Infectious Diseases Update

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Disclosures

- Nil

Outline

- Hepatitis C Virus (HCV)
  - New direct-acting antivirals (DAAs) for the treatment of HCV
  - Treatment of “special populations” with HCV
  - Drug-drug interactions with HCV DAAs
- Human Immunodeficiency Virus (HIV)
  - Improved life expectancy in people living with HIV
  - Initiation of antiretroviral therapy in early asymptomatic HIV infection
  - Organ transplantation in HIV-infected patients
- Zika Virus
  - “Emerging threat”
  - Zika virus and Guillain Barre Syndrome
  - Microcephaly and Zika virus

Hepatitis C Virus (HCV) in Australia

- HCV is the leading cause of advanced liver disease and adult liver transplantation

- 230,470 people living with chronic HCV
  - 75% diagnosed
  - 20% received treatment
  - 11% cured

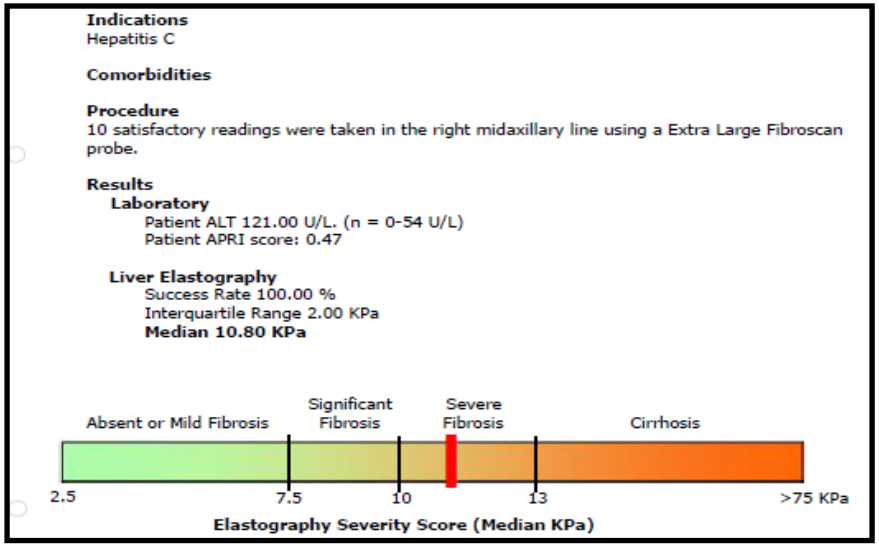
- Advanced liver disease (liver fibrosis stage ≥ F3)
  - Proportion doubled in the last decade
  - 9% (2004) → 19% (2014)

Harjarizadeh. Global Antiviral Journal 2015;11:85

Case

Tom

- 38 year old male
- Chronic HCV
  - Genotype 3
  - Treatment naïve
  - HCV RNA 247,000
  - ALT 121, AST 33
- Schizophrenia
  - Community treatment order
  - Zuclopenthixol intramuscular fortnightly
  - Quetiapine 400mg oral bd
- Smoker: 20 pack year
- No alcohol
- Intravenous drug use
  - Methamphetamines



Interferon (IFN) + Ribavirin (24 weeks)

- Sustained virological response (SVR24)
  - 75-80%
- Significant concern with IFN

