Pro-Con: To stop or not to stop hepatitis B treatment?

To Stop HBV Treatment

Resat Ozaras, MD, Professor

Istanbul University, Cerrahpasa Medical School, Infection Dept.

HBV Therapy

- Nucleos(t)ide analogues have provided sustained suppression of viral replication
  - Less complications, better health outcomes
- BUT, it is too long
  - Cost, adherence, potential side effects…
- Outcome
  - HBeAg (-): the loss of HBsAg
  - HBeAg (+): HBeAg loss, Anti-HBe seroconversion

  REQUIRES DECADES!

- Asian Pacific Association for the Study of the Liver (APASL) guidelines
  - Treatment can be discontinued if undetectable HBV-DNA has been documented on three occasions ≥ 6 months apart.

Discontinuation

- Flare
- Liver failure, decompensation

Which patients are safe to discontinue?

- Non-cirrhotics
- Under long-term suppression

Not to consider stopping

- Cirrhotics
- HBeAg (+)

Clinical Experience with Discontinuation

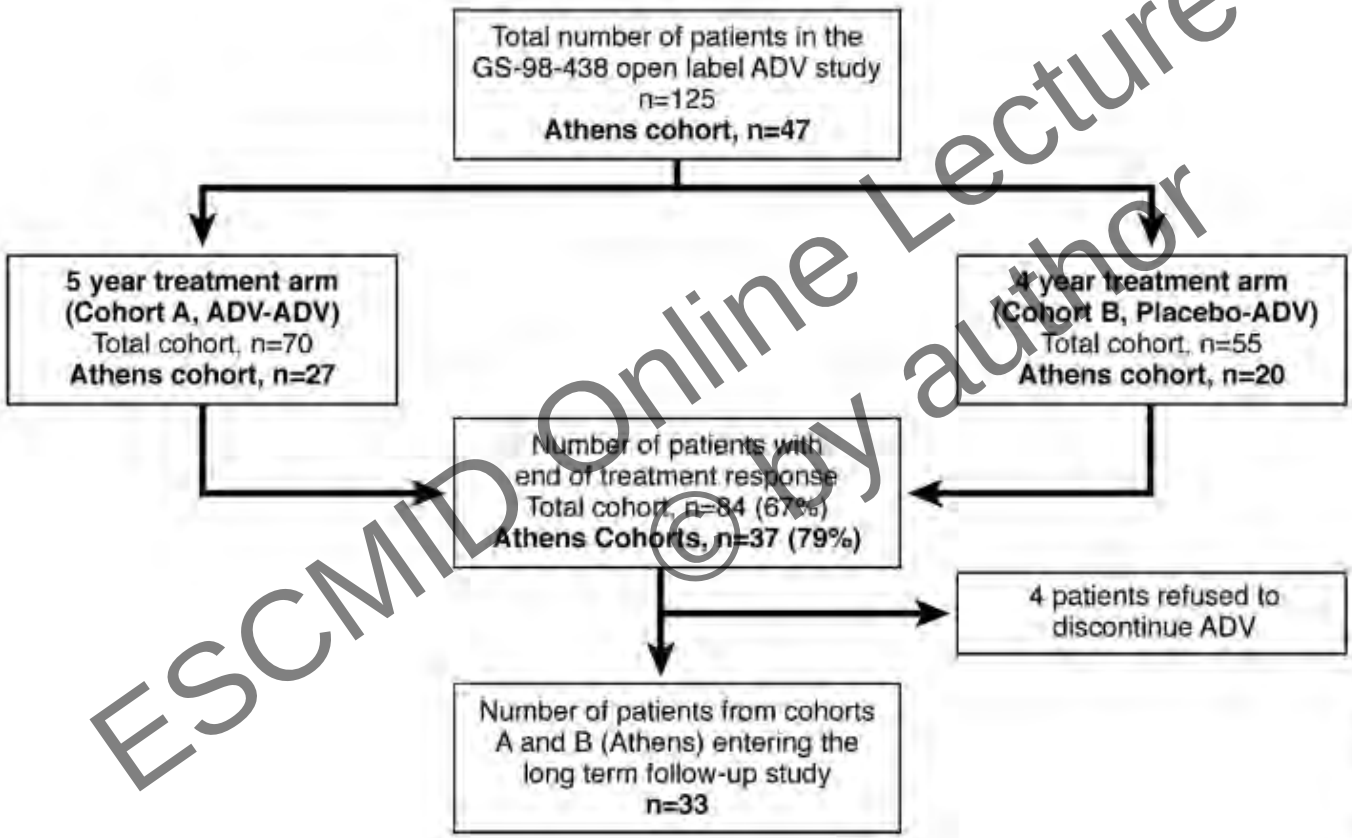


Figure 1. Flow chart showing the disposition of patients in the different cohorts of the open-label ADV study.

Hadziyannis SJ, et al. Gastroenterology 2012:143:629

- 33 HBeAg(-) patients
- Discontinued after 4-5 years adefovir
- Undetectable DNA, normal ALT
- Followed for 5.5 years

Hadziyannis SJ, et al. Gastroenterology 2012:143:629

- During first few months:
  - Virological relapse: all
  - Biochemical relapse:76%
- During follow-up
  - 18 (55%): DNA<2000 IU/mL, ALT: normal
    - 13 (72%): HBsAg clearence

Hadziyannis SJ, et al. Gastroenterology 2012:143:629

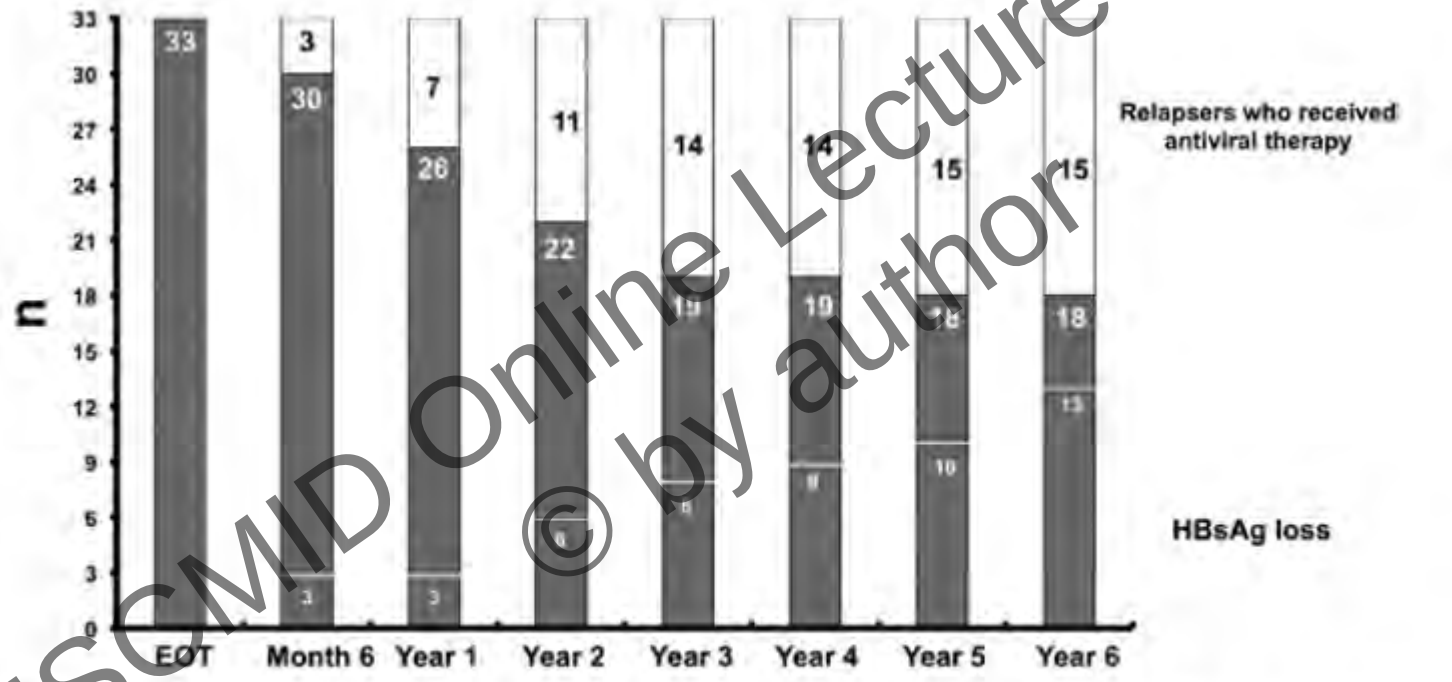


Figure 2. The number of patients who experienced a relapse and received antiviral therapy (relapsers) or lost HBsAg among the remaining patients during follow-up.

