Difficult to Treat Patients in Chronic Hepatitis B

do they still exist?

Resat Ozaras, MD, Professor
Istanbul University
Cerrahpasa Medical School
Infection Dept.

The Goal of HBV Therapy

- What is the goal of HBV therapy?

Goal of therapy

- The goal of therapy for CHB is to improve
  - quality of life and survival
    - by preventing progression of the disease to cirrhosis,
    - decompensated cirrhosis,
    - end-stage liver disease,
    - HCC and
    - death.

EASL HBV Guide 2012

- This goal can be achieved if HBV replication can be suppressed in a sustained manner.

EASL HBV Guide 2012

- Reduction in histological activity lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients (B1).

EASL HBV Guide 2012

- Chronic HBV infection cannot be completely eradicated due to the persistence of covalently closed circular DNA (cccDNA)
- The HBV genome integrates into the host genome and might favour oncogenesis and the development of HCC

EASL HBV Guide 2012

Case 1

- 59 y/M
- Diabetic, morbidly obese
- HBsAg (+), HBeAg (-), HBV-DNA 1 120 000 IU/mL
- Bx: F5/6 (Ishak's)
- Enrolled into TDF study
- After 48 weeks; DNA undetectable (for 7 years)

- During his visit (6th year), findings of decompensation
  - Emergency admission: sepsis, hepatic encephalopathy, ascites
- 7th year visit: Liver mass: HCC
- An adherent patient
- DNA levels have been negative

Case 2

- 25 y/M
- HBsAg (+)
- HBeAg (-)
- HBV-DNA: 850 000 IU/mL
- ALT: 112 U/L
- Bx (Ishak's)
  - HAI:8
  - F:2
- LAM was initiated