Sofosbuvir + Daclatasvir oral 12 weeks

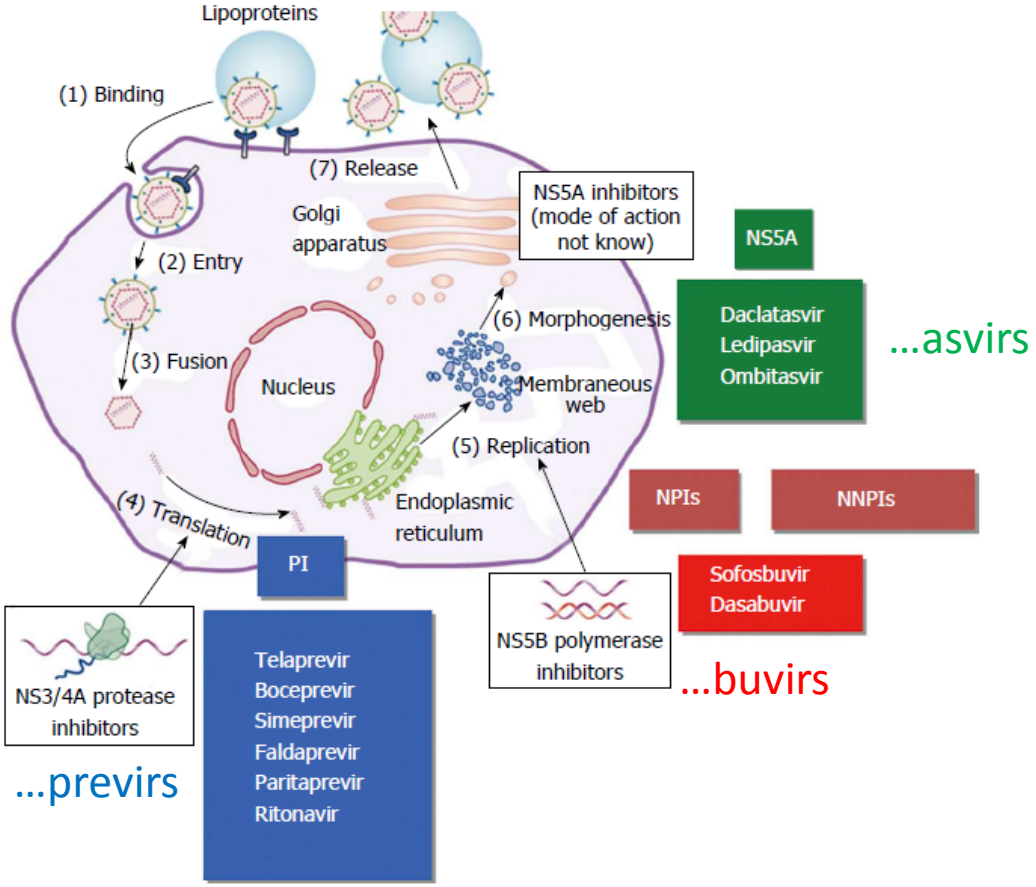
- SVR12 ≥94 %

Main issues

- Compliance
- Drug-drug interactions

Nelson. Hepatol 2015;61:1127

Direct Acting Antiviral (DAA) Therapy



- Combination therapy
- Genotype specific
- 12-24 weeks of therapy
  - Presence of cirrhosis
- Sustained virological response (SVR12) ≥ 90%

Bertino. World J Hepatol 2016;8:92
Alexopoulou. Ann Gastroenterol 2015;28:55

New DAAs in Australia

Drug	Class	Genotype Resistance profile	Adverse effects	Pharmacokinetics and contraindications
Sofosbuvir	NS5B nucleoside polymerase inhibitor	Pangenotypic High barrier to resistance	Fatigue, headache, nausea, insomnia, anaemia	Renal clearance main form elimination Dose reduction not required if glomerular filtration>30mL/minute **Transported P-glycoprotein** **Co-administration with amiodarone is contraindicated due to serious risk of bradycardia**
Ledipasvir	NS5A inhibitor	Genotype 1,4,6	Fatigue and headache	Biliary excretion main route elimination **Solubility decreases as gastric PH increases**
Daclatasvir	NS5A inhibitor	Pangenotypic	Fatigue, headache and nausea	No dose adjustment required with hepatic impairment **Substrate of CYP3A4** **Substrate and inhibitor of P-glycoprotein**
Paritapravir-ritonavir	NS3/4A protease inhibitor	Genotype 1,4,6	Fatigue and nausea	**Metabolised CYP3A4, contraindicated pregnancy** **Ritonavir strong inhibitor CYP3A4** **Contraindicated decompensated liver disease**
Ombitasvir	NS5A inhibitor	Genotype 1,4,6	Fatigue and nausea	**Hepatic metabolism** with hydrolysis **+/- CYP3A4** **Contraindicated decompensated liver disease**
Dasabuvir	NS5B non-nucleoside polymerase inhibitor	Genotype 1,4,6	Fatigue and nausea	**Metabolized CYP2C8**, predominant metabolite cleared via biliary excretion **+/- CYP3A4** **Contraindicated decompensated liver disease**

Bertino. World J Hepatol 2016;8:92. European Association for the Study of the Liver. J Hepatol 2015;63:199
US FDA. 2015. *Drug Safety Communication*. [ONLINE] Available at:http://www.fda.gov/Drugs/DrugSafety/ucm439484.htm. [Accessed 7 May 2016]

HCV Therapy in Australia

Treatment protocols for people with compensated liver disease and HCV genotype 1 infection

Regimen	HCV Gt	Treatment duration				Efficacy (SVR)
		No cirrhosis		Cirrhosis		
		Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*	
Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily	1a/b	8 weeks OR 12 weeks‡	12 weeks§	12 weeks	24 weeks§	≥ 95%
Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily† ± Ribavirin 1000/1200 mg, orally, daily (weight-based)††	1a/b	12 weeks	12 weeks OR 24 weeks¶	12 weeks + ribavirin OR 24 weeks (no ribavirin)	12 weeks + ribavirin OR 24 weeks (no ribavirin)¶	≥ 95%
Paritaprevir–ritonavir (150 mg/100 mg), orally, daily + Ombitasvir 25 mg, orally, daily + Dasabuvir 250 mg, orally, twice daily ± Ribavirin 1000/1200 mg, orally, daily (weight-based)††	1a	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin	12 or 24 weeks + ribavirin**	≥ 95%
	1b	12 weeks	12 weeks	12 weeks	12 weeks	

Thompson. Med J Aust 2016;204:268

http://www.pbs.gov.au/healthpro/explanatory-notes/general-statement-pdf/general-statement-hepatitis-c.pdf

HCV Therapy in Australia

Treatment protocols for people with compensated liver disease and HCV genotype 2 or 3 infection

Regimen	HCV Gt	Treatment duration				Efficacy (SVR)
		No cirrhosis		Cirrhosis		
		Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*	
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)**	2	12 weeks	12 weeks§	12 weeks	12 weeks§	> 90%
Sofosbuvir 400 mg, orally, daily + Daclatasvir, 60 mg, orally, daily†	3	12 weeks	12 weeks¶	24 weeks	24 weeks¶	> 85%
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)**	3	24 weeks	24 weeks§	24 weeks	24 weeks§	58%–95%‡
Sofosbuvir 400 mg, orally, daily + PegIFN, subcutaneously, weekly + Ribavirin 1000/1200 mg, orally, daily (weight-based)**	3	12 weeks	12 weeks	12 weeks	12 weeks	> 85%

