Management of Chronic HBV and HCV in the Alaska Native Population

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and AIP/CDC

Viral Hepatitis Registries

- Computerized Registries for patients with hepatitis B and C can be useful tools for managing patients via evidenced-based practice guidelines such EASL and AASLD and for research
- Public Health registries can be used to send letters to patients on a regular bases (e.g. every 6 months) reminding them to go to their provider for testing
  - Specific Tests can be recommended plus vaccination

Public Health Usefulness of Registries

- Reminder letters can include educational information, such as:
  - Recommendations for screening for other virus (HAV, HBV in persons with HCV and HIV)
  - Useful educational information about hepatitis infection: for example new treatments
  - Information for family members and close contacts
  - Information for referral options for management

Registries in National and Managed Health Care Systems

- Laboratory test slips can be included in periodic reminder letters for follow-up that provider can send into central laboratory
- Providers at central hospital or clinic can monitor tests and make recommendations for further testing and follow-up.
- Computerized letters can be sent to persons with stable laboratory findings to reassure patients and remind them of next follow-up

Alaska Population-Based HBV Cohort

- 1550 patients identified between 1974 and 1987 with chronic HBV infection
- 1350 patients are still alive
- All patients are followed similarly except HBV genotype and special studies such as HBsAg levels are only performed in consented persons

The Chronic HBV Alaska Cohort

- Five HBV genotypes found: A1, B6, C2, D2-3, F1
- 1350 enrolled in outcome study, 1100 still alive
- Median follow-up of cohort: 21 years
- Median age at entry: 20 years
- Median age at last follow-up: 41 years
- Over 20,000 stored sera available on this cohort

ANTHC Registry to Follow Hepatitis B Carriers

- Uses Microsoft Excel and Access software used for:
  - Patient tracking
  - Generate reminders for appointments for lab
  - Summarize clinical information for reports
  - Used for clinical research

ANTHC Program to Follow Hepatitis B Carriers

- Letter q. 6 months to patient with lab slip with bar code;
  - List of Patients in community/region sent to provider
- Blood drawn in village clinic or hospital then centrifuged and separated
- Blood mailed ANMC lab for liver panel, AFP
  - HBeAg/anti-HBe tested once yearly
  - All patients had baseline testing for HBV DNA in 2001
- Patients who fail to have blood drawn 3 months after 1st letter, receive a reminder letter.

Protocol for Evaluation of Testing

- Baseline HBV DNA testing is performed all persons
- Follow-up HBV DNA testing is performed in:
  - Patients with elevated ALT or AST
  - Those with personal or family history of HCC
  - Those with previous HBV DNA elevations above 2,000 IU/ml

HBV Flow Sheet

Name **Research #** **DOB** **ANMC Chart**

Diagnosis HBV **Date** 1/1/1969 **Carrier Status** Carrier **Genotype** D **SU Chart**

Age 51 **Sex** F **BMI** 36.8 2/22/2011 **Village**

Original Consent S 2/15/1998 **Narch** S 2/22/2011

HAV Date 1/15/1998 **HAV IgG** + **Hep A Vac: 1st** **Last** **Count**

HCV Date **HCV Status** **RIBA** **HCVRNA**

HDV Date **HDV Ab** **Hepatoma:**

HIV Date **Result**

Liver Biopsy:	K-HAI	Ishak	Comments
2/23/2011 HepMD	4	1	Fat. Despite severe steatosis,no steatohepatitis.Central Veins WNL.