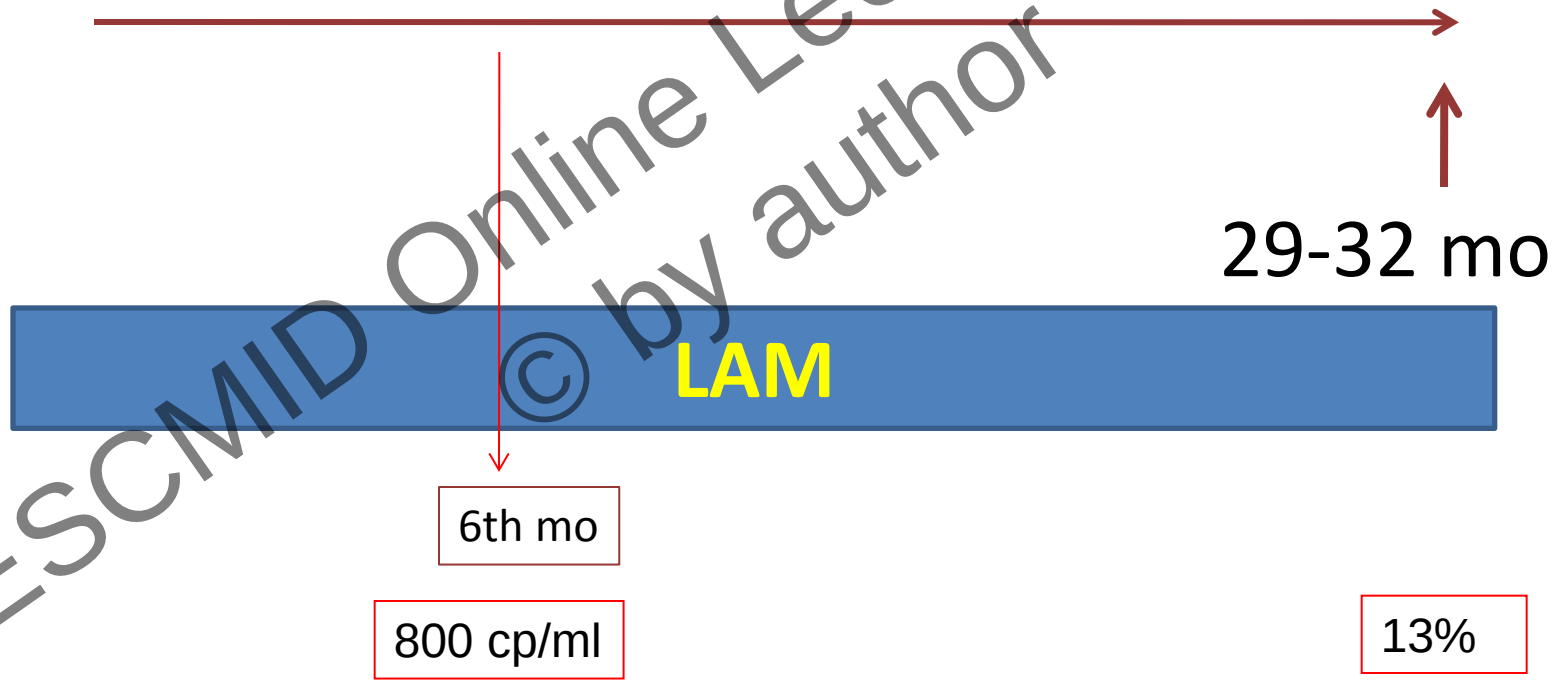
HBV-DNA

- Baseline: 850 000 IU/mL
- 6th mo: 1220 IU/ml

- Is this decrease good enough?
- Continue? Switch?

Estimating LAM resistance

HBeAg-positive 159 pts.



Modified from Yuen et al. Hepatology 2001;34:785

Resistance

- A challenge with the use of
  - LAM, TEL, ADV: even in naïve pts.
  - ETV: LAM-experience pts.
- TDF or ETV
  - May not be available
  - May not be used
    - Side effects, intolerance…