Thompson. Med J Aust 2016;204:268

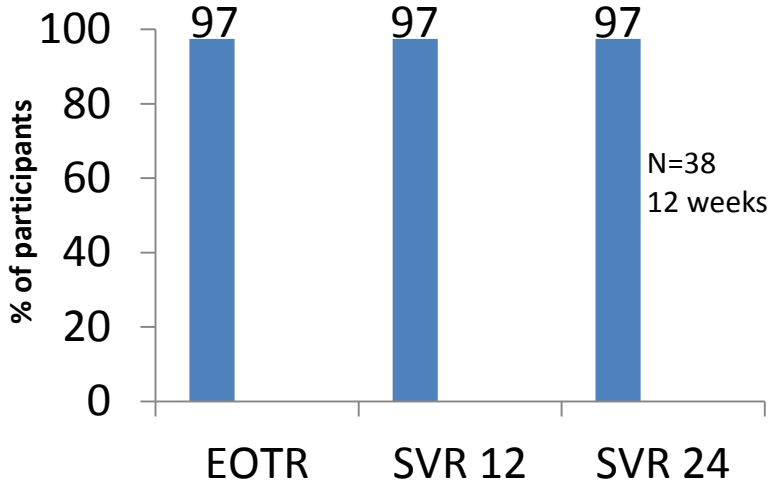
Special Populations?

Patient group	Regimen	SVR12	Issues	Reference
HIV coinfection	N=203 Genotype 1-4 Daclatasvir + Sofosbuvir 8 versus 12 weeks	8 weeks: 76% **12 weeks: 98%**	No 8 week regimens Review drug-drug interactions with antiretroviral therapy	Wyles. N Engl J Med 2015; 373:714
	N=335 Genotype 1 or 4 Ledipasvir + Sofosbuvir	**96%**	Review drug-drug interactions with antiretroviral therapy	Naggie. N Eng J Med 2015;378:705
Chronic kidney disease (CKD)	Sofosbuvir Trials recruiting		Sofosbuvir in renal impairment no data with eGFR<30mL/minute/1.73m^2	Fabrizi. Kidney International 2015;89:988
	N=20, genotype 1 Paritaprevir +ritonavir + ombitasvir +dasabuvir +/- Ribavirin (200mg genotype 1a) 12 weeks CKD stage 4-5 Ongoing	**100%** 6 patients with available data	6/20 patients required ribavirin interruption for haemaglobin drop of >2g/dL or haemaglobin < 10g/dL	Pockros. Hepatol 2015;62:S235
	N=224, genotype 1 Randomized CKD stage 4-5 N=111: Grazoprevir (NS3/4A) + elbasvir (NS5A) N=113: placebo	**99%**		Roth. Lancet 2015;386:1537
	N=34, Genotype 1 Daclatasvir + Asunaprevir 12 weeks Haemodialysis patients	**95.5%**		Suda. J Gastroenterol 2016;1007:1162-8

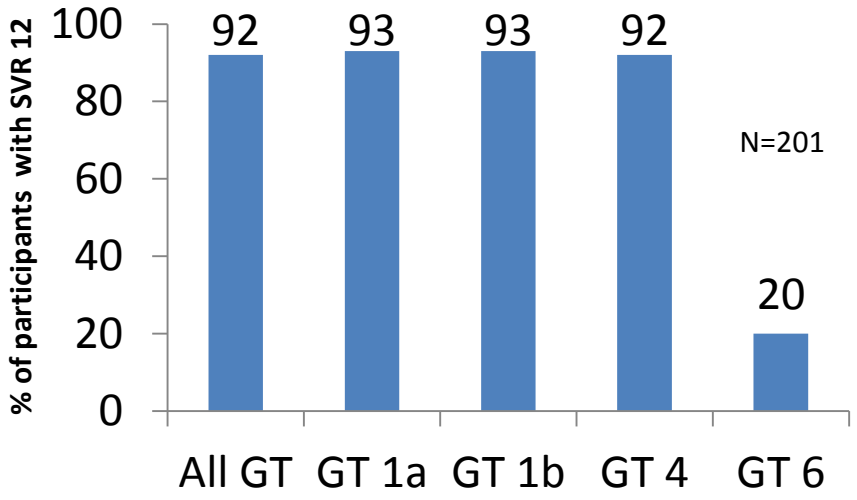
DAAs in People Who Inject Drugs (PWID)?

- Injecting drug use is the main mode of transmission in Australia
- Treatment of PWID will be key to:
  - Reduce morbidity and mortality
  - Prevent transmission
- Pegylated interferon and ribavirin in PWID resulted in pooled SVR 56%

Paritepravir/ritonavir, ombitasvir, dasabuvir +/- ribavirin among people on opiate substitution therapy



C-EDGE C0-STAR, 12 weeks grazoprevir + elbasvir



Aspinall. Clin Infect Dis 2013;57:S80, Lalezari. J Hepatol 2015; 63:364, Dore. Hepatol 2015;62:227A.

Potential for Drug-Drug Interactions (DDIs) with the new DAAs?