Hadziyannis SJ, et al. Gastroenterology 2012:143:629

Off therapy durability of response to Entecavir therapy in HBeAg(-) CHB patients

- 95 patients (39 cirrhotics) were treated with ETV for around 2 years before stopping therapy

Off therapy durability of response to Entecavir therapy in HBeAg(-) CHB patients

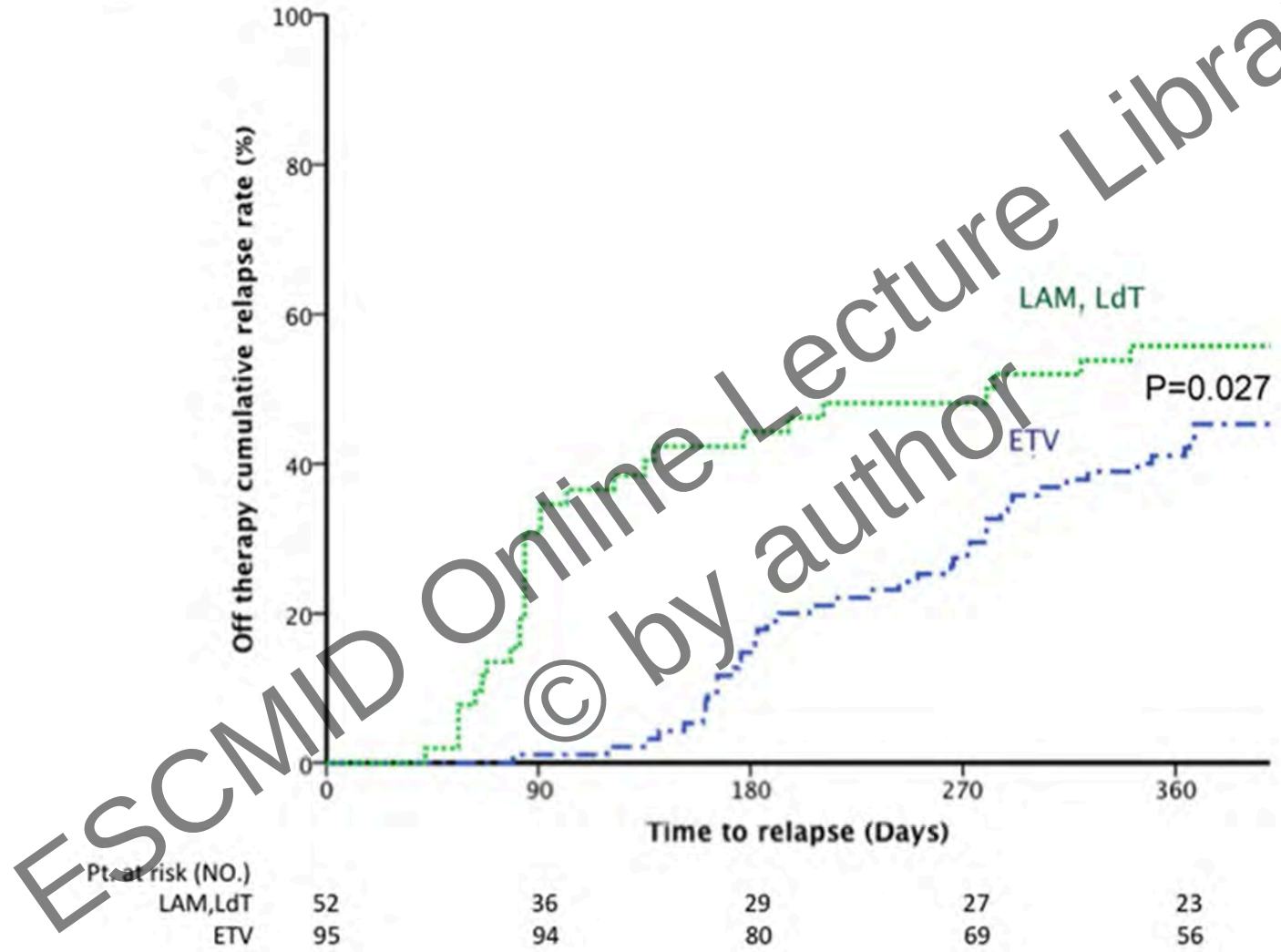
- Within 1-year after stopping ETV therapy,
  - "clinical relapse" (an episode of ALT elevation >2x upper limit of normal plus HBV-DNA>2000 IU/mL) occurred in 43 (45.3%) of the 95 patients.
  - Of the 39 cirrhotic patients, 17 (43.6%) relapsed and one (2.6%) developed decompensation.
  - The median duration till relapse was 230 days (74.4% > 6 months).

Logistic Regression Analysis

- Baseline HBV-DNA ≤$2x10^5$ IU/mL was the only significant independent factor for sustained response.
  - The 1-year relapse rate was 29% in patients with a baseline HBV DNA ≤$2x10^5$ IU/mL