Treatment **Mutations/YMDD Results**

Start	Medication	Stop	Response	Notes
3/3/2011	Tenofovir		Yes	300 mg

Date	ALT	AST	AFP	EAb	EAg	SAg	HBV-DNA	Diagnostic Imaging
2/23/2012	26	20	2.3			+	<20	
11/21/2011	23	18	2.4	+	-	+	Not Detected	
8/31/2011	35	21	3.0			+	<20	
2/22/2011							3920.0	**Comments**
12/15/2010	27	19	2.5	+	-	+	4230000.0	Family Hx HCC. Treatment.11/21/11-BUN-15,Cret-0.6,Phos-2.9/sen
1/15/2008	21	17	2.1			+		
2/6/2007	24	16	2.7	+	-	+		
7/10/2006	20	15	2.3	+	-	+		
4/23/2004	17	11	2.0	+	-	+		
6/11/2003	20	15	2.0	+	-	+	1846.0	
8/16/2002	21	13	2.7	+	-	+		
1/11/2002	21	12	2.7			+		
7/5/2001	25	17	2.6			+		
1/22/2001	49	25	2.7			+		
6/9/2000	49	107	2.2			+		
12/8/1999			2.4			+		
6/2/1999			1.9	+	-	+		
12/21/1998			1.8			+		
6/2/1998			1.0	+	-	+		
1/15/1998			1.7			+		
8/6/1997			2.5	+	-	+		
1/9/1997			1.7			+		
12/3/1996			2.2			+		
5/13/1995			1.9	+	-	+		
5/26/1994			1.6	-	-	+		
11/8/1993			2.6	-	+	+		
4/2/1993			1.3	-	+	+		
2/19/1992			2.2	-	+	+		
5/21/1991			2.2			+		
10/11/1990			2.6	+	-	+		
3/2/1990			0.0	-	-	+		
5/25/1989			9.7			-		
9/7/1988			1.0	-	-	+		

Protocol for Evaluation of Testing Continued

- Patients with HBV DNA between 2,000 and 20,000 IU/ml have repeated HBV DNA levels performed at each visit.
  - Those over age 40 or with persistently elevated levels or ALT levels > twice upper limit of normal are sent for liver biopsy
  - Patients under 40 years of age with elevated ALT and HBV DNA > 20,000 are sent for liver biopsy

Which Patients Receive further Evaluation?

- Persons with AFP > 10ng/ml are referred for to nearest hospital for ultrasound or Triphasic CT, reviewed by teleradiography
- Patients with elevated ALT and HBV DNA > 20,000 IU/ml are recommended for a liver biopsy at ANMC to see if they need treatment
- Patients with moderate or severe inflammation or fibrosis $\geq$ Metavir/Ishak 2 are treated

Evaluation of Elevated Liver Aminotransferase Levels

- Patients with HBV can have aminotransferase elevations due to causes other than HBV
- Evaluation of Persons with elevated ALT but HBV DNA < 2,000 IU/ml: most common etiologies:
  - Metabolic syndrome
  - Alcohol
  - Other hepatrophic viruses: HCV, HDV (no HDV in Alaska)
  - Alcohol
  - Autoimmune liver disease

Evaluation of Persons with Elevated ALT but HBV DNA <2,000 IU/ml

- Nurse coordinator calls to clinic and/or patient to obtain further history including medication use, history recent Alcohol use, history diabetes or hyperlipidemia
- BMI obtained
- CBC and anti-HCV (HDV no longer done in Alaska as no evidence of Delta)
- Autoimmune markers in females if HBV DNA < 2,000 IU/ml

Findings from Data Obtained from our Registry

- Persons with Immune Active HBeAg-negative HBV:
  - Who have HBV DNA over time that is above 2,000 but does not exceed 20,000 IU/ml are unlikely to have moderate to severe liver fibrosis
  - Persons who have an HBV DNA level that exceeds 20,000 on at least one occasion over time are likely to have moderate to severe inflammation and/or fibrosis.
  - HBsAg titers appear not to be helpful in detecting degree of liver inflammation or fibrosis on biopsy.

ANTHC Registry for Hepatitis C

- Reminder letters sent every 6 months to patients to take to nearest provider with list of laboratory tests
- For patients with clinical evidence of advanced fibrosis are sent separate letter every six months to take to provider recommending liver ultrasound
  - Persons with Metavir 3 or 4 fibrosis on biopsy
  - Persons with clinical evidence of cirrhosis
  - Persons with persistent AFP > 10

Status	Positive	**Dx Date**	9/15/1998	**Genotype**	1b 6/21/2011	**SU Chart**	
Age	62	**Sex**	M	**RIBA**	+ 10/1/1998	**PCR**	18,495,422 6/21/2011
Village	Wasilla	**Consent**	Yes Consent Form 11/5/2008	**BMI**	36.2 6/21/2011	**HCC**	
Last Clinic Visit	6/21/2011	**HepA Status**	I	**HAV-tot**	+	**Date**	10/20/1998
HepB Status	I	**Shots**		**IL-28b**	CT	**HIV**	N 2011
PT	12.7 6/21/2011	**INR**	<1.0 6/21/2011				
TIBC	411	**Fe**	131	**%Sat**	31.9% 11/5/2008	**Ferritin**	60 7/12/2000
Vit D	72.0 6/21/2011	**ESLD: Ascites**		**Varices**		**Enceph**	
Coag		**HOMA IR**		**Diabetes Diagnosis**		**Dx Date**	
FIBROSpect II		**Autoimmune Markers: ANA**	N 2/28/2003	**SMA**		**IgG**	