HBV Therapy and Resistance

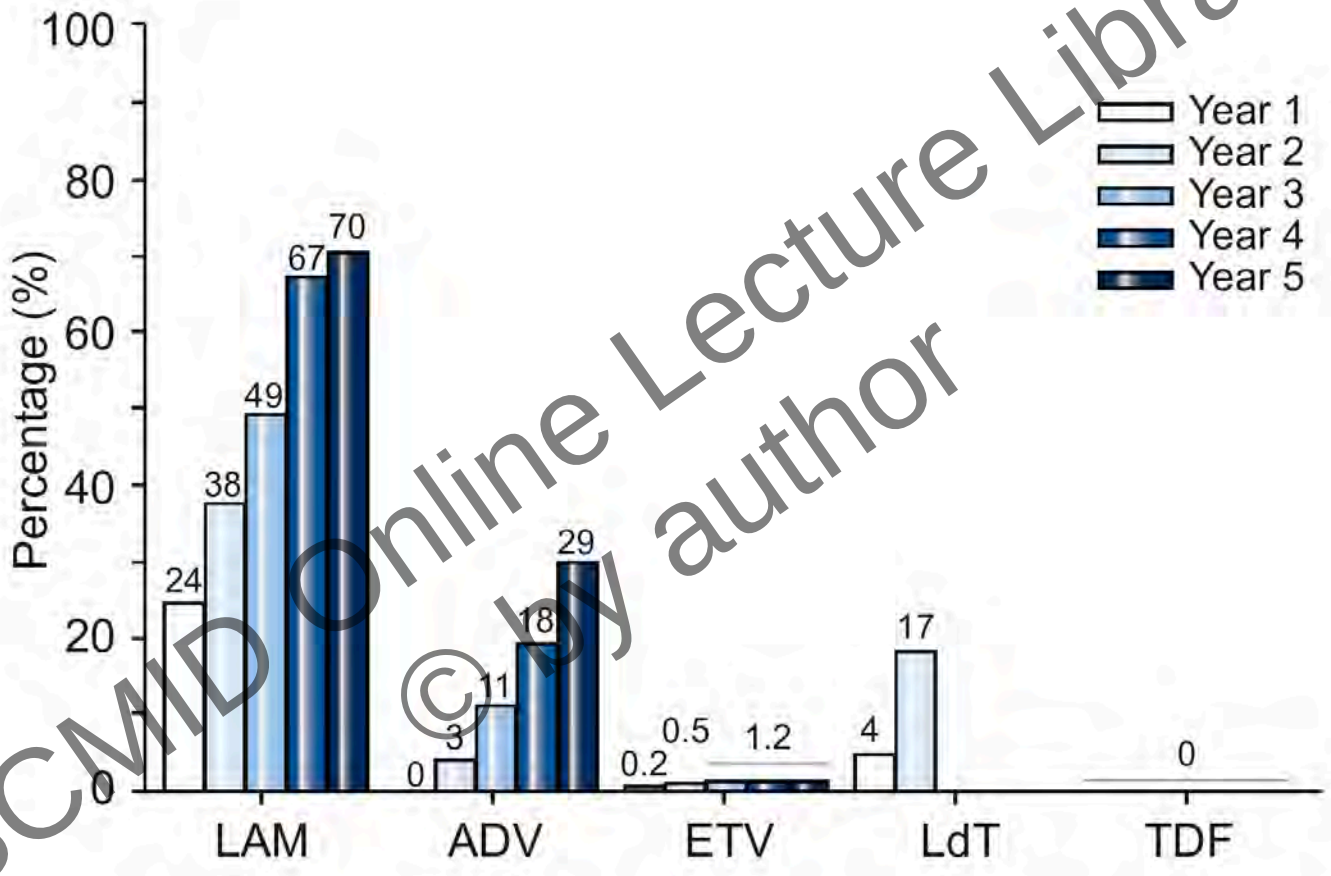


Fig. 1. Cumulative incidence of HBV resistance to lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (LdT) and tenofovir (TDF) in pivotal trials in nucleos(t)ide-naive patients with chronic hepatitis B. For method of calculation, see Ref. [41]. These trials included different populations, used different inclusion and exclusion criteria and different follow-up end points.

EASL HBV Guide 2012

Case 3

- 43 y/M
- HBeAg (+), HBV-DNA: >110 000 000 IU/mL
- Bx
  - HAI: 9
  - F:2
- In 2003, he was given LAM
- Within 1.5 years, LAM-resistance emerged (M204V)

- In 2005, he was given LAM and ADV for 3 months, and then ADV monotherapy
- ın 2008, he had still detectable HBV-DNA (5000 IU/mL)
- ADV resistance was not detected
- Switched to ETV 1 mg
- In 2012, still detectable DNA (1124 IU/mL)

- LAM--LAM+ADV—ADV—ETV--?

- ETV+TDF?
- LAM+TDF (or Truvada®)?
- ETV?
- TDF?

Multiple Treatment Failures

- (IFN)—LAM—ADV---ETV….

