Burden of HIV & HCV

- 35 million HIV
- 200 million HCV
- 7 million

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Deaths in a cohort of 23,441 HIV patients on HAART


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Progression of HCV-related liver fibrosis in HIV patients

- No HAART
  - Uncontrolled HIV replication
  - Low CD4 counts

- HAART
  - Metabolic abnormalities
  - Hepatotoxicity of meds

- HIV-neg
## RCT with PegIFN + RBV in HCV/HIV pts

<table>
<thead>
<tr>
<th></th>
<th>APRICOT</th>
<th>RIBAVIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with Peg+RBV</td>
<td>288</td>
<td>194</td>
</tr>
<tr>
<td>IDUs</td>
<td>62%</td>
<td>81%</td>
</tr>
<tr>
<td>Cirrhotics</td>
<td>15%</td>
<td>40%(F3-F4)</td>
</tr>
<tr>
<td>Genotypes 1-4</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>Normal ALT levels</td>
<td>0</td>
<td>16%</td>
</tr>
<tr>
<td>Mean CD4 count</td>
<td>520</td>
<td>525</td>
</tr>
<tr>
<td>On HAART</td>
<td>84%</td>
<td>82%</td>
</tr>
<tr>
<td>EOT (ITT)</td>
<td>49%</td>
<td>36%</td>
</tr>
<tr>
<td>SVR (ITT)</td>
<td>40%</td>
<td>27%</td>
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</table>
Unique AEs in HCV/HIV-coinfected patients under pegIFN+RBV

<table>
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<th>RIBAVIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>860</td>
<td>383</td>
</tr>
<tr>
<td>Mitochondrial toxicity</td>
<td>20</td>
<td>11**</td>
</tr>
<tr>
<td>Hepatic decompensation</td>
<td>14*</td>
<td>7***</td>
</tr>
</tbody>
</table>

* All seen in cirrhotics. Overall, it affected 10% of cirrhotics; associated to ddI (± RBV)
** 1 out of 5 patients treated with ddI
*** Associated with ddI and cirrhosis (OR = 9)
How to improve response rates?

Minimize toxicities & interactions

- CD4 > 200 cells/ul
- No didanosine, nor AZT, nor abacavir, nor d4T
- Application of 2 log stopping rules

Enhance efficacy

- Use of higher ribavirin doses (1000-1200 mg/day)
- Extended duration of therapy

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
RBV exposure matters

**APRICOT**  
(overall SVR 40%)

- Geno 1: 29%  
- Geno 3: 62%  
- All 48 weeks therapy  
- HIV-pos; low RBV dose  
- n=176

**PRESCO**  
(overall SVR 50%)

- Geno 1: 36%  
- Geno 3: 72%  
- 24, 48 or 72 weeks therapy  
- HIV-pos; weight-based RBV  
- n=191

**FRIED**  
(overall SVR 56%)

- Geno 1: 46%  
- Geno 3: 76%  
- 48 weeks therapy  
- HIV-neg; weight-based RBV  
- n=298

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Algorithm for HCV therapy in HIV patients

HCV-RNA neg

- W4
- W12
- W24
- W48
- W72

HCV-RNA pos

- G2/3
- G1/4

> 2 log drop in HCV-RNA

- 24 weeks therapy
- 48 weeks therapy
- 72 weeks therapy

< 2 log drop in HCV-RNA

- Stop


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Predictors of response to HCV therapy

- HCV genotype
- Baseline serum HCV-RNA
- Liver fibrosis stage
- RVR
- EVR
- IL28b polymorphism
**IL28B polymorphisms & hepatitis C outcome**

- **IL28B gene**
  - SNP: rs12979860 (CC, CT, TT)

- **Chromosome 19**

- **Interferon λ3**
  - Spontaneous HCV clearance
  - Response to pegIFN+RBV

References:

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients

Norma I. Rallón, Susanna Naggie, José M. Benito, José Medrano, Clara Restrepo, David Goldstein, Kevin V. Shianna, Eugenia Vispo, Alex Thompson, John McHutchison and Vincent Soriano

SVR

AIDS 2010

<table>
<thead>
<tr>
<th></th>
<th>CC</th>
<th>CT/TT</th>
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<tbody>
<tr>
<td>All HCV-1</td>
<td>75</td>
<td>89</td>
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<tr>
<td>HCV-3</td>
<td>35</td>
<td>46</td>
</tr>
<tr>
<td>HCV-4</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