- Numerous and complex drug interactions possible
  - DDIs should be assessed in all patients
  - Liverpool Hep Interactions available at www.hep-druginteractions.org/

- New DAAs
  - P-glycoprotein
  - Cytochrome P450 enzymes

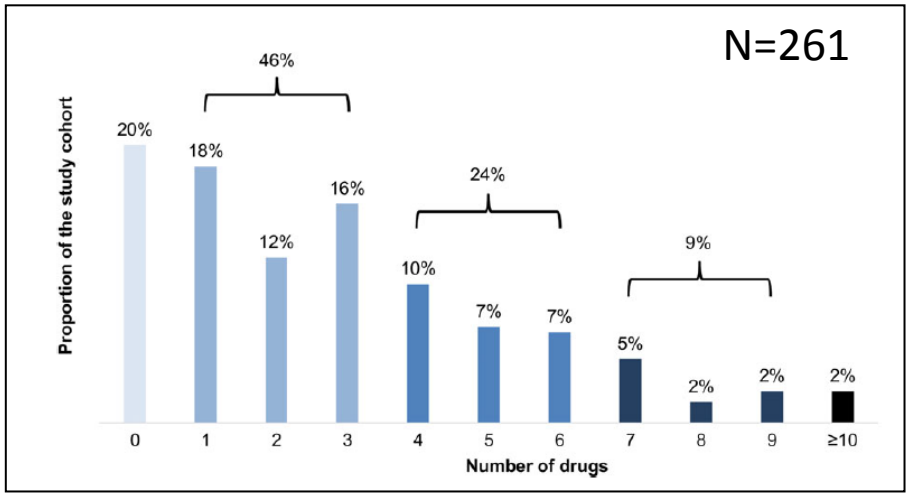
- Combination DAA therapy

- Eligibility for HCV therapy increased
  - Co-morbidities
  - Advanced disease

Siederdissen. Clin Infect Dis 2016; 62: 561
European Association for the Study of the Liver. J Hepatol 2015;63:199

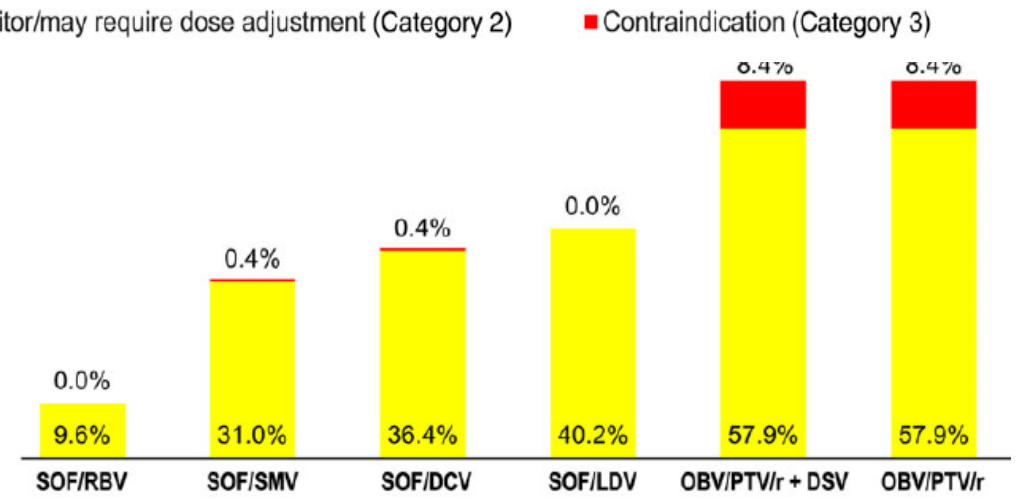
Drug-Drug Interactions

Number of drugs at baseline



SOF: sofosbuvir
RBV: ribavirin
SMV: simeprevir
DCV: daclatasvir
LDV: ledipasvir
OBV: ombitasvir
PTV: paritaprevir
DSV: dasabuvir

Proportion with significant interactions



Siederdissen. Clin Infect Dis 2016;62:561

Drug-Drug Interactions

DDIs between DAAs and lipid lowering agents

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

DDIs between DDAs and illicit recreational drugs

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hy-droxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

DDIs between DDAs and immunosuppressants

	SIM	DCV	SOF	SOF/ LDV	3D
Azathioprine	•	•	•	•	•
Cyclosporine	•	•	•	•	•
Etanercept	•	•	•	•	•
Everolimus	•	•	•	•	•
Mycophenolate	•	•	•	•	•
Sirolimus	•	•	•	•	•
Tacrolimus	•	•	•	•	•

Green: No clinically significant drug interaction

Amber: Potentially significant drug interaction

Red: Drugs should not be co-administered

3D: Paritapravir/ritonavir, ombitasvir + dasabuvir

European Association for the Study of the Liver. J Hepatol 2015;63:199

Summary

- HCV infection is CURABLE
- All patients with HCV should be considered for treatment (HCV RNA detectable) including PWID
- All patients should be evaluated for cirrhosis
- Highly efficacious and tolerable therapy with HCV DAAS is available on the PBS
- Drug-drug interactions with concomitant medications need to be assessed

Narrowing the Gap in Life Expectancy Between HIV-infected and HIV-uninfected

- Cohort study California 1996-2011
  - 25,768 HIV-infected and 257,600 HIV-uninfected
  - Estimated "life expectancy" at age 20

	Life expectancies at age 20 , 2008-2011 (95% confidence interval)		
	HIV-infected CD4≥500 cells /µL	**HIV-uninfected**	**Difference**
Overall	54.5 (51.7-57.2)	62.3 (61.9-62.8)	7.9 (5.1-10.6)
No hepatitis B or C	55.4 (52.6-58.2)	62.6 (62.1-63.1)	7.2 (4.4-10.0)
No drug or alcohol abuse	57.2 (54.6-59.9)	63.8 (63.3-64.3)	6.6 (3.9-9.3)
No smoking	58.9 (55.8-62.1)	64.3 (63.6-65.0)	5.4 (2.2-8.7)
No hepatitis B or C, drug or alcohol abuse or smoking	59.2 (56.0-62.4)	65.0 (64.2-65.7)	5.7 (2.4-9.0)

