Which of the following statements is true?

A. HIV is now just a chronic disease that does not reduce an individuals life expectancy
B. HIV causes an average decrease in life expectancy of 5-10 years
C. HIV causes an average decrease in life expectancy of 10-20 years
D. HIV continues to reduce life expectancy by more than 20 years; infected individuals cannot get life insurance
Life Expectancy of patients with HIV

Fig. 1. Kaplan–Meier plots of time to death (all-cause mortality) from HIV infection by HIV diagnosis rate and for people without HIV.

Nakagawa et al. AIDS 2012;26:335-343
Mathematical modeling of HIV mortality

• Predict the life expectancy for a 30 year old MSM infected with drug-sensitive virus in 2010
• Assuming a 40% chance of being a smoker and no hepatitis co-infection
• Estimated life expectancy = 75 years
• General population = 82 years
• Thus, 7 years lost attributable to HIV
• Smoking → reduces life expectancy by 7 years
• Diabetes → reduces life expectancy by 5 years
"New medicines have transformed HIV from a death sentence into a chronic disease that has a very, very small impact on your life expectancy if you start treatment early and do not smoke, drink or have diabetes,"

"HIV has a much lower impact on survival and life expectancy than cancer, severe diabetes or nasty high blood pressure."

Charles Gilks, UNAIDS country coordinator for India, December 2011
Hepatitis C has a tremendous negative impact on individuals with HIV infection
Deaths Among People With Hepatitis C in New York City, 2000–2011

Figure 2. Causes of death by quartile of age at death for all decedents reported with hepatitis C virus (HCV) monoinfection, New York City, 2000–2011. Excludes “other” category and human immunodeficiency virus/AIDS; HCV-related includes liver cancer, cirrhosis, and HCV.

Figure 3. Causes of death by quartile of age at death for all decedents reported with hepatitis C virus (HCV)/human immunodeficiency virus (HIV) coinfection, New York City, 2000–2011. Excludes “other” category; HCV-related includes liver cancer, cirrhosis, and HCV.

Epidemiology of Hepatitis C and HIV Co-infection in the US

~240,000 (30%) HIV-HCV coinfected

~800,000 HIV infected individuals in the United States

1Sulkowski et al, Clin Infect Dis 2000, supplement 1, 77-84
Natural History of HIV and Hepatitis C

Acute HIV → AIDS → Opportunistic Infections → Death

Acute hepatitis C → 85% Chronic hepatitis C → 70% Chronic hepatitis (abnormal liver biopsy) → 20% Cirrhosis → 1% Hepatocellular CA

20 years
HIV is an accelerant for Hepatitis C

Acute HIV → AIDS → Opportunistic Infections → Death

Acute hepatitis C → 20% Cirrhosis → ? years
Successful treatment of HCV reduces adverse outcomes of coinfection

Methods: Model structure

We model HIV/ HCV coinfected individuals through stages of hepatitis C disease and care

Successful HCV treatment:

- Liver fibrosis progression: 10x
- Progression to DC: 10x
- Progression to HCC: 2.6x

Delaying HCV treatment increases the likelihood of liver related deaths

- Liver-related deaths
  - Treat one year after diagnosis
  - Treat one month after diagnosis
  - Treat in F₃ vs F₂:
  - Treat in F₄ vs soon after diagnosis:

Infectious duration

- 4x↑
Hepatitis C treatment in patients with HIV
Hepatitis C: Treatment Landscape

- IFN 24 Wks: 6%
- IFN 48 wks: 13-19%
- IFN/RBV 24 wks: 31-35%
- IFN/RBV 48 wks 1998: 38-43%
- IFN/RBV 48 wks 2001: 45-47%
- PegIFN/RBV 48 wks: 54-63%
Hep C: Mono-infected versus coinfected

- **MONOINFECTED**: PegIFN/RBV 48 wks, 54-63%
- **COINFECTED**: PegIFN/RBV 48 wks, 17-35%
Available regimens for the treatment of hepatitis C

• Ledipasvir – Sofosbuvir (Harvoni)
  – ION-4 trial
• Paritaprevir/r/Ombitasvir & Dasabuvir+RBV
  – Turquoise-1 trial
• Daclatasvir - Sofosbuvir
  – ALLY-2 trial
Ledipasvir-Sofosbuvir

- **Ledipasvir**
  - Once-daily, oral, 90-mg NS5A inhibitor

- **Sofosbuvir**
  - Once-daily, oral, 400-mg NS5B inhibitor

- **Ledipasvir/Sofosbuvir FDC**
  - Once-daily, oral, fixed-dose (90/400 mg) combination tablet
  - Single-tablet regimen for hepatitis C
Ledipasvir-Sofosbuvir (ION-4 Trial)