75% 38% 65% 30% 86% 81% 67% 25%

p<0.0001 p=0.001 p=0.087 p=0.087
IL28B polymorphisms in HIV-HCV coinfection

- HCV-RNA <600,000 IU/ml: p<0.001
- HCV genotype 3: p<0.001
- rs12979860 CC genotype: p=0.002
- Liver fibrosis stage F0-F2: p=0.009

Odds ratio (95% confidence interval)

Rallon et al. AIDS 2010
Modeling the Probability of Sustained Virological Response to Therapy with Pegylated Interferon plus Ribavirin in Patients Coinfected with Hepatitis C Virus and HIV

Clinical Infectious Diseases 2010;51(10):1209-1216

Prometheus index

- HCV genotype
- Fibrosis stage (KPa)
- Serum HCV-RNA
- IL28B SNPs

http://ideasydesarrollo.com/fundacion/prometheusindex.php

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Prediction of Sustained Virological Response (SVR) after treatment of Hepatitis C with Pegylated Interferon plus weight adjusted Ribavirin

http://ideasydesarrollo.com/fundacion/prometheusindex.php
## New Therapies for Hepatitis C Virus Infection

*Clinical Infectious Diseases* 2009; 48:313–20

Vincent Soriano,¹ Marion G. Peters,² and Stefan Zeuzem³

¹Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain; ²Division of Gastroenterology, University of California, San Francisco; and ³Medizinische Klinik I, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany

<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>Polymerase inhibitors</th>
<th>NS5A inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>Nucleoside analogues</td>
<td>BMS-790052</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>RG-7128</td>
<td></td>
</tr>
<tr>
<td>Danoprevir</td>
<td>PSI-7851</td>
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<tr>
<td>Vaniprevir</td>
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<td></td>
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<td>BI-1335</td>
<td></td>
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</tr>
<tr>
<td>TMC-435</td>
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<tr>
<td>GS-9256</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-nucleoside analogues</td>
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</tr>
<tr>
<td></td>
<td>GS-9190</td>
<td></td>
</tr>
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<td></td>
<td>Filibuvir</td>
<td></td>
</tr>
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<td></td>
<td>BI-7127</td>
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</tr>
<tr>
<td></td>
<td>ANA-598</td>
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</tr>
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<td></td>
<td>VX-222</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VCH-759</td>
<td></td>
</tr>
</tbody>
</table>
Main differential features of new direct anti-HCV drugs

**Protease inhibitors**
- Interact with the catalytic triad
- Geno/subtype-dependent activity
- Rapid selection of resistance

**Nucleoside analogues**
- Analogues of natural substrates
- Need to be phosphorylated
- Inhibitory competition
- Chain terminators
- Similar activity across all genotypes
- High genetic barrier to resistance

**Non-nucleoside inhibitors**
- 4 target sites at the polymerase
- Allosteric inhibition
- Genotype-dependent activity
- Rapid selection of resistance
- Polymorphisms may influence susceptibility

Challenges using DAA in HIV-HCV coinfection

- More elevated HCV load. More virological failures?
- Faster selection of drug resistance?
- Drug-drug interactions
- Overlapping toxicities
- Drug compliance with polymedication
Viral kinetics on HCV antiviral therapy

Patient ID: 013703J

Log(base 10) HCV RNA eq/ml

HIV-pos (?)

HIV-neg

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Study 110
Telaprevir in HIV-HCV coinfected pts

% HCV-RNA <10 IU/ml

Week 4

- Total: 37, No ARV: 22, ATV/r: 14, EFV: 8
- PRT: 70, PR: 5
- % HCV-RNA <10 IU/ml: 70

Week 12

- Total: 37, No ARV: 22, ATV/r: 14, EFV: 8
- PRT: 68, PR: 14
- % HCV-RNA <10 IU/ml: 75

Sulkowski et al. CROI 2011, LB146

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Categorization of HIV-HCV populations (West Europe vs North America)

Non-1 genotypes 25%

- HIV ARV-naive & HCV IFN-naive
- HIV ARV-naive & HCV IFN-experienced
- HIV ARV-experienced & HCV IFN-naive
- HIV ARV-experienced & HCV IFN-experienced
Why are there different dynamics in the selection of drug resistance in HIV and hepatitis B and C viruses?