Biopsies		HAI	Fibrosis	Ishak
Clinic	6/1/2006	5	3	3
Study	6/1/2006	9	1	2

Date	ALT	AST	AFP	HGB	HCT	PLT	AlkP	ALB	TBIL	PCR
6/21/2011	52	34	3.8	14.9	43.6	198	104	4.4	0.5	18,495,422
3/10/2011	95	48		17.8	53.3	196	127	5.0	0.8	
11/5/2010	65	40		16.5	48.3	193	117	4.6	4.0	
9/1/2010	63	43	4.4	16.1	48.5	221				
11/5/2008	53	30	2.5							
6/9/2008	54	34		16.5		210	96	4.4	1.0	
6/8/2008	55	38		16.8		200	107	4.4	1.1	
3/27/2008	55	38	2.4	18.5		248	101	4.4	0.9	
1/25/2008	51	32					136	4.4	0.7	
6/25/2007	42	25	2.5				110	5.0	0.6	
11/2/2006	32	23	1.9	16.0		207	129	4.7	0.4	
8/1/2006	52	29					128	5.3	0.6	
5/30/2006	64	41	2.9	17.3		221	135	5.2	0.6	
3/7/2006	87	49					138	5.3	0.7	57.8 million
11/9/2005	67	38	2.8			230				
5/10/2005	40	24	3.0				122	5.0	0.8	
2/4/2005	65	49					137	5.1	0.6	
5/27/2004	43	27					126	4.9	0.6	
5/4/2004	37	24	2.4				126	5.0	0.5	>7,692,310
1/26/2004	47	31					122	5.1	0.5	
11/5/2003	29	20	2.7							
5/29/2003	43	25	2.4				159	4.9	0.5	
2/28/2003	38	27				227	138	4.9	0.5	
10/7/2002	36	22	2.9				140	5.1	0.4	
1/16/2002	30	21	2.5			237	152	4.9	0.5	
10/3/2001	28	20	2.3							
4/4/2001	31	21				226		4.9		

Diagnostic Imaging

Date	Procedure	Result
3/15/2011	CT	Extensive fatty replacement of pancreas, fatty liver
3/15/2011	U/S	Diffuse increased echogenicity of liver, probable fatty liver. Pancreas not well seen.
6/25/2009	U/S	Normal RUQ ultrasound.
12/10/2008	CT	No pancreatic mass seen. Spleen normal.
11/5/2008	U/S	5.1x2.8x3.5cm panc mass. Liver normal.

Comments

PCP is Ellen Lentz, FNP, in Wasilla (private sector).907-376-4644
Has bridging fibrosis, RUQ US q6mos. Next one due 9/11. JG
See Livingston or McMahon at that time. LT

Alaska HCV Outcome Study

- Retrospective-prospective population-based study
- 1300 patients followed 1994-2005
  - Mean years prospectively: 12 years
  - Mean years retrospectively: 12.1 years
  - Over 6,000 sera stored