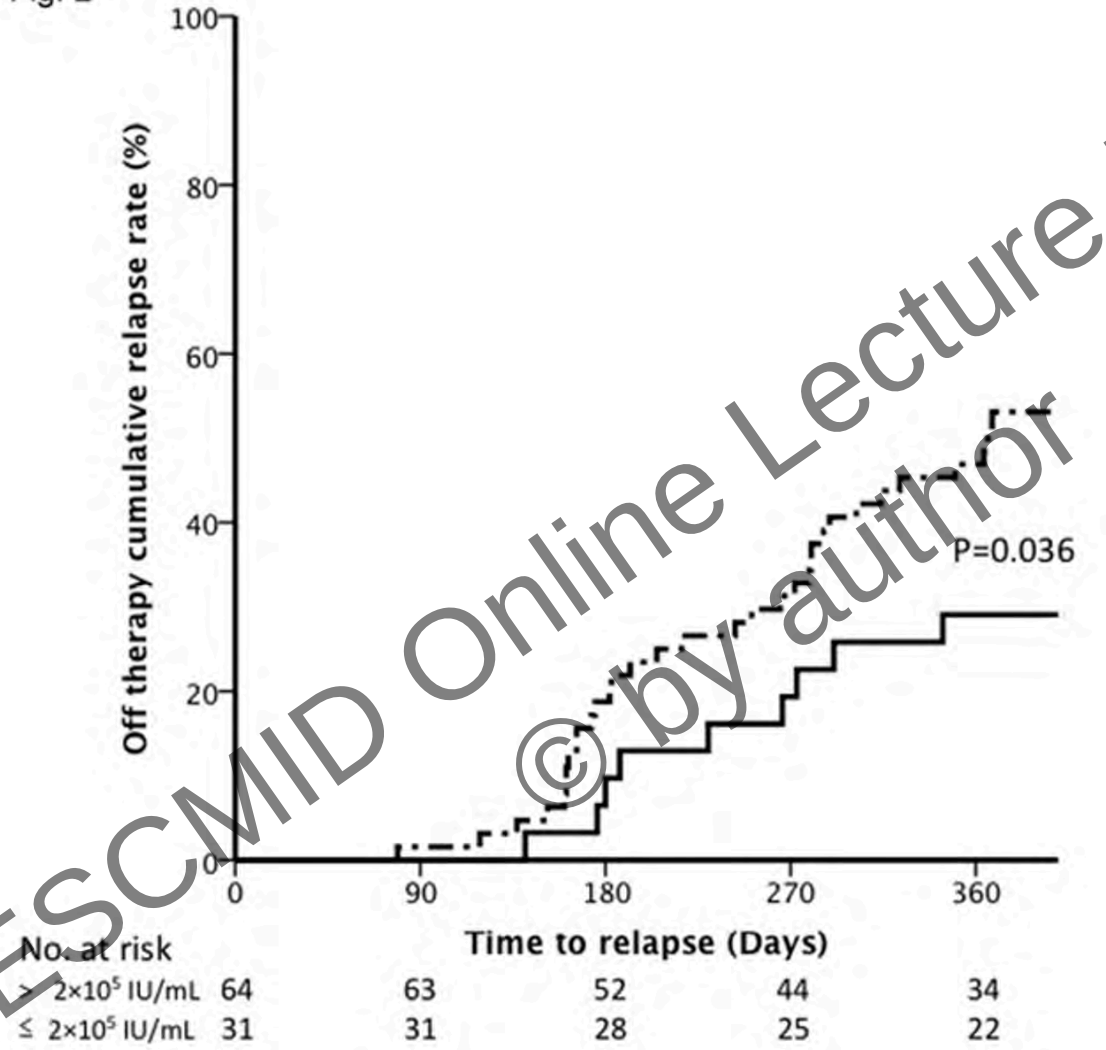
    vs

  - 53% with HBV DNA >$2x10^5$ IU/mL, p=0.027
    - For the later, consolidation therapy > 64 weeks reduced relapse rate to 33.3% in non-cirrhotic patients.



One-year cumulative relapse rate after cessation of entecavir (ETV) therapy was 45.3%, significantly lower and relapses occurred later than those after cessation of lamivudine (LAM) or telbivudine (LdT).

Fig. 2



Baseline >2x10^5 IU/mL

Baseline ≤2x10^5 IU/mL

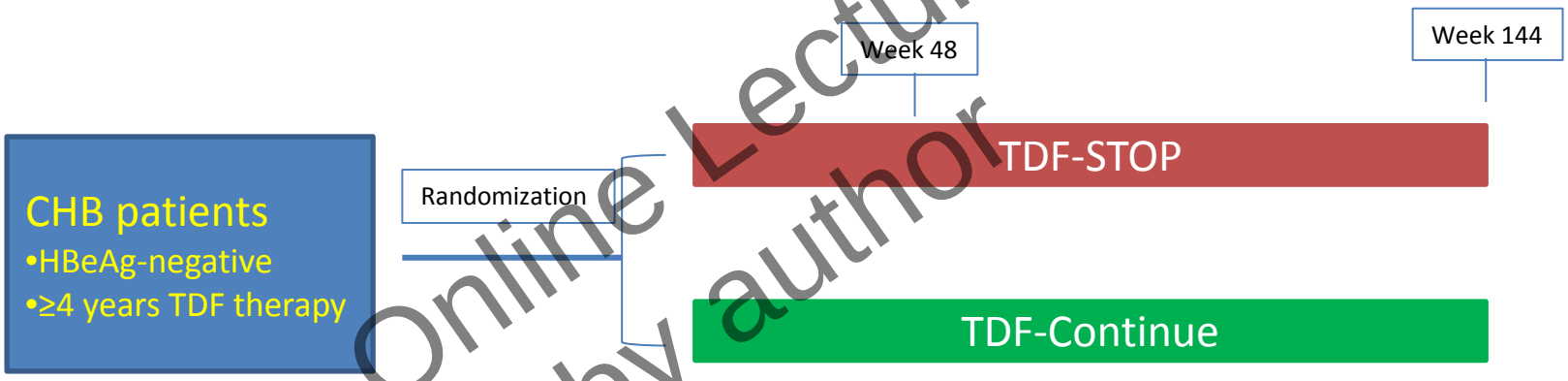
The cumulative relapse rate in patients with a baseline serum HBV DNA ≤ 2×105 IU/mL (solid line) was significantly lower than those with a level > 2x105 IU/mL (broken line)

Rationale for Stopping

- Stopping NUC treatment after a long-term suppression: reactivation in nearly all cases
- This relapse may lead to loss of HBsAg:

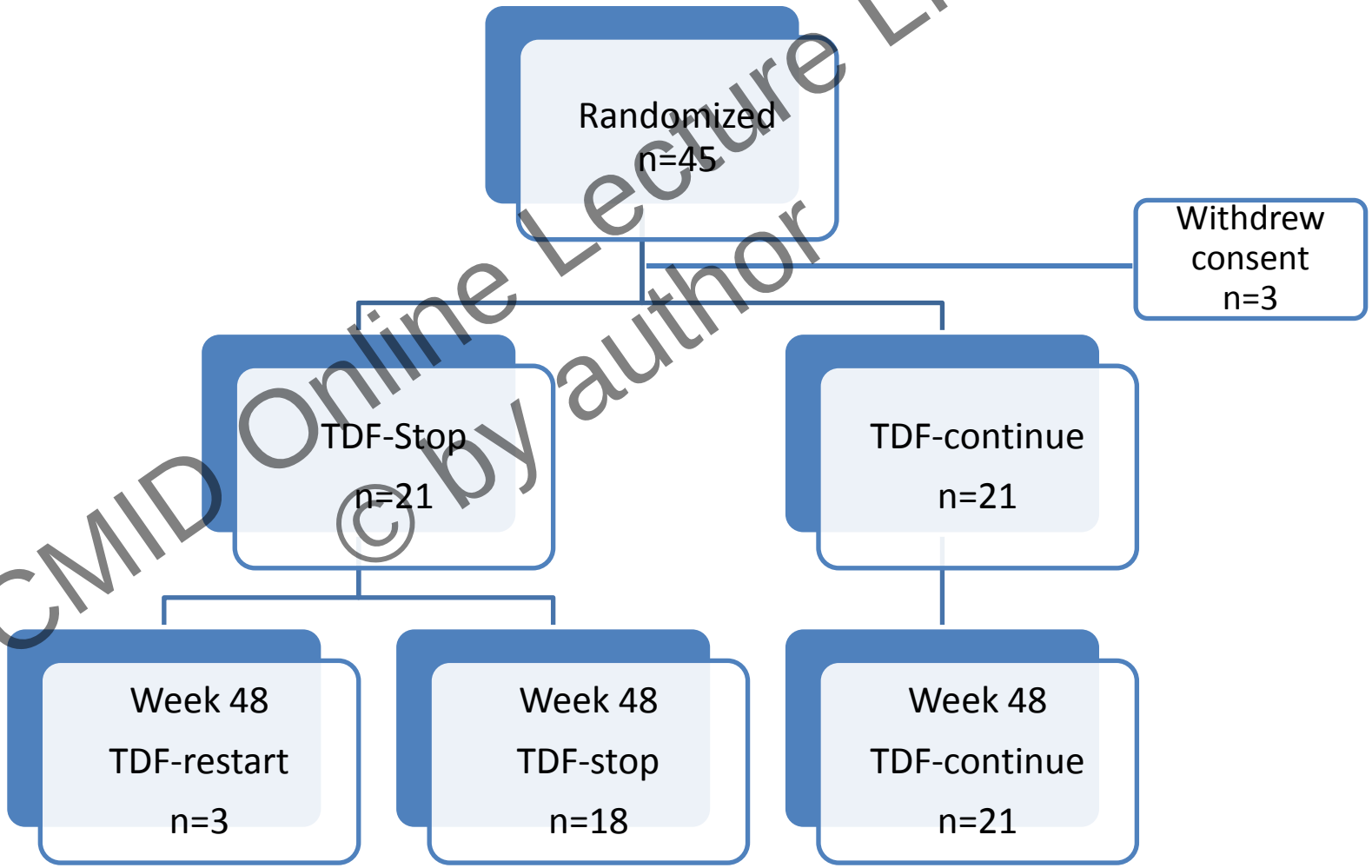
  "stop to relapse" approach

FINITE-CHB Study

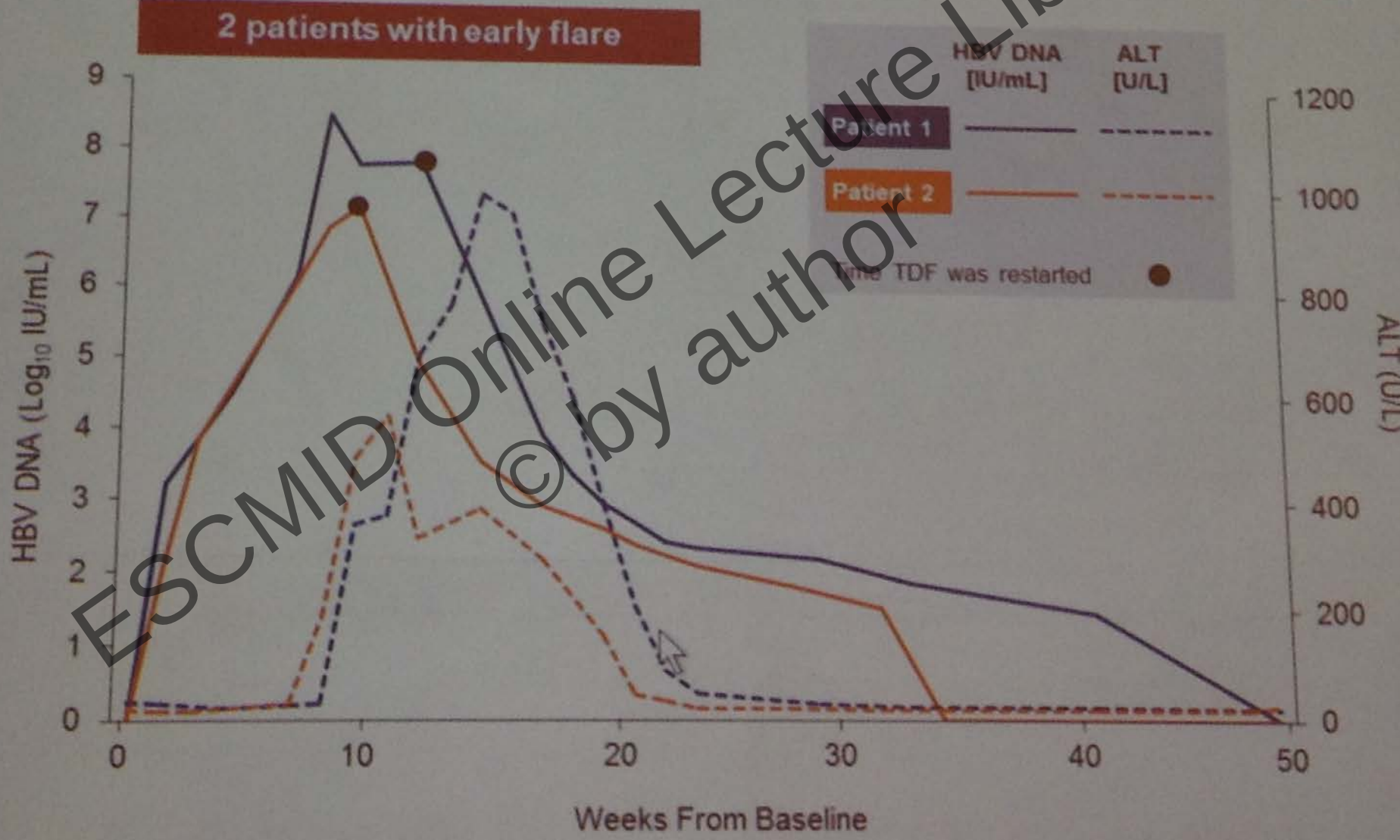


Open-label, randomized study
HbeAg-negative at initiation of TDF and randomization
HBV-DNA<400 cps/ml, >3.5 years
No cirrhosis (Fibroscan <kPa)

Berg T, et al. FINITE CHB Study, EASL 2015



TDF-Restart (n=3)

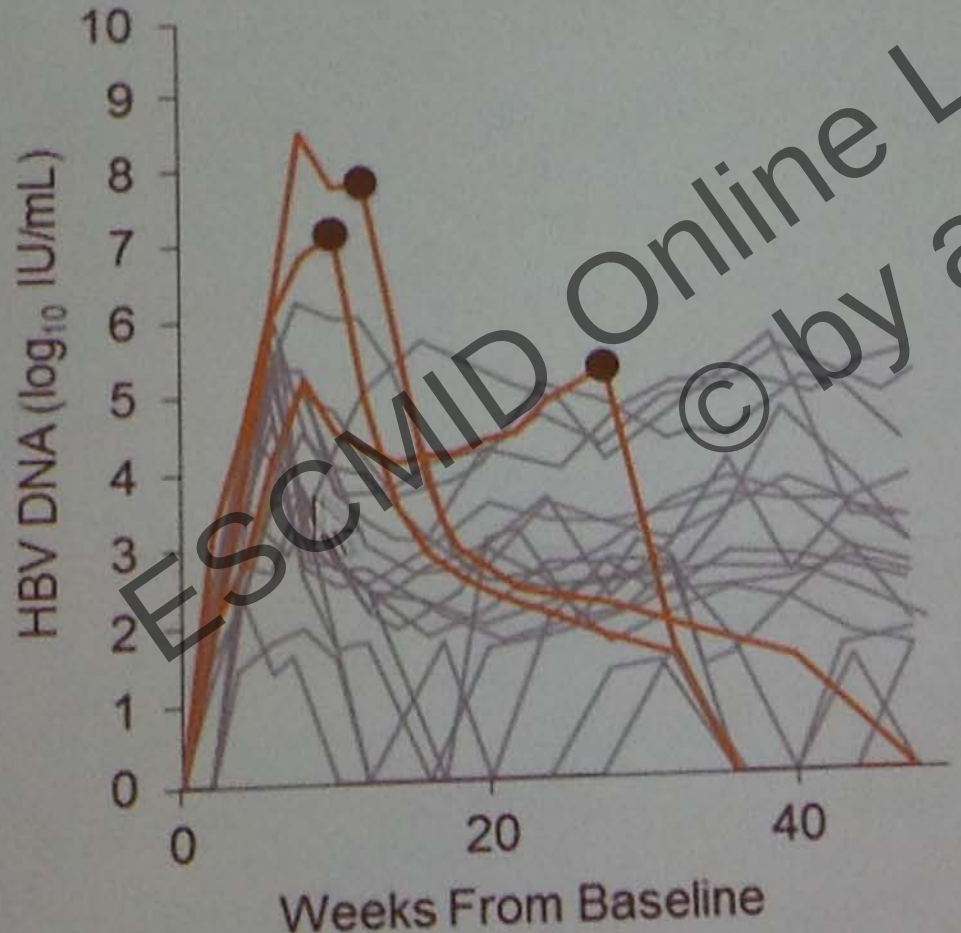


HBV DNA Profiles

Patients requiring TDF re-initiation (n=3)

