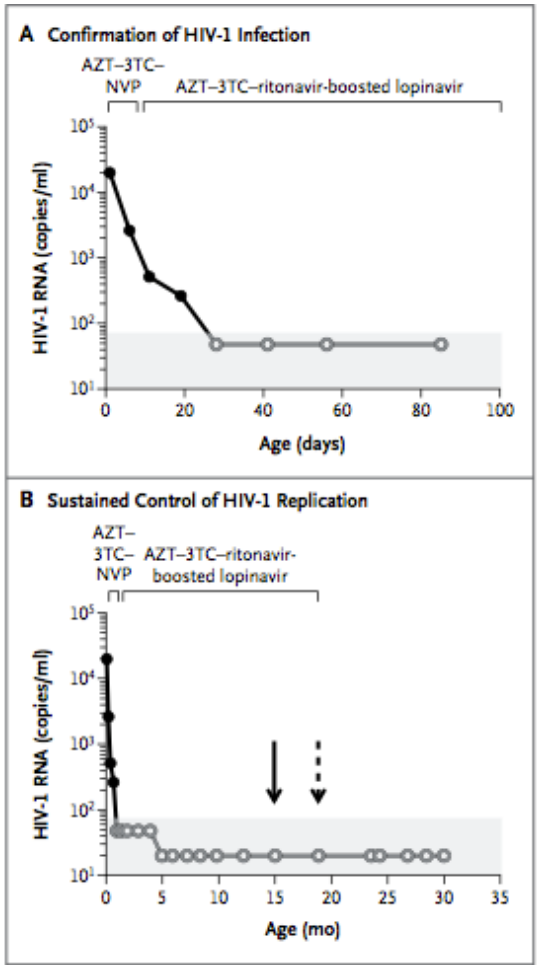
- Once daily dosing
- Fixed dose formulation with ABC/3TC to follow
- Higher genetic barrier to resistance than raltegravir
- Compares favourably to raltegravir in treatment-naïve and treatment-experienced populations

N Engl J Med 2013;369:1807-18.

*Lancet* 2013; 382: 700–08

# Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.




## Functional Cure #2?

- Congenitally infected infant treated from 30h after birth with VL 19,812 c/mL
- Child lost to follow-up and stopped treatment at 15 months
- No virologic rebound at 23 months, 36 months
- Potential implications for treatment cessation in children, after treatment for primary infection

N Engl J Med 2013;369:1828-35.

# The end of AIDS: HIV infection as a chronic disease

Steven G Deeks, Sharon R Lewin, Diane V Havlir

| | Past | Present | Future |
|---|---|---|---|
| Epidemiology | Exponential increase in new infections<br>Disease affects mainly young adults and children<br>Disproportionate burden of new infections in high-risk* populations<br>Life expectancy of less than 2 years after AIDS illness<br>Low proportion of people with access to chronic ART | Fewer new adult infections, but more people living with HIV<br>Disease increasingly common in middle-aged people<br>Reduced number of HIV-infected children; more HIV-exposed uninfected children<br>Disproportionate burden of new infections in high-risk* populations<br>Greater proportion of people treated with ART<br>Life expectancy of decades in treated patients | Few new HIV infections<br>Elimination of HIV infection in children<br>Disease spans age spectrum, with growing burden of disease in geriatric populations<br>More HIV-infected but cured people<br>Few AIDS-related deaths |
| Immune profile | Severe immune deficiency in untreated patients<br>Partially restored immune deficiency in treated patients | Partially restored immune deficiency with ART<br>Persistent inflammation contributing to incomplete health restoration | Restored immune function through earlier initiation of ART; anti-inflammatory interventions and functional cure in some patients |
| Disease burden | AIDS-defining illnesses and tuberculosis<br>ART toxicity from early ART combinations | Decreasing AIDS-defining illness with residual persistent tuberculosis risk in ART-treated patients<br>Increasing importance of cardiovascular, liver, renal, and cognitive complications of HIV | Morbidity reflecting age, as seen in HIV-uninfected general population<br>No increased risk for tuberculosis |
| Health system | Hospital-based detection and care for symptomatic patients | Clinic and hospital based<br>Move towards integrated HIV care cascade | Community-based and clinic-based integrated HIV care model, with specialty HIV cure services |

ART=antiretroviral therapy. *Men having sex with men, transgender people, sex workers, injection drug users.