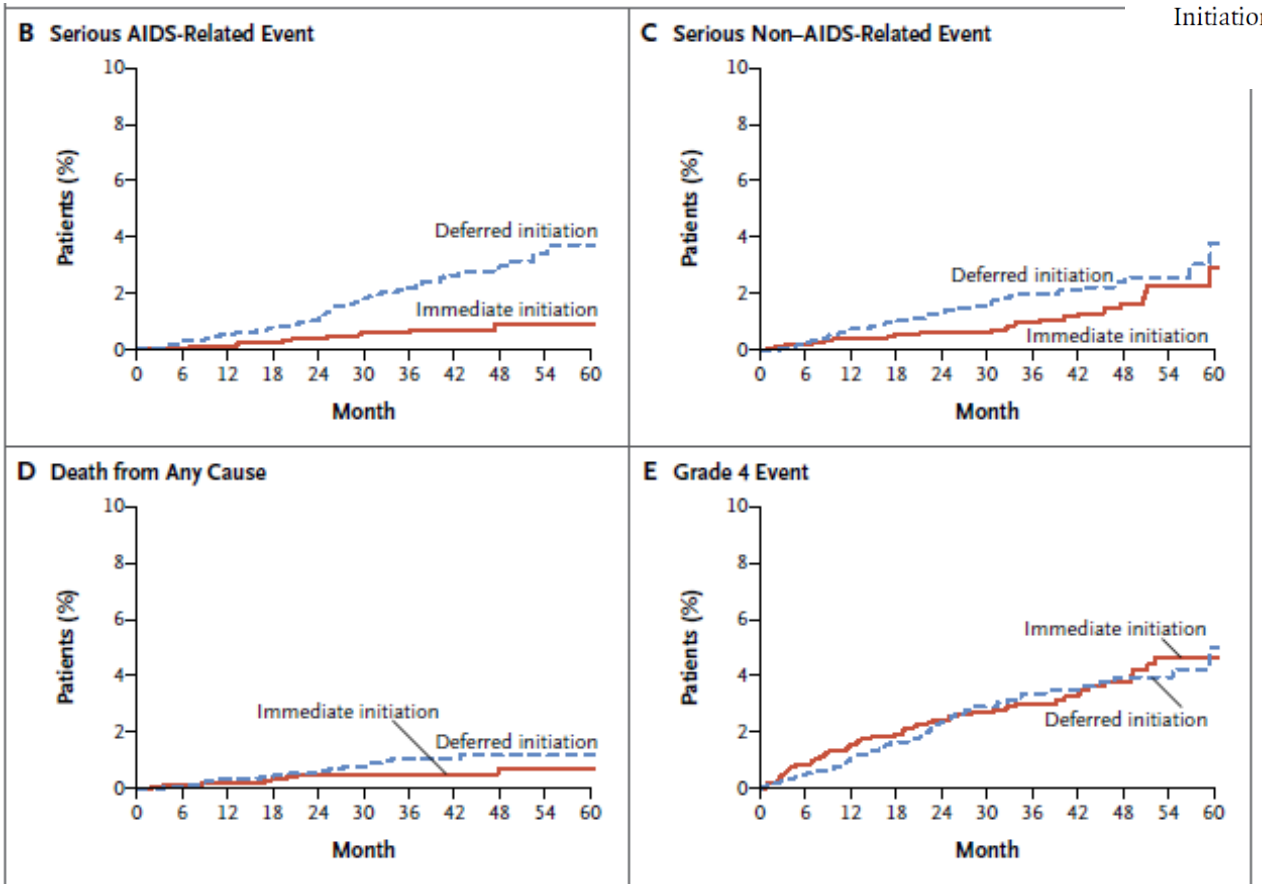
Marcus. J Acquir Immune Defic Syndro 2016; [Epub ahead of print]

When to Start Antiretroviral Therapy?

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*



N=4685
Mean follow up 3 years
Randomised CD4 >500 cells /µL
Immediate antiretroviral therapy
Versus
Deferred antiretroviral therapy
CD4 <350 cells /µL

INSIGHT START Study Group. N Engl J Med 2015;373:795

HIV and Organ Transplantation

- Observational cohort study
  - 125 liver and 150 kidney HIV-positive transplant recipients
  - Compared with candidates that were not transplanted and HIV-negative national registry controls

Table 2. Graft failure and death among HIV-positive transplant recipients and HIV-uninfected registry control groups[a].

	Graft failure	Death
Kidney recipients		
HIV-TR recipients ($N=150$)	46 (30.7%)	17 (11.3%)
Unmatched controls ($N=85\,153$)	20 757 (24.4%)	10 933 (12.8%)
Demographic-match controls ($N=600$)	174 (29.0%)	76 (12.7%)
Risk-match controls[a] ($N=600$)	162 (27.0%)	71 (11.8%)
Liver recipients		
HIV-TR recipients ($N=124$)	57 (46.0%)	45 (36.3%)
Unmatched controls ($N=32\,399$)	10 342 (31.9%)	8475 (26.2%)
Demographic-match controls ($N=496$)	170 (34.3%)	133 (26.8%)
Risk-match controls[a] ($N=496$)	161 (32.5%)	147 (29.6%)

[a]For each endpoint, separate risk models were used to identify the two risk match control groups.