Time TDF was restarted

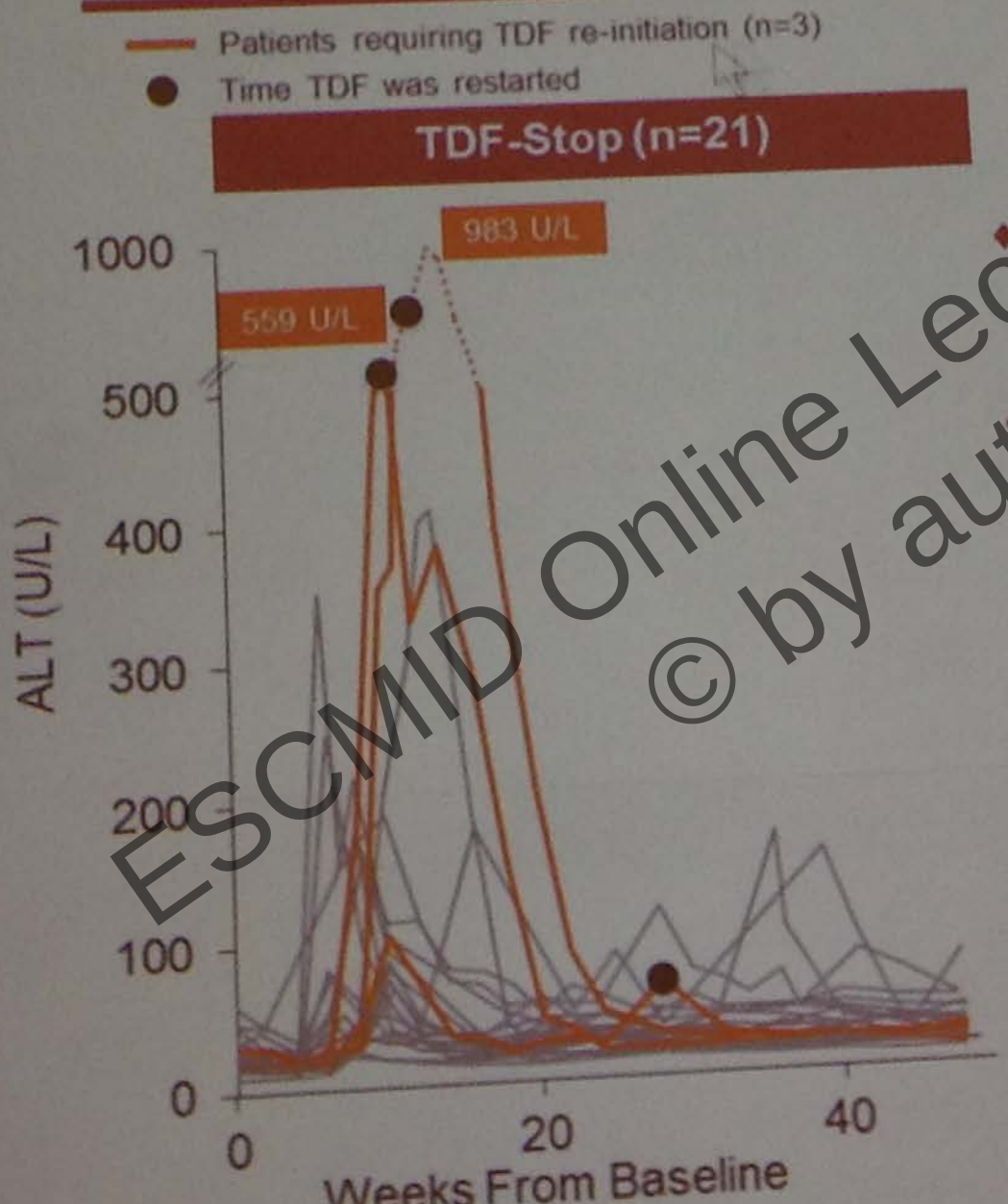
TDF-Stop (n=21)



- HBV DNA became detectable in 21/21 (100%) of TDF-Stop subjects
- HBV DNA up to W48:
  - Median: 5.32 log_{10} IU/mL
  - Min: 4.41 log_{10} IU/mL
  - Max: 8.50 log_{10} IU/mL
- At W48*
  - 89% (16/18) HBV DNA < 20.000 IU/mL
  - 78% (14/18) HBV DNA < 2.000 IU/mL