McMahon et al Gastroenterology 2010; 138:922-31

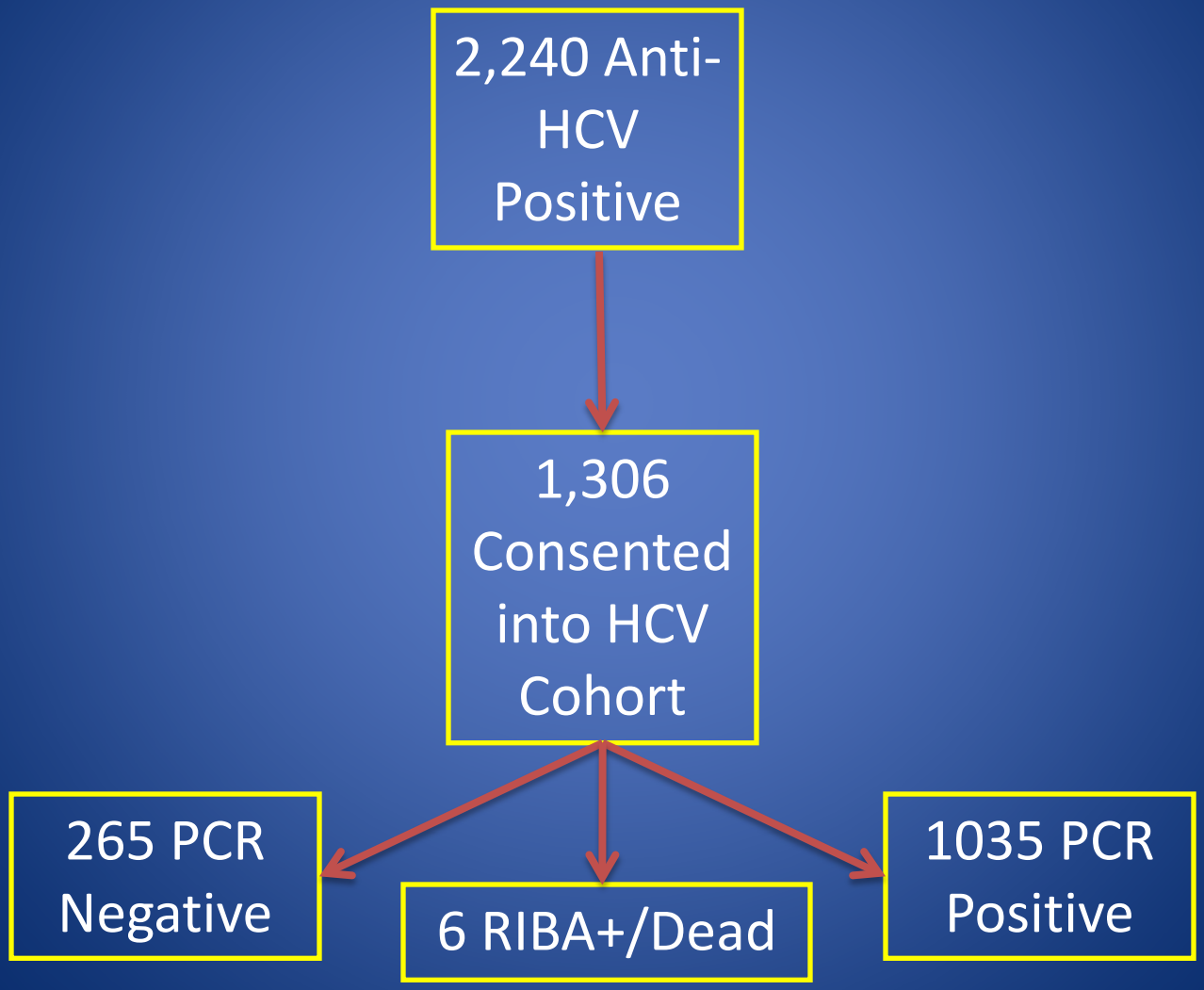
Alaska HCV Cohort Characteristics

Characteristic	N (%) or mean (range)
Age	50.6 years (13, 88)
Sex	Male 603 (46%) Female 696 (54%)
HCV Genotype	1 (66%); 2 (20%); 3 (13%); 4 (0.4%)
Co-infections	HIV (n = 38; 16 living); Hepatitis B (n = 15)
Risk Behaviors	History of IVDU (57%) Blood Transfusion (20%)
Diabetes Type 2	83 Cases Known
% BMI ≥ 30	27%
Treated for HCV	150 (14% of PCR +)
Liver Biopsy	361 Patients (28%); 479 biopsies
Estimated Length of HCV Infection	24.4 Years (4, 60)

Conclusions: Epidemiology of HCV in Alaska Natives

- Prevalence of HCV within NHANES estimates for US
- Risk Factor distribution same as US
- Proportion who recovered from HCV same as NHANES study
- Genotype distribution similar to NHANES except slightly increased proportion of genotype 3

Alaska HCV Cohort Recruitment



Alaska Cohort: HCV Outcomes

Outcome	N Cases
# Biopsied*	361
Ishak 0-2	69% (250)
Ishak 3-6	31% (111)
End Stage Liver Disease	121
Ascites	74
Varices	69
Coagulopathy	59
Hepatic Encephalopathy	32
HCC	36
Death	266
Liver-Related Death	66

*Includes most recent result for those with > 1 biopsy

HCV Treatment (167 courses in 156 patients)