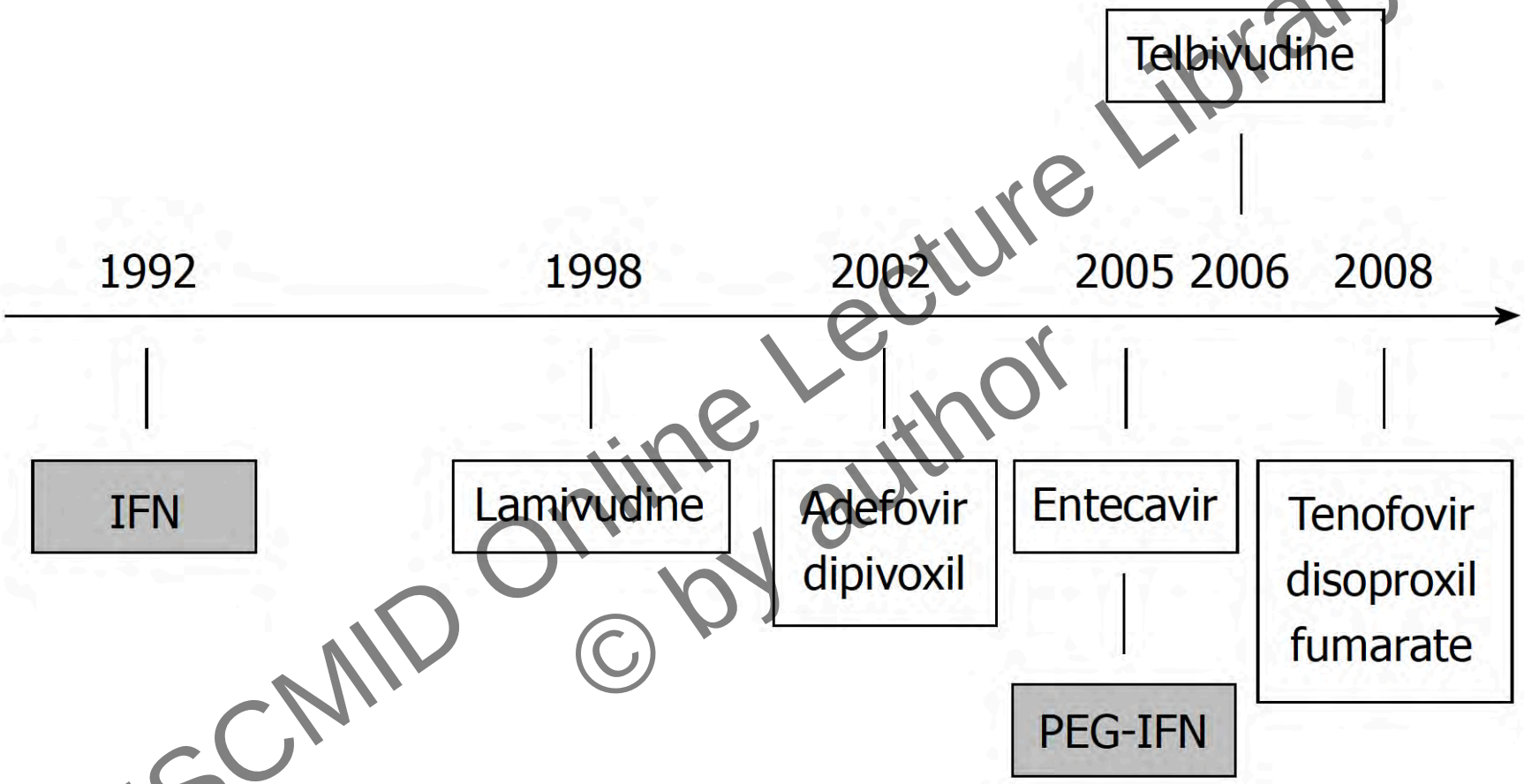


Figure 2 Approval dates for chronic hepatitis B therapeutics. IFN: Interferon.

World J Gastroenterol 2014;20:7707

Journal of Medical Virology

Tenofovir Rescue Regimen Following Prior Suboptimal Response to Entecavir and Adefovir Combination Therapy in Chronic Hepatitis B Patients Exposed to Multiple Treatment Failures

Qian Zhang,[1,2] Tao Han,[2,3,4]* Cai-Yun Nie,[1,2] Fu-Shuang Ha,[2,3,4] Lei Liu,[2,3,4] and Hua Liu[2,3,4]

TABLE I. Baseline Patient Characteristics and Genotypic Mutation Patterns as Demonstrated by UDPS Prior to the TDF Rescue Regimen

					Rt domain		
Patient	Gender	Age (years)	Treatment history	Genotype	Well-recognized resistant mutations[a]	Putative resistant mutations[b]	Surface gene mutations[c]
1	Male	43	LAM→LAM+ADV→ LDT→LDT+ADV → ETVETV+ADV	C	rtL80I, rtV173L, rtL180M, rtA181T, rtT184I/L/P, rtS202G, rtM204V/I	rtL229V, rtN238H rtS256C	sT126I, sW172*
2	Male	44	LAM→ADV→ ETV+ADV	C	rtV173L, rtL180M, rtA181T/V, rtM204V/I	rtS53N, rtV84M, rtF221Y, rtL229V, rtN238H/D, rtS256C	sW36*, sW74*, sT126I, sG130R, sK141T, sD144E, sG145R, sW156*, sW172*, sW196*, sW199*, sW223*
3	Male	62	ADV→LAM+ADVETV+ ADV	C	rtL80I, rtL180M, rtM204I	rtV191I, rtS256C	sC69*, sT126I, sW182*,
4	Male	61	LAM→LAM+ADV→ ETV+ADV	C	rtL180M, rtM204V	rtL229V	sT126I, sP127T, sM133K
5	Male	31	LAM→ETV→ ETV+ADV	B	rtL80V, rtM204I	rtS53N, rtI91L, rtF221Y, rtN238H	sT123P, sQ129H, sK141T, sS143T
6	Female	56	LAM→ETV→ETV+ADV	C	rtV173L, rtM204I	rtV207L	sM1*

