Using DAA therapy to eliminate HCV
Dream Or Reality?

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NZLTU, Auckland City Hospital

The Life cycle of an Infectious Disease

1. Discovery  ✓
2. Reliable diagnostic test  ✓
3. Effective therapy  ✓
4. Protective vaccination
5. Control of disease burden
6. Elimination of infection
7. Global eradication of infection

Control vs. Elimination vs. Eradication

**Control:** reduction in prevalence, morbidity/mortality of an infectious disease to a locally acceptable level.

**Elimination:** reduction to zero of the incidence of disease or infection in a defined geographical area, but requires continued measures to prevent re-establishment of transmission (e.g. measles, polio)

**Eradication:** permanent reduction to zero of the worldwide incidence of infection, with no further control measures required (e.g. smallpox).

Hepatitis C is silent global epidemic of 21st Century

- 1.1% i.e. 80 million (62-103) infected

Global burden from liver disease is increasing more rapidly than any other disease

Global Burden of Disease study 1990 - 2013
estimated age-sex-specific all-cause mortality

- CVS
- Diarrhoea
- Trauma
- Resp
- Neonatal
- AIDS
- Liver
- Tropical ID
- GI
- Malaria
- Diabetes

HCV is now the leading cause of liver-related morbidity and mortality

Global Burden of Disease study 1990 - 2013 estimated age-sex-specific all-cause mortality

Deaths due to HCV more than doubled between 1990 - 2013; Liver cancer deaths due to HCV increased 300%

Disease burden from hepatitis C will continue to increase as the infected population gets older

Live expectancy reduced in HCV-infected adults

Premature death (<65 years) and median age at death among all deaths, NYC (2000–2011)

Liver transplant Decompensation HCC

Germany France

Can Vaccination eradicate HCV?
Best candidates in development

<table>
<thead>
<tr>
<th>Approach</th>
<th>Antigen</th>
<th>Company</th>
<th>Subjects</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>Recombinant proteins</td>
<td>gpE1; gpE2</td>
<td>Chiron; CSL InnoGenetics</td>
<td>Chimps; Humans</td>
<td>N; N</td>
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<tr>
<td>Core</td>
<td>Novartis</td>
<td>Chimps</td>
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<td>NS3-core</td>
<td>Globeimmune</td>
<td>Humans</td>
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<tr>
<td>Peptides</td>
<td>T-cell epitopes</td>
<td>Intercell AG</td>
<td>Humans (HLA-A2+)</td>
<td>N</td>
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<tr>
<td>Viral vectors</td>
<td>Adenovirus</td>
<td>Okairos; NIH</td>
<td>Chimps; Humans</td>
<td>Y; ?</td>
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<tr>
<td>Vaccinia</td>
<td>Transgene; NYBC</td>
<td>Chimps</td>
<td></td>
<td>Y</td>
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<tr>
<td>Virus-like particles</td>
<td>Core-E1E2</td>
<td>NIH</td>
<td>Chimps</td>
<td>Y</td>
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<tr>
<td>DNA vaccine with electroporation</td>
<td>HCV NS3, 4a, 4b, 5a</td>
<td>Tripart; VGX/Inovio</td>
<td>Humans</td>
<td>?</td>
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The Life cycle of an Infectious Disease

1. Discovery
2. Reliable diagnostic test
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5. Control of disease burden
6. Elimination of infection
7. Global eradication of infection
Can Vaccination eradicate HCV?  
Many barriers to successful vaccine development

HCV FACTORS
- HCV genomic diversity
  - An6-E1/E2 escape mutants
  - CD4+/CD8+ escape mutants
- T cell exhaustion
- Impaired DC maturation
- HCV NS3/5A inhibits IFN

PATIENT FACTORS
- Host genomic diversity
  - IL28B SNP
- Limited TCR repertoire
- MHC Class 1 restriction
- Aging population
- HIV co-infection

OTHER FACTORS
- Chimpanzee is the only animal model for vaccine
- Preclinical results do not translate to humans
- Reduced interest in need for prophylaxis
- Vaccinating PWID may not be practical

Can Public Health interventions eradicate HCV?  
Recent decrease in Incidence of HCV infection

HCV notifications in Australia: 1991-2013

Can Public Health measures eradicate HCV?  
HCV Prevention through Harm Reduction

- HCV incidence among PWID in Australian NSP Survey

Can Public Health measures eradicate HCV?  
Harm reduction cannot eliminate HCV in isolation

- OST and NEX alone will reduce prevalence in PWID by maximum of 30% over 10 years
- BUT prevent HIV, drug-related deaths, crime

Can Public Health measures eradicate HCV?  
Only 41% countries have needle syringe programmes

Can Public Health measures eradicate HCV?  
Only 35% countries have opioid substitution therapy
Could HCV be eliminated through antiviral therapy?

Current situation

- All HCV patients
- Diagnosed
- Treatment uptake
- CURE

PEG/RBV ± PI
- 100%
- 40%

Could HCV be eliminated through antiviral therapy?