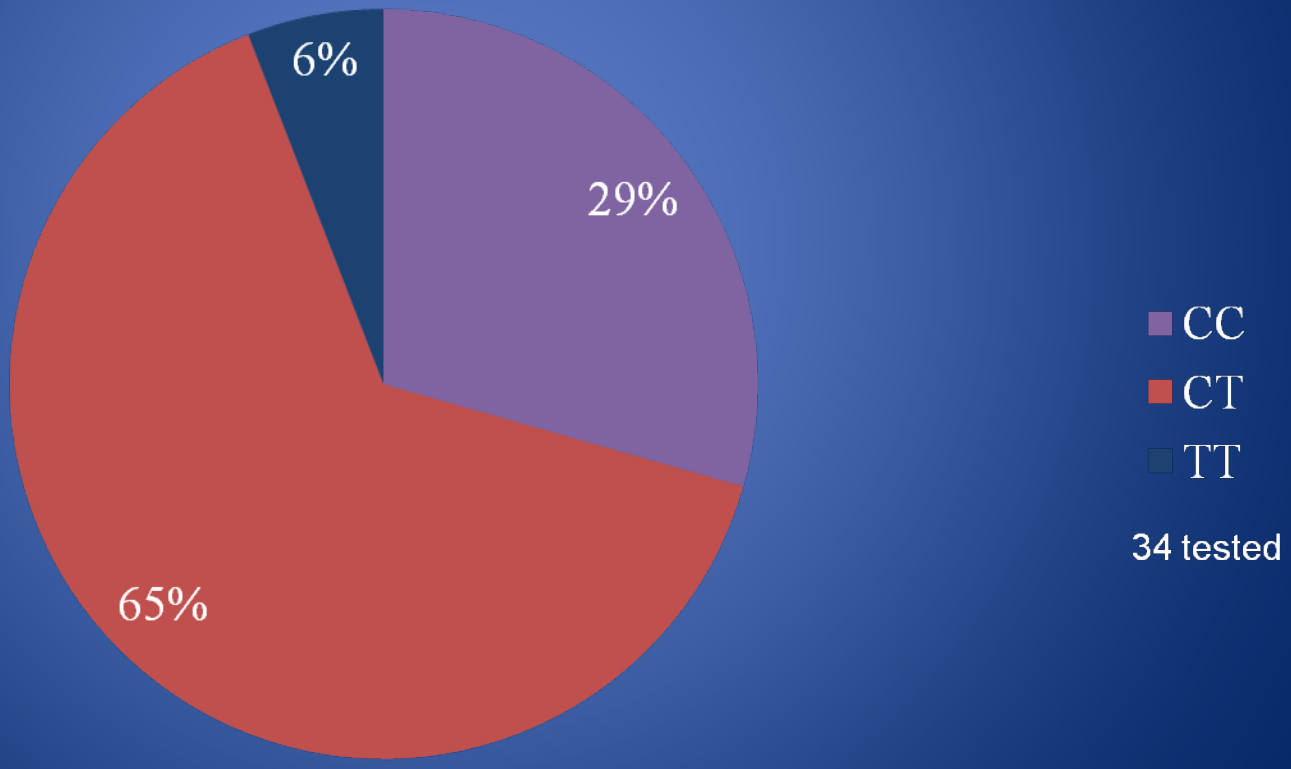
- Standard interferon 15
- Standard interferon/ribavirin 34
- Peginterferon/ribavirin 110*
- Interferon lambda (Infergen) 1
- Telaprevir or Boceprevir/peginterferon/ribavirin 12