Multiple Treatment Failures

- (IFN)—LAM—ADV---ETV….

- Switch to TDF

Case 4a

- 45 Y/M
- HBeAg(+)
- **On TDF**
- Adherent

	Baseline	m6	m12
HBV-DNA (IU/mL)	>110,000,000	1,250,000	4500
ALT (U/L)	128	82	60

Case 4a

- 45 Y/M
- HBeAg(+)
- **On TDF**
- Adherent

	Baseline	m6	m12	m18	m24
HBV-DNA (IU/mL)	>110,000,000	1,250,000	4500	1200	1120
ALT (U/L)	128	82	60	58	36

Case 4a

- 45 Y/M
- HBeAg(+)
- **On TDF**
- Adherent

	Baseline	m6	m12	m18	m24	m30	m36
HBV-DNA (IU/mL)	>110,000,000	1,250,000	4500	1200	1120	240	Undetectable
ALT (U/L)	128	82	60	58	36	38	36

Case 4b

- 45 Y/M
- HBeAg(+)
- **On LAM**
- Adherent

	Baseline	m6	m12
HBV-DNA (IU/mL)	>110,000,000	1,250,000	4500
ALT (U/L)	128	82	60

Case 4b

- 45 Y/M
- HBeAg(+)
- **On LAM**
- Adherent

	Baseline	m6	m12	m18	m20	
HBV-DNA (IU/mL)	>110,000,000	1,250,000	4500	340,000	25,000,000	
ALT (U/L)	128	82	60	58	650	

- Always check adherence
- Consider modifying therapy at 6th month of therapy if you use LAM or TEL
- TDF or ETV
  - DNA decreasing: monitor
  - DNA stable: monitor closely
  - DNA increasing: consider modifying the therapy

Case 5

- A 23 y/F
- HBsAg (+) on screening in Gynecology

- HBeAg (+)
- ALT 32 U/L
- Ultrasound: normal
- HBV-DNA: >110 000 000 IU/mL

- Immunotolerant
- No indication for therapy
- Monitor

- Transmission to baby
  - HBIG+Vaccine series: Enough?

- Serum HBV DNA >$10^{6–7}$ IU/mL, mostly HBeAg-positive mothers carry a >10% risk of vertical HBV transmission despite HBIG and vaccination

Vaccine 1997;15: 1624–1630.
J Viral Hepat 2009;16:94–103.
J Hepatol 2011;55:1215–1221.
World J Gastroenterol 2011;17:4321–4333.

- HBV therapy during pregnancy
  - For the mother; severe disease
  - For decreasing perinatal transmission
- HBV therapy during breastfeeding

Table 1 Oral nucleos(t)ide analogs for the treatment of chronic hepatitis B

Drugs	Dosage	Antiviral activity	Drug resistance	Specific side effects	Pregnancy category
Lamivudine	100 mg daily	Low	70% in 5 y	Negligible	C
Adefovir dipivoxil	10 mg daily	Low	29% in 5 y	Nephrotoxicity, hypophosphatemia	C
Entecavir	0.5 mg daily	High	1.2% in 5 y	Negligible	C
Telbivudine	600 mg daily	High	30% in 3 y	Myopathy	B
Tenofovir disoproxilfumarate	300 mg daily	High	0% in 5 y	Nephrotoxicity, hypophosphatemia, bone loss	B

Semin Liver Dis 2013;33:122–129.