* TDF-Restart excluded

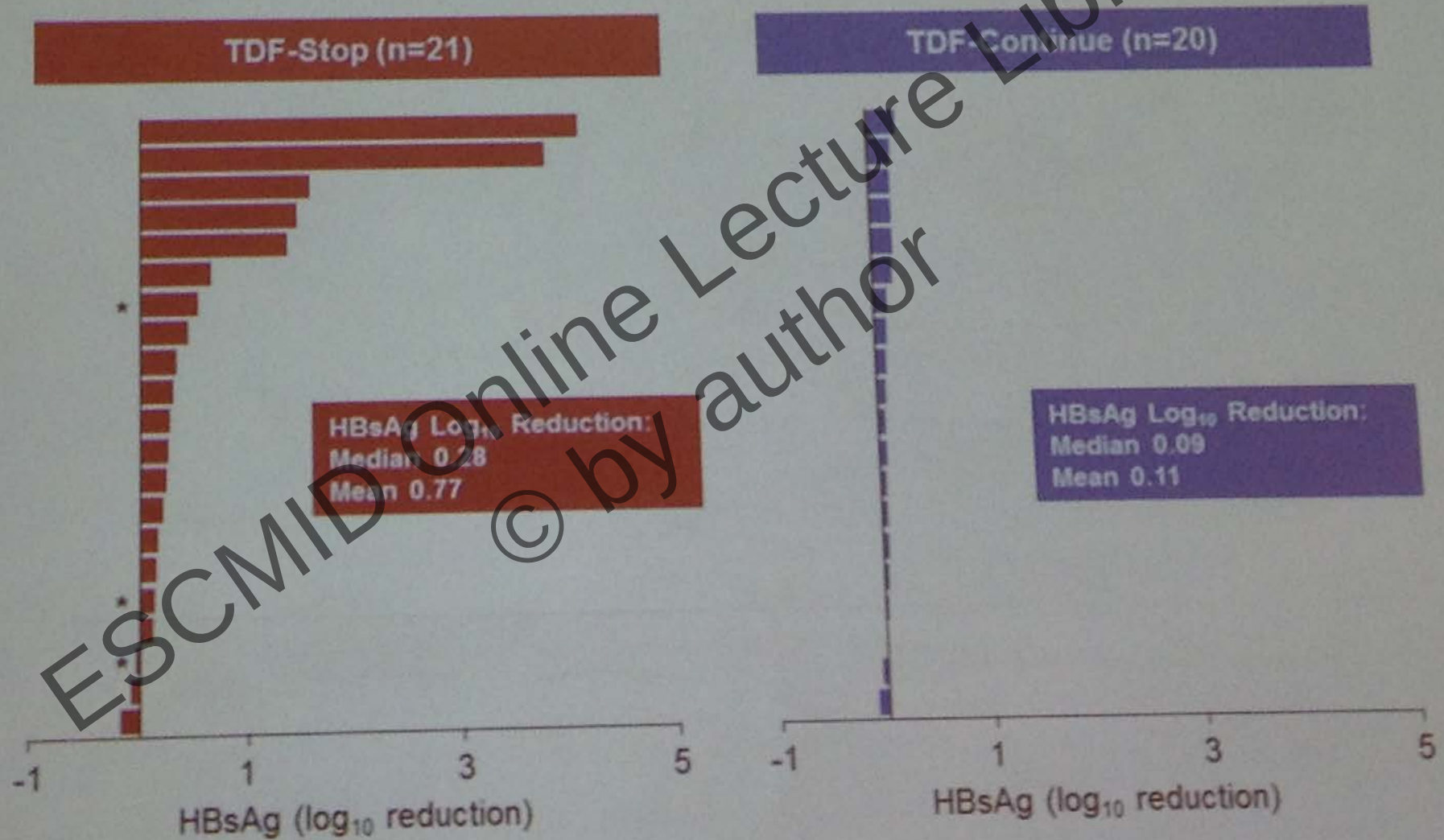
ALT Profiles



- ALT peaked at >2xULN in 12/21 TDF-Stop subjects (57%)
- ALT up to W48
  - Median: 162 U/L
  - Min: 25 U/L
  - Max: 983 U/L
- At W48*
  - 100% (18/18) ALT < 2xULN
  - 83% (15/18) ALT < ULN

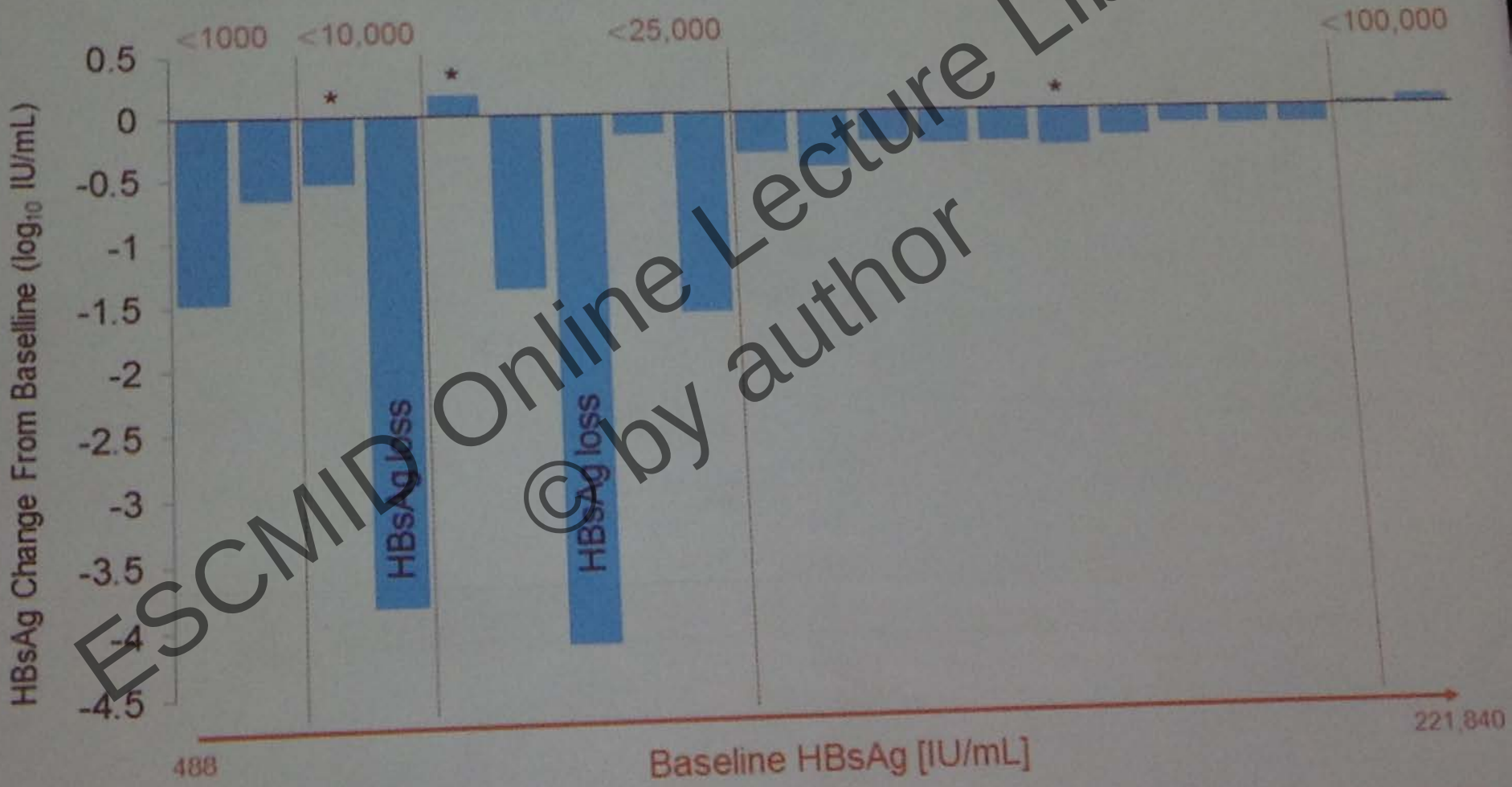
* TDF-Restart excluded

Week 48 HBsAg log_{10} Reduction (Individual Patients)