- Phase 3, multicenter, open-label study (NCT02073656)
- HCV GT 1 or 4 patients in US, Canada, and New Zealand
- Broad inclusion criteria
  - HCV treatment-naïve or treatment-experienced
  - 20% with compensated cirrhosis
  - Platelets $\geq$50,000/mm$^3$; hemoglobin $\geq$10 mg/dL, CrCl $\geq$60 mL/min
  - HIV-1 positive, HIV RNA $<$50 copies/mL; CD4 cell count $>$100 cells/mm$^3$
- ART regimens included emtricitabine and tenofovir disoproxil fumarate plus efavirenz, raltegravir, or rilpivirine
Results: SVR12 by Prior Treatment Experience and Cirrhosis Status
HIV-HCV (ION-4)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Naive vs Experienced</th>
<th>Cirrhosis Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF 12 Weeks</td>
<td>321/335</td>
<td>142/150</td>
<td>258/268</td>
</tr>
<tr>
<td>Naive</td>
<td>96</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>Experienced</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Cirrhosis</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>94</td>
<td></td>
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</tr>
</tbody>
</table>

SVR12 (%)
Results: SVR12 in Subgroups
HIV-HCV (ION-4)

<table>
<thead>
<tr>
<th>Overall</th>
<th>LDV/SOF 12 Weeks, N=335</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
</tr>
<tr>
<td>HCV Genotype</td>
<td>1a</td>
</tr>
<tr>
<td>Baseline HCV RNA (IU/mL)</td>
<td>&lt;800,000</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
<td>&lt;30</td>
</tr>
<tr>
<td>IL28B</td>
<td>CC</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>No</td>
</tr>
<tr>
<td>Prior HCV Treatment</td>
<td>No</td>
</tr>
<tr>
<td>ARV Regimen</td>
<td>EFV + FTC + TDF</td>
</tr>
<tr>
<td>Baseline CD4 (cells/µL)</td>
<td>&lt;350</td>
</tr>
</tbody>
</table>

Statistically significant in multivariate analysis
3 Direct-Acting Antiviral (3D) Regimen

The multi-targeted 3D regimen includes:

- **Ombitasvir (OBV):** a potent NS5A inhibitor
- **Paritaprevir (PTV):** a potent NS3/4A protease inhibitor (identified by AbbVie and Enanta)
  - Boosted with ritonavir* (PTV/r)$^1$
- **Dasabuvir (DSV):** a non-nucleoside NS5B RNA polymerase inhibitor

OBV/PTV/r are coformulated as a single tablet
TURQUOISE-I: safety and efficacy of ABT-450/r/Ombitasvir, Dasabuvir, and Ribavirin in patients co-infected with hepatitis C and HIV-1

The vast majority of patients were HCV suppressed below 25 IU/mL by week 2.
TURQUOISE-I: safety and efficacy of ABT-450/r/Ombitasvir, Dasabuvir, and Ribavirin in patients co-infected with hepatitis C and HIV-1

<table>
<thead>
<tr>
<th>HCV RNA, log_{10} IU/mL</th>
<th>HCV mono-infected</th>
<th>HCV/HIV-1 co-infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>% SVR</td>
</tr>
<tr>
<td>&lt;6.09</td>
<td>504/509</td>
<td>99</td>
</tr>
<tr>
<td>6.09 – 6.56</td>
<td>495/504</td>
<td>98</td>
</tr>
<tr>
<td>6.57 – 6.91</td>
<td>492/510</td>
<td>96</td>
</tr>
<tr>
<td>&gt;6.91</td>
<td>485/504</td>
<td>96</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
We extend our thanks to:

The patients and their families

All participating investigators throughout the US, Canada, and New Zealand


CANADA: Curtis Cooper, Emmanuelle Huchet, Mark Hull, Marina Klein, David Wong

PUERTO RICO: Javier O. Morales-Ramirez, Jorge L. Santana-Bagur

NEW ZEALAND: Edward Gane, Catherine Stedman

This study was funded by Gilead Sciences, Inc.
ALLY-2 Trial
Daclatasvir-Ledipasvir (ALLY-2)

**Daclatasvir (DCV)**
- Pangenotypic* NS5A inhibitor, low potential for drug–drug interactions
- Safe and well tolerated
- Studied in > 13,000 patients
- Approved in Japan, Europe, and Brazil; under regulatory review in the US

**Sofosbuvir (SOF)**
- Pangenotypic nucleotide NS5B inhibitor, low potential for drug–drug interactions
- Safe and well tolerated
- Approved in combination with other HCV agents in the US, Europe, and Canada
Daclatasvir-Ledipasvir (ALLY-2)