Table 1 Oral nucleos(t)ide analogs for the treatment of chronic hepatitis B

Drugs	Dosage	Antiviral activity	Drug resistance	Specific side effects	Pregnancy category
Lamivudine	100 mg daily	Low	70% in 5 y	Negligible	C
Adefovir dipivoxil	10 mg daily	Low	29% in 5 y	Nephrotoxicity, hypophosphatemia	C
Entecavir	0.5 mg daily	High	1.2% in 5 y	Negligible	C
Telbivudine	600 mg daily	High	30% in 3 y	Myopathy	B
Tenofovir disoproxilfumarate	300 mg daily	High	0% in 5 y	Nephrotoxicity, hypophosphatemia, bone loss	B

Semin Liver Dis 2013;33:122–129.

Case 6

- 54 y/F
- HBsAg (+)
- HBV-DNA: 110 000 IU/mL
- ALT 32 U/L
- Under hemodialysis
- Kidney transplantation is planned

- Treatment? Dose?
  - IFN
  - LAM
  - ETV
  - TDF

HBV in Pts with Renal Failure

- HBV persists in pts undergoing maintenance hemodialysis
- Therapy is a challenge

- A few anecdotal studies about IFN in hemodialysis patients with hepatitis B
- No information exists on peg-IFN.
- The concern regarding antiviral therapy with IFN in the dialysis population
  - its safety and tolerability.

- HCV experience: A meta-analysis
  - 16 clinical trials, 254 patients
  - The dropout rate was 23%
- The most frequent side effects requiring interruption of the treatment were
  - hematological (18%),
  - gastrointestinal (14%),
  - neurological (10%), and
  - cardiovascular (10%) abnormalities.
- Influenza-like symptoms were common but did not frequently lead to discontinuation of peg-IFN.

J Viral Hep 2008; 15: 79-88.

- The higher frequency of side effects leading to IFN discontinuation.
  - The altered pharmacokinetics of IFN
    - The half-life of alpha-IFN is longer in dialysis patients than normal controls,
    - The area under the curve was twice that of patients with normal kidney function .
- Higher rate of the adverse effects in dialysis patients
  - IFN activity per se?
  - The high prevalence of comorbid conditions, including the older age?

J Am Soc Nephrol 1998; 9: 2344-8

Nucleos(t)ide analogues

- LAM
  - Addressed in 5 small clinical trials;
  - Overall, the rate of HBV DNA clearance with lamivudine was 78.9% (30/38)
  - Administered at a dose of 50 to 100 mg after each dialysis session, three times weekly or at 10 to 20 mg daily.

TABLE III - EFFICACY SUMMARY OF LAMIVUDINE MONOTHERAPY IN PATIENTS ON MAINTENANCE DIALYSIS WITH CHRONIC HEPATITIS B

Authors	Pts, n	HBV DNA Clearance	Reference Year	Country
Fontaine H, et al	5	5 (100%)	2000	France
Ben-Ari Z, et al	6	5 (83%)	2000	Israel
Boyacioglu S, et al	7	7 (100%)	2002	Turkey
Schmilovitz-Weiss H, et al	4	4 (100%)	2003	Israel
Lapinski TW, et al	16	9 (56%)	2005	Poland

Int J Artif Organs 2010;33:329-338

Drug	GFR (mL/min)				Hemodialysis
	50-90	30-50	10-30	<10	
TDF	300 mg q24h	300 mg q48h	300 mg q72-96 h	No data	300 mg q7d or after 12 hrs of HD

Drug	GFR (mL/min)			Hemodialysis
	50-90	10-50	<10	
ETV	0.5 mg	0.15-0.25 mg	0.05 mg	0.05 mg

The Sanford Guide 2010

Drug	GFR (mL/min)				Hemodialysis
	50-90	30-50	10-30	<10	
TDF	300 mg q24h	300 mg q48h	300 mg q72-96 h	300 mg q7d	300 mg q7d
ETV	0.5 mg q24h	0.25 mg q24h	0.15 mg q7h	0.5 mg q7d	0.5 mg q7d

The patient was initiated ETV once in a week

World J Gastroenterol 2015;21:1738-1748
Kidney Int 2013; 84: 880-885