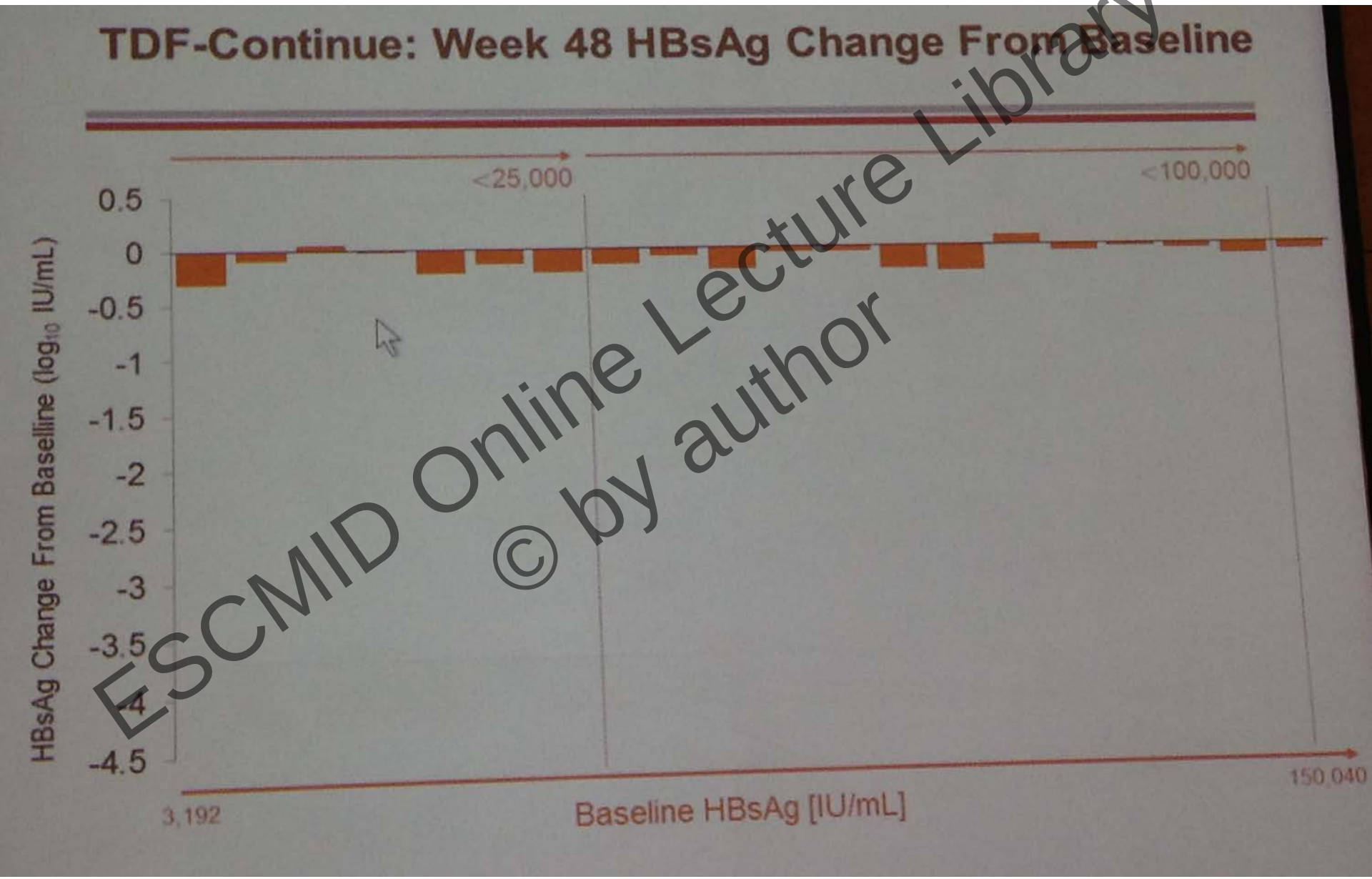


*TDF-Restart
Week 48 HBsAg value missing for 1 patient

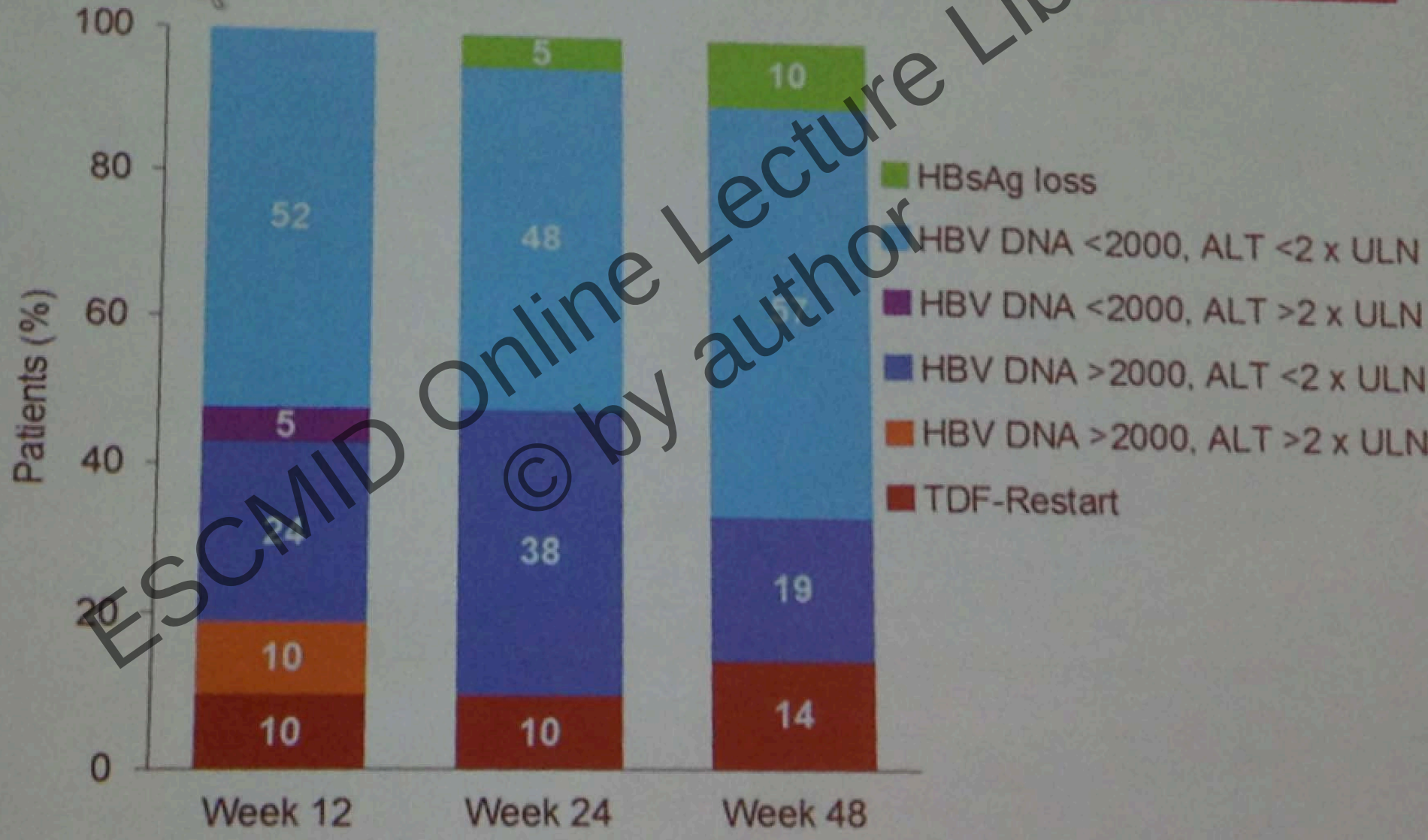
TDF-Stop: Week 48 HBsAg Change From Baseline



Positive correlation between baseline HBsAg and %change from baseline in HBsAg at Week 48 (corr.=0.62, p=0.003)



TDF-Stop: HBsAg loss, HBV DNA, ALT, TDF-Restart



FINITE-CHB Conclusions

- Stopping TDF in HBeAg (-) patients with undetectable HBV-DNA for >3.5 years is safe
- After stopping therapy, 86% have not restarted by week 48
- Stopping TDF was associated with a more profound decline in HBsAg level
- HBsAg loss was observed in two subjects (9.5%)