All-Oral DCV + SOF in Patients With High Unmet Medical Need

**ALLY-1**
- Patients with cirrhosis or post-liver transplant
- GT 1 to 6
- DCV + SOF + RBV, 12 weeks
  
  N = 113

**ALLY-2**
- Patients with HIV coinfection
- GT 1 to 6
- DCV + SOF, 8 or 12 weeks
  
  N = 203

**ALLY-3**
- Patients with GT 3 infection
- Treatment-naive or treatment-experienced
- DCV + SOF, 12 weeks
  
  N = 152

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Daclatasvir-Ledipasvir (ALLY-2)

- **Primary endpoint:** SVR12 in treatment-naive patients with GT 1 treated for 12 weeks
- **Standard DCV dose is 60 mg**
  - Dose-adjusted for concomitant ARV therapy: 30 mg with ritonavir-boosted PIs, 90 mg with NNRTIs except RPV

* HCV RNA <LLOQ (TD or TND) at posttreatment Week 12, assessed using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).
Conclusions from Coinfection Trials

- All-Oral Regimens for Coinfected patients are highly effective with response rates >90%
- Regimens are safe and well-tolerated and there is no loss of control of HIV infection
- Response rates are similar to that of monoinfected patients
- There are some drug-drug interactions to consider with regards to HIV therapy
Not

“It’s the immune system, stupid”
Hep C: Mono-infected versus coinfected

PegIFN/RBV 48 wks
MONOINFECTED
54-63%

PegIFN/RBV 48 wks
COINFECTED
17-35%
Hep C: Mono-infected versus coinfected

DAAs 12 weeks MONOINFECTED

DAAs 12 weeks COINFECTED

90-98%
HIV treatment (HAART)
HIV treatment in a nutshell

- We always use at least 3 drugs
- Most popular backbone is Truvada (tenofovir + emtricitabine)
- 3rd drug is often Efavirenz (non-nucleoside analogue)
- Other popular 3rd drug option is Atazanavir/R (protease inhibitor, causes hyperbilirubinemia)
- Raltegravir is an integrase inhibitor that is being used more frequently due to potency and lack of side effects
Objective:
- Determine need for ART switch prior to initiation of simeprevir-containing HCV regimen
- Determine feasibility of ART switch to allow for use of simeprevir

Key Results:
- Majority of our HIV-HCV patients (76%) will need a change to antiretroviral therapy in order to accommodate use of simeprevir for treatment of HCV
- Limitations were primarily driven by protease inhibitor (PI) regimens
  - 31% on a boosted -PI could not be switched to a safe and effective ART regimen
  - Most often due to use of salvage regimen where PI has become indispensable

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>N (%)</th>
<th>N=127</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>90 (71%)</td>
<td></td>
</tr>
<tr>
<td>Race, African American</td>
<td>69 (54%)</td>
<td></td>
</tr>
<tr>
<td>Known HCV Genotype: 1*</td>
<td>81 (66%)</td>
<td></td>
</tr>
<tr>
<td>CD4 &lt;200 cells/mm³</td>
<td>14 (13%)</td>
<td></td>
</tr>
<tr>
<td>HIV Viral Load &gt;200</td>
<td>22 (17%)</td>
<td></td>
</tr>
<tr>
<td>Advanced Liver Disease</td>
<td>29 (23%)</td>
<td></td>
</tr>
<tr>
<td>Not on ART</td>
<td>8 (7%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>ART Switch Required</th>
<th>ART Switch Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>97 (76%)</td>
<td>30 (24%)</td>
</tr>
</tbody>
</table>

-safe Regimens
- SMV + RAL, RPV, T20, MVC, TDF, FTC, 3TC, ABC
- IDV + all regimens except EVG/cobi and TDF + EFV or PI/r
- FTV/a + RAL, TDF, FTC, 3TC, ATV, T20
Need to switch with other regimens

Key Results:
- Majority of our HIV-HCV patients (76%) will need a change to antiretroviral therapy in order to accommodate use of simeprevir for treatment of HCV
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<th>ART Switch Not Required</th>
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<tr>
<td>Simeprevir</td>
<td>97 (76%)</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>81 (64%)</td>
</tr>
<tr>
<td>Paritaprevir/r</td>
<td>91 (72%)</td>
</tr>
</tbody>
</table>
CONCLUSIONS

• Hepatitis C substantially reduces the life expectancy of individuals with HIV infection
• Don’t delay treatment of Hep C in HIV coinfected patients
• Treatment is short (12 weeks), highly effective (>90%), and safe
• Most patients will need an anti-retroviral treatment switch before starting treatment for Hep C