Roland. AIDS 2016;30:435

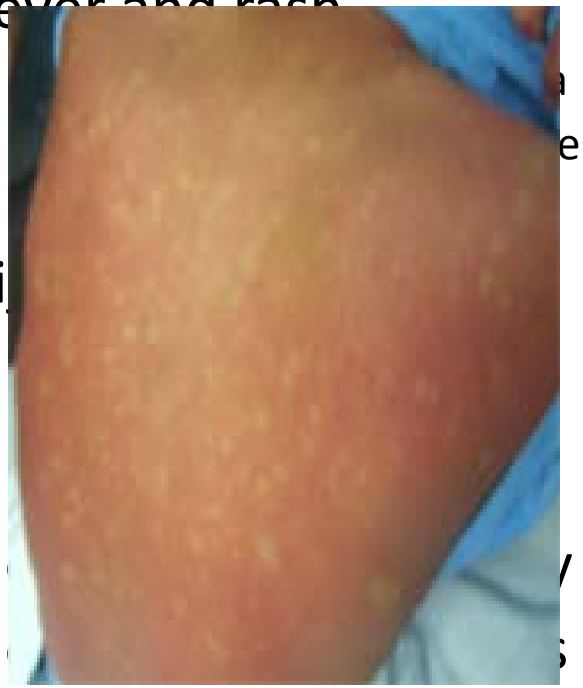
HIV and Organ Transplantation

- Liver transplantation
  - Survival benefit in patients with model for end-stage liver disease (MELD) ≥ 15
  - Higher relative hazard of graft loss and death but not related to HIV factors
- Kidney transplantation
  - Higher rate of graft loss ?related to rejection
  - No significant increase in risk of death
- Liver and kidney transplantation is a proven option in HIV-positive individuals

Roland. AIDS 2016;30:435

Returned Traveller

- 30 year old male
- Fever and rash
- Fi
- N
- N
- No new sexual contacts



Differential diagnosis

- Dengue fever
- Chikungunya
- Measles
- Enterovirus/adenovirus
- Rickettsia
- Zika virus

Zika virus

- Flavivirus
- 80% asymptomatic
- Low grade fever
- Arthralgia + myalgia
- Headache
- Conjunctivitis
- Maculopapular rash

Zika Virus an "Emerging Threat"

February 1, 2016
Public Health Emergency of International Concern declared by Director-General World Health Organization