**Table 1: HIV as a chronic disease**

# Towards HIV Eradication

- Treatment at time of acute infection not likely to occur for most
- Can the latent cell reservoir be eliminated?
  - histone deacetylase inhibitors (vorinostat)
  - Gene therapy to interrupt CCR5 receptor expression

*Lancet* 2013; 382: 1525–33

# The end of AIDS: HIV infection as a chronic disease

Steven G Deeks, Sharon R Lewin, Diane V Havlir

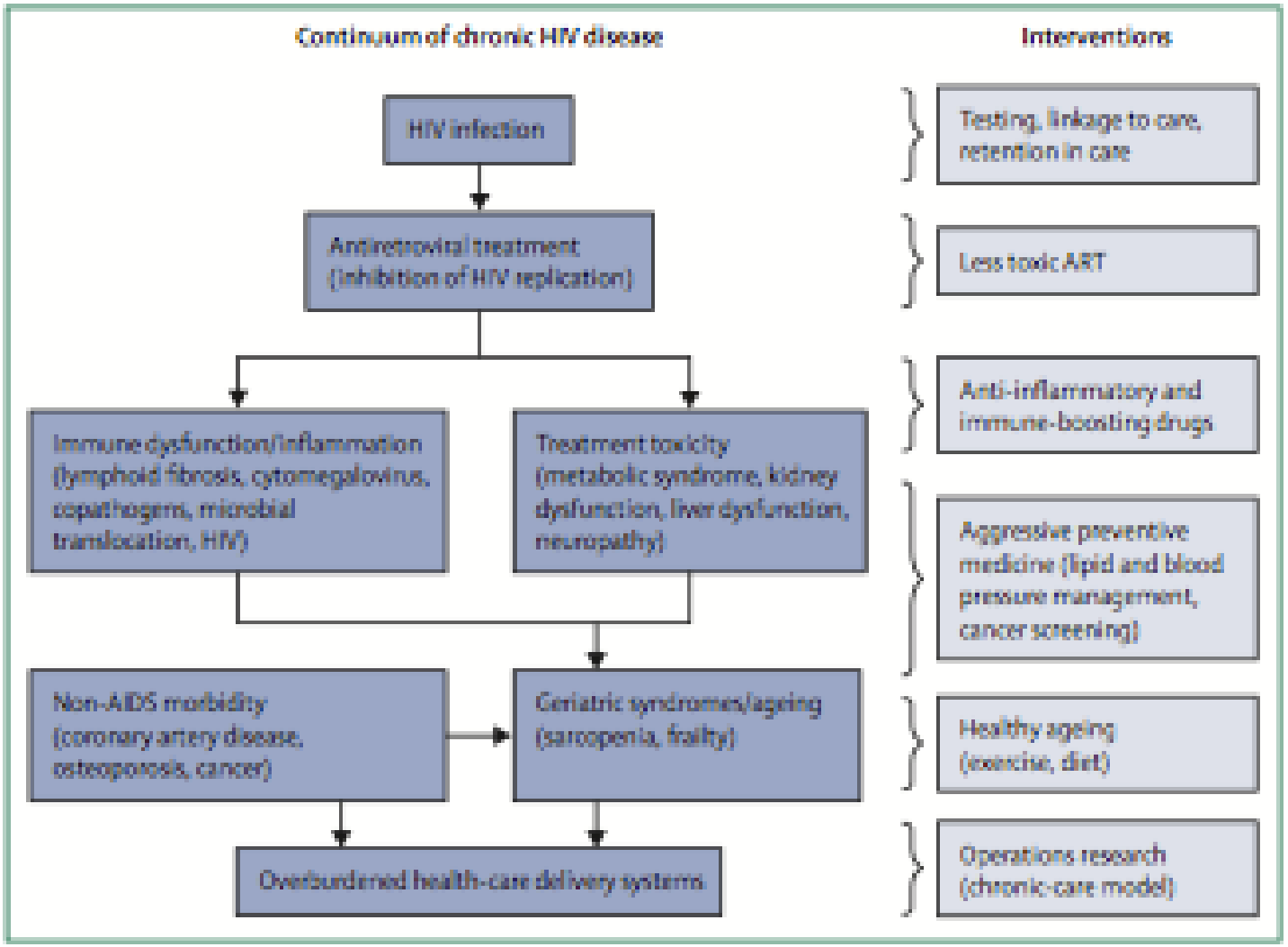



*Figure 1:* HIV infection as a chronic disease

# Towards HIV Eradication

- Treatment at time of acute infection not likely to occur for most
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*Lancet* 2013; 382: 1525–33