* Includes 14 on treatment or pending SVR testing

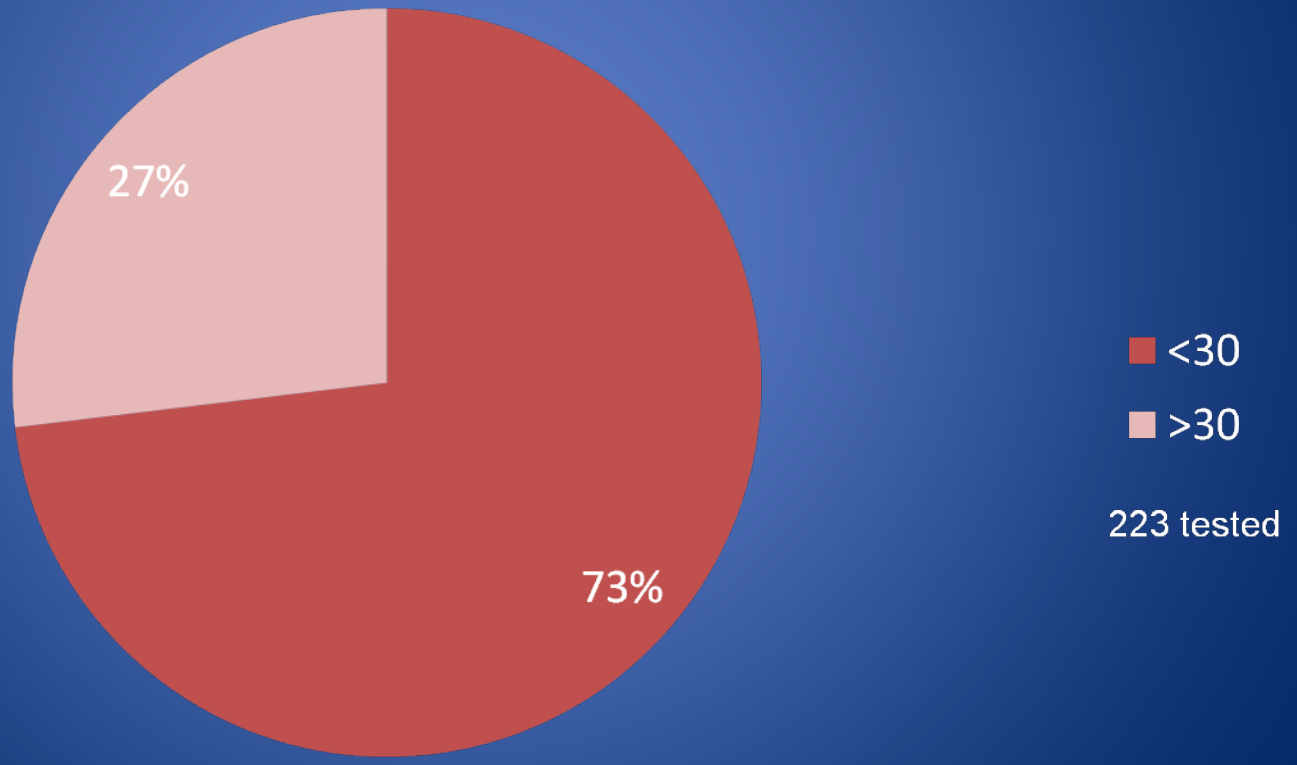
TREATMENT OUTCOMES
Peg-IFN/RBV through August 2011

Genotype	Treated	Discontinued	Failed	Relapsed	SVR	SVR in those who completed tx
1	47	22 (47%)	11	4	15 (32%)	10/25 (40%)
2	37	7 (19%)	3	3	27 (73%)	24/27 (89%)
3	18	6 (33%)	1	2	9 (50%)	9/12 (75%)
Total	102	35 (34%)	15	9	51 (50%)	43/64 (67)%

IL28b Genotypes



Vitamin D Levels in HCV



Upcoming Analyses

- Examine effect of HCV treatment on ESLD/LRD
- Determine risk factors for HCC
- Re-examine other variables
  - ALT, AFP over time
  - HCV RNA over time
  - Genotype
- Project number/prevalence of ESLD/LRD in treated/untreated in upcoming decade
- Examine IL28b as risk factor for development of ESLD and LRD in genotype 1 (pending funding)

Plan for HCV Treatment For Alaska

- Both Telepavir and Boceprevir are on the formulary
- Genotype 1 patients with moderate to severe fibrosis will be offered triple therapy
  - Compatible liver biopsy or FIBROSpect2 above 80
  - Those with bridging fibrosis or cirrhosis will be prioritized
- Genotype 1 patients with mild or no fibrosis will be encourage to wait for all oral combinations
- Genotype 2 and 3 patients will be offered Peg IFN/RBV regardless of disease stage

LIVER CONNECT: Alaska Telemedicine Semimonthly Program

Evaluation of Elevated AFP

- Persons with AFP > 10ng/ml are referred for ultrasound or triphasic CT done at nearest hospital, reviewed by teleradiography at ANMC
- Patients with small tumors may have surgical resection or radiofrequency ablation.
  - Alcohol injection of small tumors also option

Translation Studies: Effectiveness of HBV/HCV Registries in Alaska

- Studies to determine if Registries:
  - Improve patient management increasing proportion of patients with regular follow-up
  - Improve rates of vaccination for HAV (HBV in HCV) and screening of close contacts for HBV/HCV
  - Result in treatment of appropriate candidates per evidenced-based guidelines
  - Ultimately decrease rates of cirrhosis, end stage liver disease, HCC and liver related death

Information on Viral Hepatitis and Liver Disease at ANTHC

- Website: www.anthctoday.org/community/hep
- Information on treatment of HCV with materials for primary care providers etc.