Discontinuation and qHBsAg

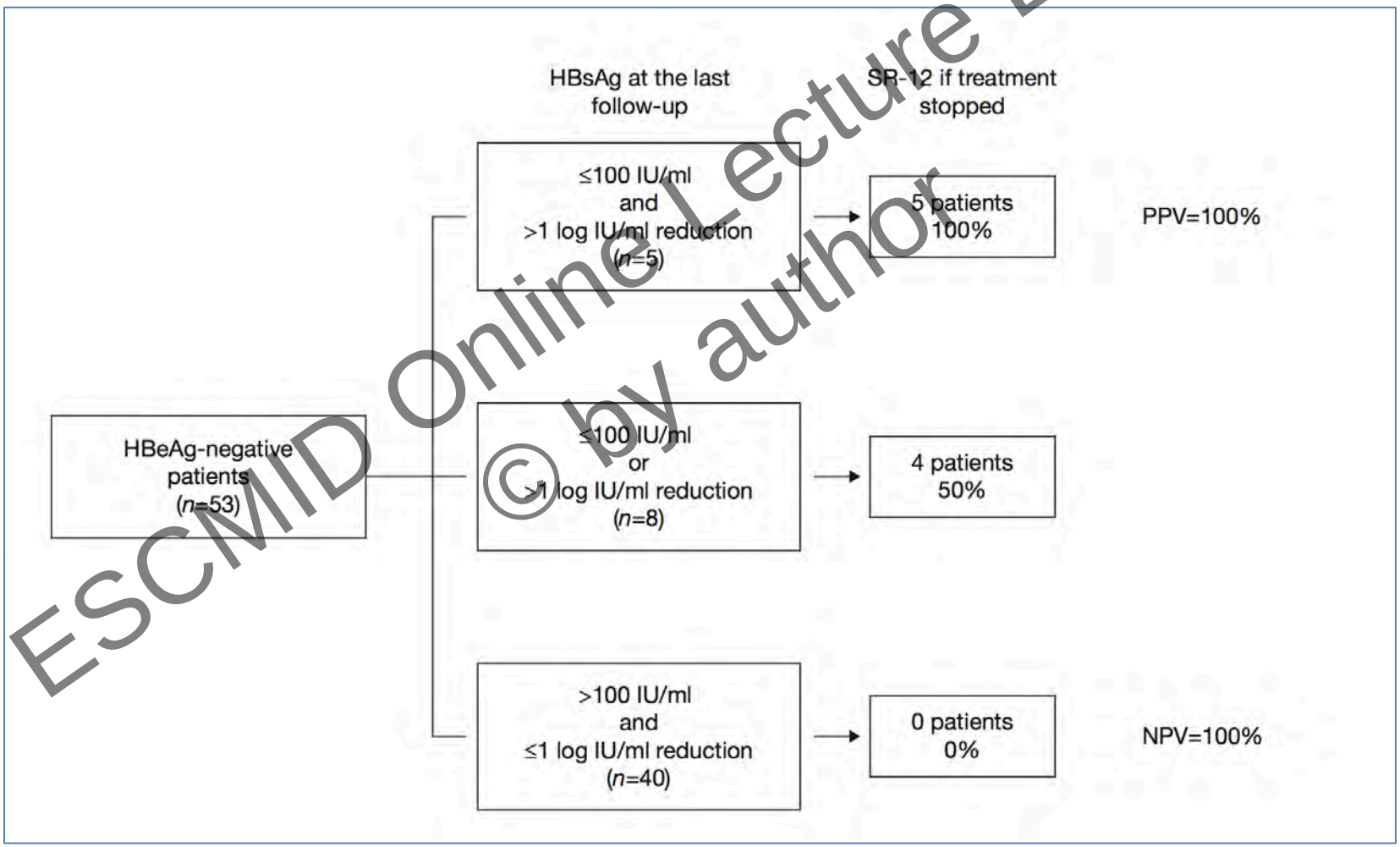
HBsAg decline >0.5 log 2 years after HBV DNA suppression correlated with HBsAg loss

Antiviral Therapy 2011; **16:**915–924

- Serum HBsAg levels < 100 IU/ml at treatment week 104 are highly predictive of SR to telbivudine at 2 years off-treatment

J Clin Virol 2010;48:22–26

- HBsAg decline >1 log after 1 year corresponds with HBsAg loss



Antivir Ther 2011;16:1249-1257.

HBsAg to Predict Off-Response-IFN

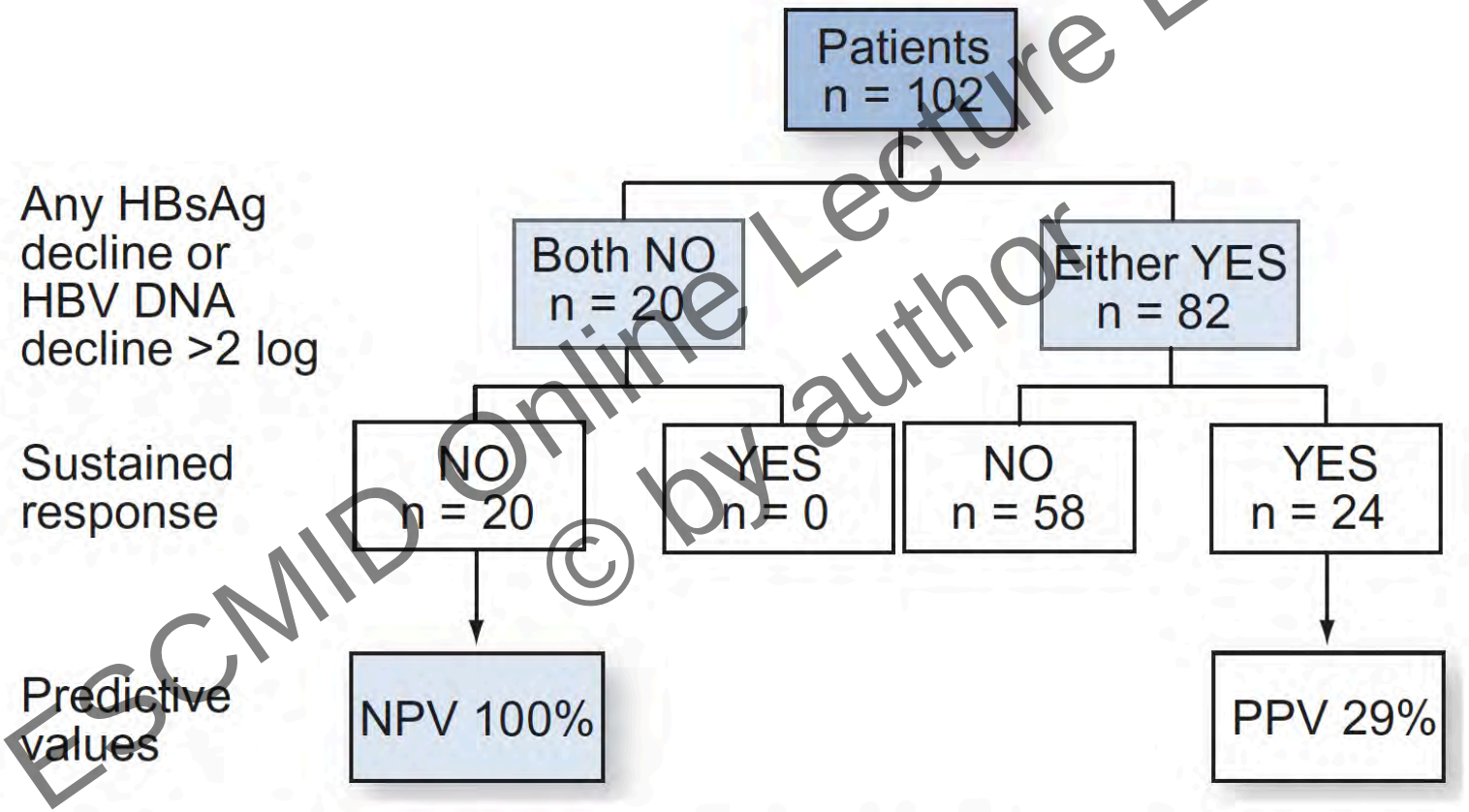


Fig. 3. Flow chart on the use of HBV DNA and HBsAg to predict response to peginterferon treatment in the PARC study.

J Hepatol 2011;55:1121–1131

HBsAg to Predict Off-Response-NA

- A rapid serum HBsAg decline during NA therapy may identify patients who will clear HBsAg in the long-term.
  - Asian patients; HBsAg level of <100 IU/ml might predict lower risk of relapse after stopping NA

Conclusion

- NA treatment can be discontinued in HBeAg-negative, non-cirrhotic patients
- Discontinuation of NA after suppression of HBV for >3 years seems safe
- Discontinuation is followed by a virological and (in some) biochemical relapse

Conclusion

- Relapse improves during follow-up
  - Around 1/3 may need re-treatment
- In some patients, HBsAg loss can be seen