Vincent Soriano¹*, Alan S. Perelson² and Fabien Zoulim³

¹Department of Infectious Diseases, Hospital Carlos III, Sinesio Delgado 10, 28029 Madrid, Spain; ²Theoretical Biology and Biophysics, Los Alamos National Laboratory, Los Alamos, New Mexico, USA; ³INSERM, U871, Université Lyon 1, Hospices Civils de Lyon, Lyon, France

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
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<tr>
<td>Virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daily production of</td>
<td>$10^{10}$</td>
<td>$10^{12}-10^{13}$</td>
<td>$10^{12}$</td>
</tr>
<tr>
<td>virions per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>half-life of free</td>
<td>1</td>
<td>3–24</td>
<td>2–3</td>
</tr>
<tr>
<td>virions (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>half-life of</td>
<td>days (dependent on</td>
<td>months (dependent on</td>
<td>hours (not dependent on</td>
</tr>
<tr>
<td>intracellular virions</td>
<td>infected cells $t_{1/2}$)</td>
<td>infected cells $t_{1/2}$)</td>
<td>infected cells $t_{1/2}$)</td>
</tr>
<tr>
<td>mutation rate</td>
<td>very high</td>
<td>high</td>
<td>very high</td>
</tr>
<tr>
<td>constraints due to</td>
<td>high</td>
<td>high</td>
<td>none</td>
</tr>
<tr>
<td>ORFs in targeted</td>
<td>moderate</td>
<td>high</td>
<td>none</td>
</tr>
<tr>
<td>viral enzymes</td>
<td>frequent</td>
<td>infrequent</td>
<td>frequent</td>
</tr>
<tr>
<td>immune-mediated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>escape mutants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>half-life of infected</td>
<td>days</td>
<td>months</td>
<td>weeks</td>
</tr>
<tr>
<td>cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>size of susceptible</td>
<td>large</td>
<td>small</td>
<td>probably large</td>
</tr>
<tr>
<td>cells compartment</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>intracellular viral</td>
<td>yes (integrated cDNA)</td>
<td>yes (cccDNA)</td>
<td>no</td>
</tr>
<tr>
<td>reservoir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
HIV, HBV & HCV life cycles
drug resistance & and treatment strategy

Suppression

Cure

Eradiication

Soriano et al. JAC 2008

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Drug resistance in HCV. Protease inhibitors.

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Drug resistance in HCV. NS5B polymerase inhibitors.

Nucleoside analogue inhibitors

RG-7128 / PSI-6130

Non-nucleoside inhibitors

GS-9190

BI-7127

Filibuvir

ABT-333

VHC-759

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Natural polymorphisms associated with resistance to new antivirals against HCV in newly diagnosed HIV–HCV-coinfected patients

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus

<table>
<thead>
<tr>
<th>GenBank Database</th>
<th>Bartels et al.72</th>
<th>Kuntzen et al.73</th>
<th>Gaudieri et al.74</th>
<th>Sun et al.83</th>
<th>Bae et al.75</th>
<th>Treviño et al.76</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS3 Protease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>No. tested</strong></td>
<td>3197-3328</td>
<td>570</td>
<td>507*</td>
<td>192**</td>
<td>39</td>
<td>55</td>
</tr>
<tr>
<td>V36A/M/L/G</td>
<td>0.03%</td>
<td>0.9%</td>
<td>1.6%***</td>
<td>1%</td>
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<td>0</td>
</tr>
<tr>
<td>T54S/A</td>
<td>1.4%</td>
<td>-</td>
<td>1.8%</td>
<td>3%***</td>
<td>5%</td>
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</tr>
<tr>
<td>V55A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
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<tr>
<td>Q80R/K</td>
<td>47%****</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28%</td>
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<td>0</td>
<td>1%</td>
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<td>R155K/T/I/M/G/L/S</td>
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<td>0.6%***</td>
<td>0.5%</td>
<td>0</td>
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<tr>
<td>A156S/T/V/I</td>
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<td>-</td>
<td>0</td>
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<tr>
<td>D168A/V/E</td>
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<td>-</td>
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<td>0</td>
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<tr>
<td>V170A</td>
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<td>0.2%</td>
<td>0</td>
<td>5%***</td>
<td>0</td>
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<td><strong>NS5B Polymerase</strong></td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>212**</td>
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<td>47</td>
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<td>C316Y/N/F/S</td>
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<td>V499A</td>
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<td></td>
<td>75%***</td>
<td>-</td>
<td>51%***</td>
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<td>S556N/G</td>
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<td>0</td>
<td>6%</td>
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</tr>
</tbody>
</table>