DAA therapies with higher SVR rates

- All HCV patients
- Diagnosed
- Treatment uptake
- CURE

PEG/RBV ± PI
- 90% SVR
- 40%

Treatment and Diagnosis Rate by Country, 2013

- Estimated HCV prevalence, diagnosis and treatment rates in 2013

Could HCV be eliminated through antiviral therapy?

DAA therapies combined with increased uptake

- All HCV patients
- Diagnosed
- Treatment uptake
- CURE

PEG/RBV ± PI
- 90% SVR
- 90% SVR and increased uptake

DAAs offer a new treatment paradigm for HCV

More effective and safer therapies

- Receptor binding and endocytosis
- Fusion and uncoating
- Transport and release
- RNA replication
- N-terminus

Combine 2 or more DAAs
- Additive antiviral effect
- High barrier to resistance
- IFN-free and RBV-free
- Shortened duration

Simple
- Short duration
- Low pill burden
- Minimal monitoring
- Minimal drug-drug interactions

Affordable
- all populations

Effective
- Pangenotypic
- >95% Cure rates
- Improved survival
- Improved QoL

Safe
- NO Interferon
- No Ribavirin
- No toxicity
- No DDIs

Special Pops
- Elderly
- Liver failure
- Renal failure
- HIV co-infection

DAAs
- Non-NUC NS5B inhibitors
- NUC NS5B inhibitors

Ledipasvir plus Sofosbuvir (Harvoni™) 1st IFN and RBV-free Single Tablet Regimen

- Ledipasvir (LDV)
  - Picomolar potency against GT 1a and 1b
  - Effective against NS5B RAV S282T
  - Once-daily, oral, 90 mg
- Sofosbuvir (SOF)
  - Potent antiviral activity against GT 1–6
  - Effective against NS5A RAVs
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet
- Ledipasvir/Sofosbuvir STR
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet
  - >2000 patients treated in clinical trials
  - >200,000 treated in real world

AbbVie Multi-Targeted 3-DAA (3D) Regimen

Ombitasvir (OBV)
N5S5A inhibitor

Paritaprevir (PTV)
NS3/4A protease inhibitor boosted with ritonavir

Dasabuvir (DSV)
A non-nucleoside NS5B RNA polymerase inhibitor

AbbVie 3D Phase III Trials in HCV GT-1

- Ombitasvir (OBV)
- Paritaprevir (PTV)
- Dasabuvir (DSV)

Merck MK2 regimen in HCV GT 1, 4, 5 and 6: Grazoprevir/Elbasvir Fixed Dose Combination

- Grazoprevir (MK-5172)
  - HCV NS3/4A inhibitor
  - 100 mg once daily, oral

- Elbasvir (MK-8742)
  - HCV NS5A inhibitor
  - 50 mg once daily, oral

- Broad in vitro activity against most HCV genotypes
- Retains in vitro activity against many clinically relevant RAVs
- All-oral, once-daily regimen

AbbVie-3D Phase III Trials in HCV GT-1

SAPPHIRE-1.2 GT1a no cirrhosis
PEARL-2.3 GT1b no cirrhosis
TURQUOISE-2 GT1a Cirrhosis
TURQUOISE-3 GT1b Cirrhosis

Merck Phase III Trials in HCV GT-1/4/6 12 weeks GZR/EBR without RBV: C-EDGE Studies

Overall Efficacy across the Phase 3 Program

SVR in 97% (1886/1951) Relapse in 1.8% (36/1951)

ION-1 Treatment-naïve including cirrhotics
ION-3 Treatment-naïve non-cirrhotics
ION-2 Treatment-experienced including cirrhotics

Data on File, Gilead Sciences, Inc.

References:
Patients with decompensated cirrhosis
- HIV/HCV co-infection
- Some DDIs with SOF/RBV
- Safe and well tolerated

ALLY 3 Study (GT 1 or 4)
- SVR12 (%)
  - 100
  - 96
  - 92
  - 88
  - 84
  - 80
  - 76
  - 72
  - 68
  - 64
  - 60
  - 56
  - 52
  - 48
  - 44
  - 40
  - 36
  - 32
  - 28
  - 24
  - 20
  - 16
  - 12
  - 8
  - 4
  - 0

SVR Rates in Compensated HCV GT 1

Safe & effective therapy in decompensated cirrhosis
SOLAR Studies of 12 and 24 wks Harvoni + RBV
- 12 Wks LDV/SOF+RBV
- 24 Wks LDV/SOF+RBV

SVR12 (%)
- 67
- 100
- 80
- 66
- 40
- 20
- 5
- 0

Pan-genotypic Regimen NUC + NS5AI
Sofosbuvir + Daclatasvir in GT 1 - 6
- ALLOY 3 Study (GT-3)
- All I Study (GT 1-6)
- Compensated
- Decompensated