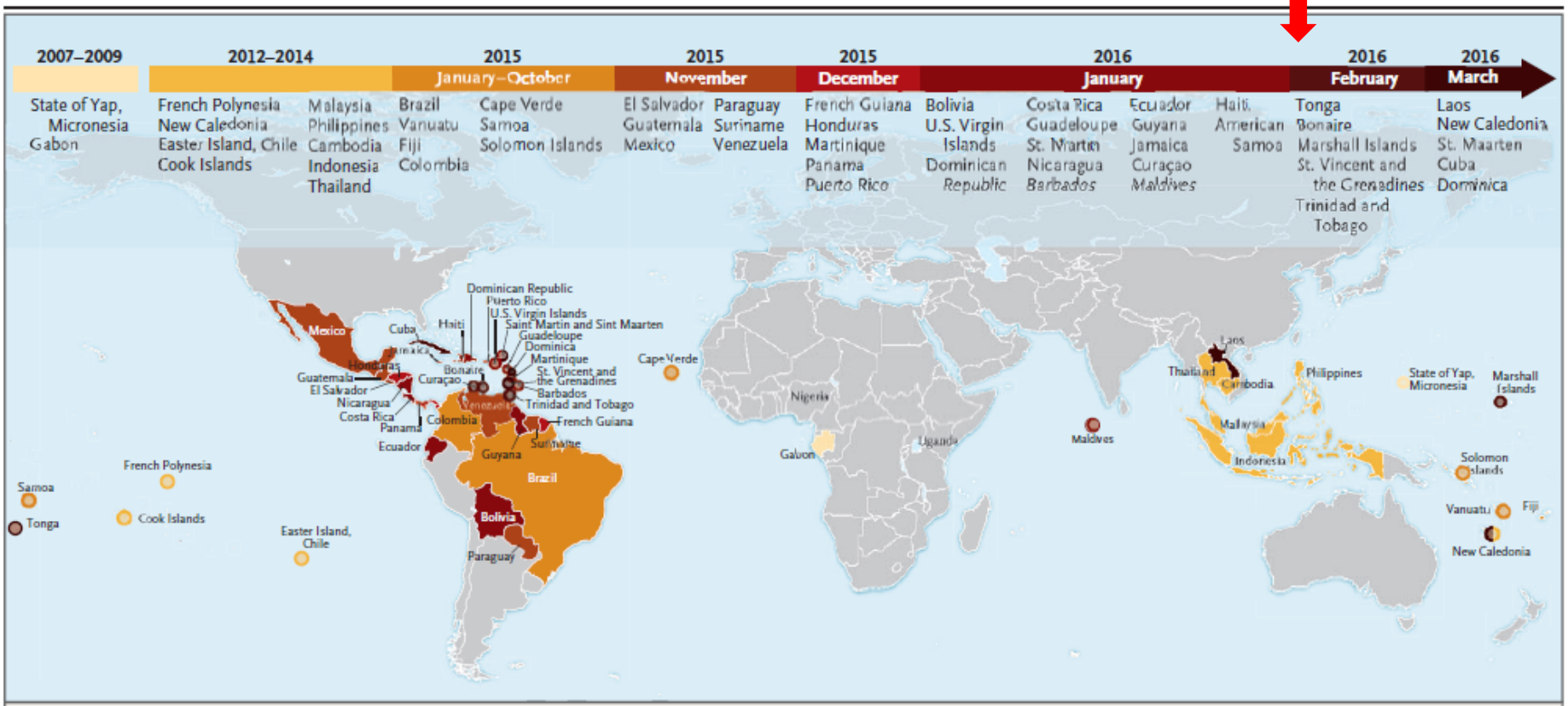
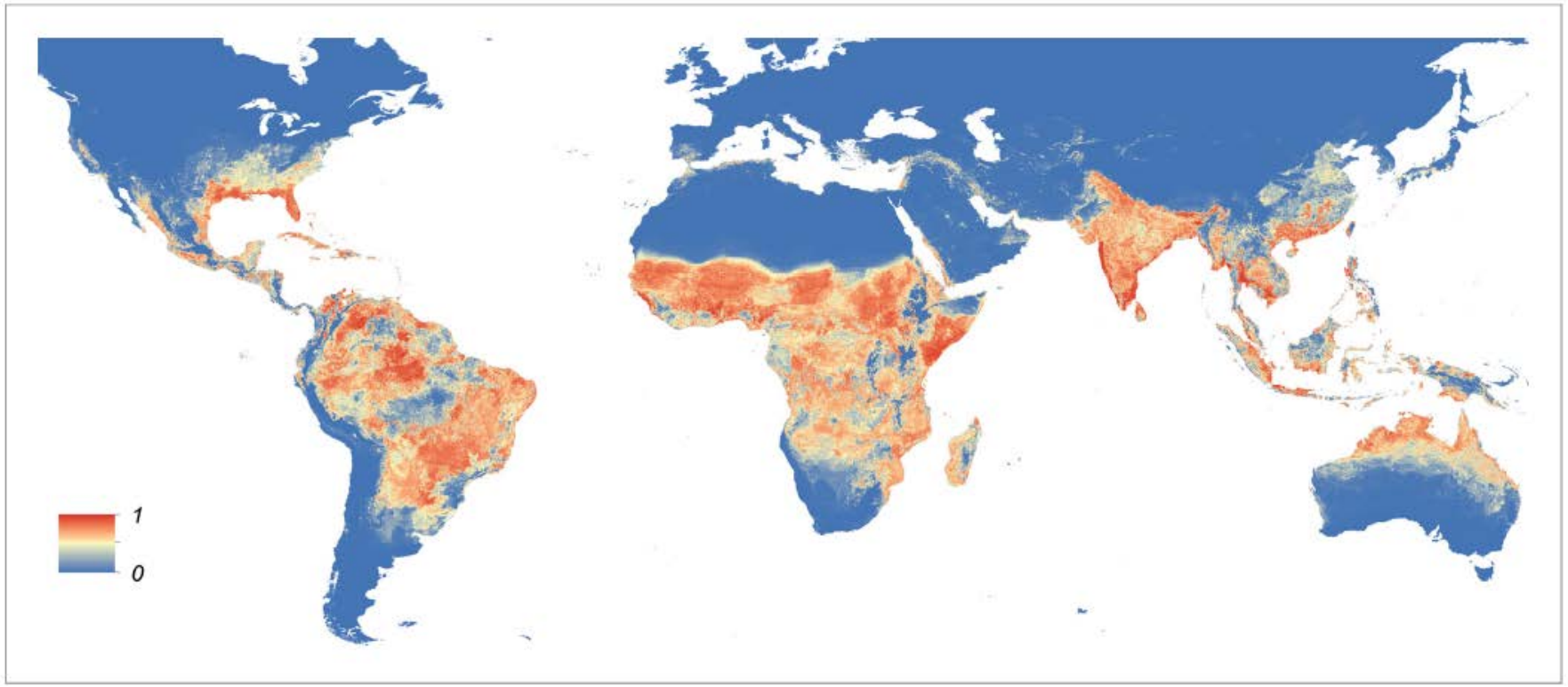


Figure 1. Areas in Which Zika Virus Infections in Humans Have Been Noted in the Past Decade (as of March 2016).
Only sporadic infections have occurred in Southeast Asia, the Philippines, and Indonesia.

Peterson. N Engl J Med 2016;374:1552. Gulland. BMJ 2016;352:i657

Zika Virus an “Emerging Threat”

Predicted distribution of *Aedes aegypti*



Kraemer. eLife 2015;4:e08247

Transmission

- Mosquito-borne transmission[1] (suburban-urban cycle)
  - *Aedes aegypti, aedes albopictus*
- Sexual transmission[1,2,3]
  - Zika virus detected in semen[2]
  - Transmission from returned male travellers to their female or male sexual partners[3,4]
- Vertical transmission[1]
  - No evidence of transmission via breast milk

[1.] Peterson. N Engl J Med 2016;374:1552, [2.] Atkinson. Emerg Infect Dis 2016;22:90 , [3.] D'Oretenzio. N Eng J Med 2016;13:[Epub ahead of print], [4.] Deckard. MMWR Morb Mortal Wkly Rep 2016;65:372

Guillain-Barre Syndrome (GBS) and Zika Virus?