* Overall 28% coinfected with HIV; ** Overall 42% coinfected with HIV; *** Significantly more frequent in HCV subtype 1a than 1b; **** Combined Los Alamos and Gilead databases for HCV subtype 1a.

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Drug resistance testing technology

- Bulk sequencing (20%)
- Allele-specific PCR (1%)
- Ultra-deep sequencing (0.001%)
HCV drug resistance in HIV-HCV coinfection

• Most DAA (but NAs) exhibit low genetic barrier for resistance and may select resistance mutations very rapidly (more than in HIV).
  → No room for monotherapy (always use in combination)
  → Predictive value of very early viral kinetics

• Broad cross-resistance between agents of the same family but for NNAs, which may be split out in 4-5 distinct groups
  → Limited use of sequential therapy for PIs

• Baseline HCV drug resistance mainly as result of natural polymorphisms (1a > 1b for PIs and NNAs) rather than as result of transmission of HCV-resistant strains.
  → Baseline drug resistance testing for HCV
  → Use of AS- PCR or alternative sensitive methods

• No effect of HIV neither ARVs on the likelihood of selecting drug resistance in HCV. Nor viceversa.
  → The risk of concomitant use of HCV and HIV antivirals is limited to drug interactions
Additive/synergistic side effects:
- anemia with telaprevir or boceprevir, ribavirin and AZT

Pharmacokinetic:
- CYP450 inhibitors or inducers

CROI: unexpected reduction of TVR and BOC with PI/r

Pharmacodynamic:
- Phosphorylation interference of RG-7128 by 3TC/FTC
Potential pharmacodynamic interactions between nucleoside analogues used as antivirals

<table>
<thead>
<tr>
<th></th>
<th>Cytidine</th>
<th>Guanosine</th>
<th>Adenosine</th>
<th>Thymidine</th>
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<tbody>
<tr>
<td><strong>HIV</strong></td>
<td>Lamivudine</td>
<td>Abacavir</td>
<td>Didanosine</td>
<td>Zidovudine</td>
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<tr>
<td></td>
<td>Emtricitabine</td>
<td></td>
<td></td>
<td>Stavudine</td>
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<tr>
<td><strong>HBV</strong></td>
<td></td>
<td>Entecavir</td>
<td>Tenofovir</td>
<td>Telbivudine</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>Adefovir</td>
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<tr>
<td><strong>HCV</strong></td>
<td>RG-7128</td>
<td>Ribavirin</td>
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<tr>
<td><strong>CMV</strong></td>
<td></td>
<td>Ganciclovir</td>
<td></td>
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<tr>
<td><strong>Herpes</strong></td>
<td></td>
<td>Acyclovir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The new hepatitis C treatment paradigm

- Test all
- Treat hard and short
- Cure most
Is HCV eradication feasible? How long will it take?

200 million

DAA

The case of Japan or Australia

HCV cases

Years

2011

New HCV diagnoses

Incident cases

Immigration flow

Spontaneous cure

Treatment-induced clearance

Death

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Implications of widespread use of DAA

- Shift in HCV genotypes in the infected population, being other genos replacing geno 1.

- Changes in HCV-infected populations, with accumulation in poor regions and/or communities within rich countries.

- Growing number of patients with drug-resistant mutant viruses and potential for transmission.
Acknowledgments

Clinic
- Pablo Barreiro
- Pablo Labarga
- Luz Martín-Carbonero
- Eugenia Vispo
- Jose Medrano

Laboratory
- Norma Rallón
- Ana Treviño
- Carmen de Mendoza
- Eva Poveda
- Sonia Rodríguez-Novoa
- Jose Miguel Benito
- Judit Morello
- Tamara Bar-Magen