SVR12 (%)
- 96
- 63
- 82
- 80
- 83
- 64
- 44
- 24
- 0

Pan-genotypic Regimen: NUC + 2nd Wave NS5AI
Sofosbuvir + Velpatasvir (GS-5816) in GT 1 - 6
- Phase 2, open-label studies of GS-5816/SOF+RBV for 12 weeks

AbbVie Viekira Pak, Gilead Harvoni and Merck MK2
Oral DAA therapies in HCV GT 1

- In clinical trials and real world studies, IFN-free DAA regimens are well tolerated with >95% SVR after 8-12 weeks in treatment-naive GT 1
- What about other “difficult-to-cure” populations
  1. Patients with decompensated cirrhosis
  2. Patients with HIV co-infection
  3. Patients infected with other HCV genotypes

Safe & effective therapy in HIV co-infection
No longer a baseline predictor of response?
The regimen which is the shortest duration possible

What DURATION of treatment is needed to eradicate HCV without Interferon?

What DURATION of treatment is needed?
New 3 Phase Model with Intra-cellular dynamics

Can these new therapies be used to eliminate HCV?
What would it take to reduce disease burden in ANZ
- Funding of new oral therapies for all cirrhotics
- Access to Fibroscan to identify cirrhotics
- Capacity to treat 2%/year (100% increase)

What would it take to eliminate HCV from ANZ
- Funding of the new oral therapies for everyone
- Community testing to identify the 60,000 Australians and New Zealanders who remain undiagnosed
- Capacity to treat 10%/year (1000% increase)
- Treat those who are transmitting HCV (PWID, prisoners) i.e. “treatment as prevention

What would it take to eliminate HCV from ANZ
- Funding of new oral therapies for all cirrhotics
- Access to Fibroscan to identify cirrhotics
- Capacity to treat 2%/year (100% increase)

What barriers still remain to national elimination and global eradication of Hepatitis C?
1. Low diagnosis rates
   - Targeted testing, Point-Of-Care tests in community
   - Community access to Fibroscan
2. Low treatment uptake
   - Wide access to DAA Therapy
     - Simplified referral and treatment algorithms
     - Test and treat in the community
3. High cost of DAA
   - Government investment in High Income countries
   - Donor access programs in Low Income countries

What would it take to eliminate HCV from ANZ
PBAC recommendations: March 2015

<table>
<thead>
<tr>
<th>GT</th>
<th>Therapy</th>
<th>Weeks</th>
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<tbody>
<tr>
<td>1</td>
<td>Harvoni (LDV/SOF) SOF/PEG/RBV</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td></td>
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<tr>
<td></td>
<td>Viekira Pak (AbbVie-3D)</td>
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</tr>
<tr>
<td>2</td>
<td>SOF + RBV</td>
<td>12-16</td>
</tr>
<tr>
<td>3</td>
<td>SOF + Daclatasvir</td>
<td>12</td>
</tr>
</tbody>
</table>

- **ALL STAGES** of liver disease
- **S85 PRESCRIBING**: Community Pharmacy & GPs

POSSIBLE PBS LISTING DEC 2015 OR EARLY 2016
What would it take for global eradication of HCV?

**DAA Access Programmes**

**FIERCE PHARMA** (http://www.fiercepharma.com)

Gilead in talks with Indian drugmakers to sell Sovaldi at cut-rate prices

February 4, 2014 | By Tracy Staton

"We are going to give license[s] to Indian companies," Gilead is aiming for a price on Sovaldi of about $2,000 for a treatment course. He said. The U.S. sticker price is $84,000 for a 12-week cycle.

**GILEAD OFFERS EGYPT NEW HEPATITIS C DRUG AT 99 PERCENT DISCOUNT**

BY MAGGIE FICK CAIRO/LONDON Fri Mar 21, 2014 4:10pm EDT

(Reuters) - Sovaldi, has offered to supply the medicine to Egypt at a 99 percent discount to the U.S. price. While the drug will still cost $900 for a 12-week course of treatment, that is a fraction of the $84,000 charged for a course of treatment in the United States.

What would it take for global eradication of HCV?

**World Health Organisation Targets for 2030**

WHO Resolution on Viral Hepatitis (WHA67.6) May 22nd 2014

Expand and enhance services

Decrease new infections

Decrease deaths

Reduce global suffering and costs

- 90% diagnosed
- 60% eligible-tREATED
- 90% treated-cURED
- 50% PWID within harm reduction services by 2020
- 70% reduction in HCV incidence (95% by 2020)
- 0 new infections from unsafe medical practices by 2020
- 75% reduction in new infections from unsafe blood transfusion
- 75% reduction in HCV-related deaths

• 50% PWID within harm reduction services by 2020
• 70% reduction in HCV incidence (95% by 2020)
• 0 new infections from unsafe medical practices by 2020
• 75% reduction in new infections from unsafe blood transfusion
• 75% reduction in HCV-related deaths


PWID: people who inject drugs
WHO: World Health Organization

Thanks to

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