- Biologic plausibility
    - Neurotropic in animal experiments
    - Neurological illness associated with dengue virus, Japanese encephalitis virus, West Nile virus
- Surveillance data
    - Rise in incidence of GBS reported in 2013 French Polynesia
    - Probable increased incidence of GBS in Brazil
- Case reports
    - Clinical syndrome GBS with Zika PCR positive from cerebrospinal fluid (CSF)

Broutet. N Engl J Med 2016;16:1506, Araujo. Arq Neuropsiquiatr 2016;74:253, Brasil. Lancet 2016; 387:1482

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Van-Mai Cao-Lormeau, Alexandre Blake*, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub, Laure Baudouin, Anita Teissier, Philippe Larre, Anne-Laure Vial, Christophe Decam, Valérie Choumet, Susan K Halstead, Hugh J Willison, Lucile Musset, Jean-Claude Manuguerra, Philippe Despres, Emmanuel Fournier, Henri-Pierre Mallet, Didier Musso, Arnaud Fontanet*, Jean Neil*, Frédéric Ghawché**

- Median duration between viral symptoms and GBS onset 6 days [IQR 4-10]
- 16 (38%) required intensive care admission, 12 (29%) respiratory support
- Tests for *Campylobacter jejuni,* HIV, cytomegalovirus, Epstein-Barr virus negative
- Risk of GBS 0.24 per 1000 Zika Virus infections (based on attack rate of 66%)

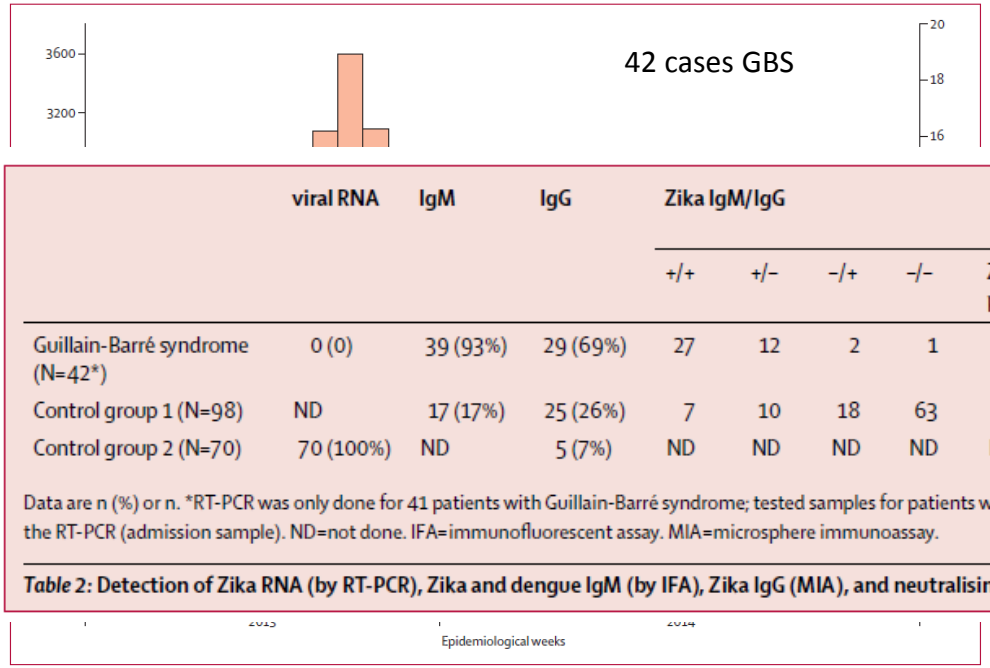


Figure: Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014

	viral RNA	IgM	IgG	Zika IgM/IgG					Neutralising antibodies	IgM Zika/IgM dengue			
				+/+	+/−	−/+	−/−	Zika virus positive		+/+	+/−	−/+	−/−
Guillain-Barré syndrome (N=42*)	0 (0)	39 (93%)	29 (69%)	27	12	2	1	41 (98%)	42 (100%)	8 (19%)	31 (74%)	0	3 (7%)
Control group 1 (N=98)	ND	17 (17%)	25 (26%)	7	10	18	63	35 (36%)	54 (56%)	6 (6%)	11 (11%)	8 (8%)	73 (75%)
Control group 2 (N=70)	70 (100%)	ND	5 (7%)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Data are n (%) or n. *RT-PCR was only done for 41 patients with Guillain-Barré syndrome; tested samples for patients with Guillain-Barré syndrome are late samples (around 3 months after admission), except for the RT-PCR (admission sample). ND=not done. IFA=immunofluorescent assay. MIA=microsphere immunoassay.

Table 2: **Detection of Zika RNA (by RT-PCR), Zika and dengue IgM (by IFA), Zika IgG (MIA), and neutralising antibodies**

Cao-Lormeau. Lancet 2016;387:1531

Zika Virus and Microcephaly?

- Epidemiological
  - Reports of increased rates of microcephaly in Brazil – 20 fold
- Causal link?
  - Zika virus isolated from human fetal brain
  - Zika virus IgM detected from CSF in 30 neonates with microcephaly
  - Zika virus RNA detected in amniotic fluid with foetal ultrasonography findings of microcephaly
  - Large-scale prospective cohort or case-control study required
- Insufficient data to quantify risk
  - Trans-placental transmission
  - Adverse pregnancy outcomes

European Centre for Diseases Prevention and Control. 11 April 2016 [online] Available at http://ecdc.europa.eu/en/publications/Pages/Publications.aspx [Accessed 1 May 2016], Chan. J Infect 2016;72:507, Mlakar. N Engl J Med 2016;10:951, Corderio. Lancet 2016;387:1811

Summary

- All patients with HCV should be considered for treatment
- Life expectancy for HIV-infected patients has significantly improved
  - Antiretroviral therapy is recommended for all people living with HIV independent of CD4 count
  - Kidney and liver transplantation is a proven option in HIV-infected patients
- Zika virus
  - Causative link between Zika and GBS
  - Growing evidence of an association between Zika and microcephaly