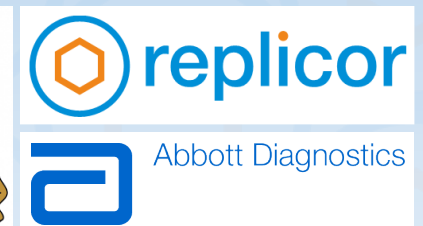
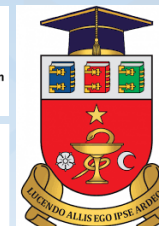


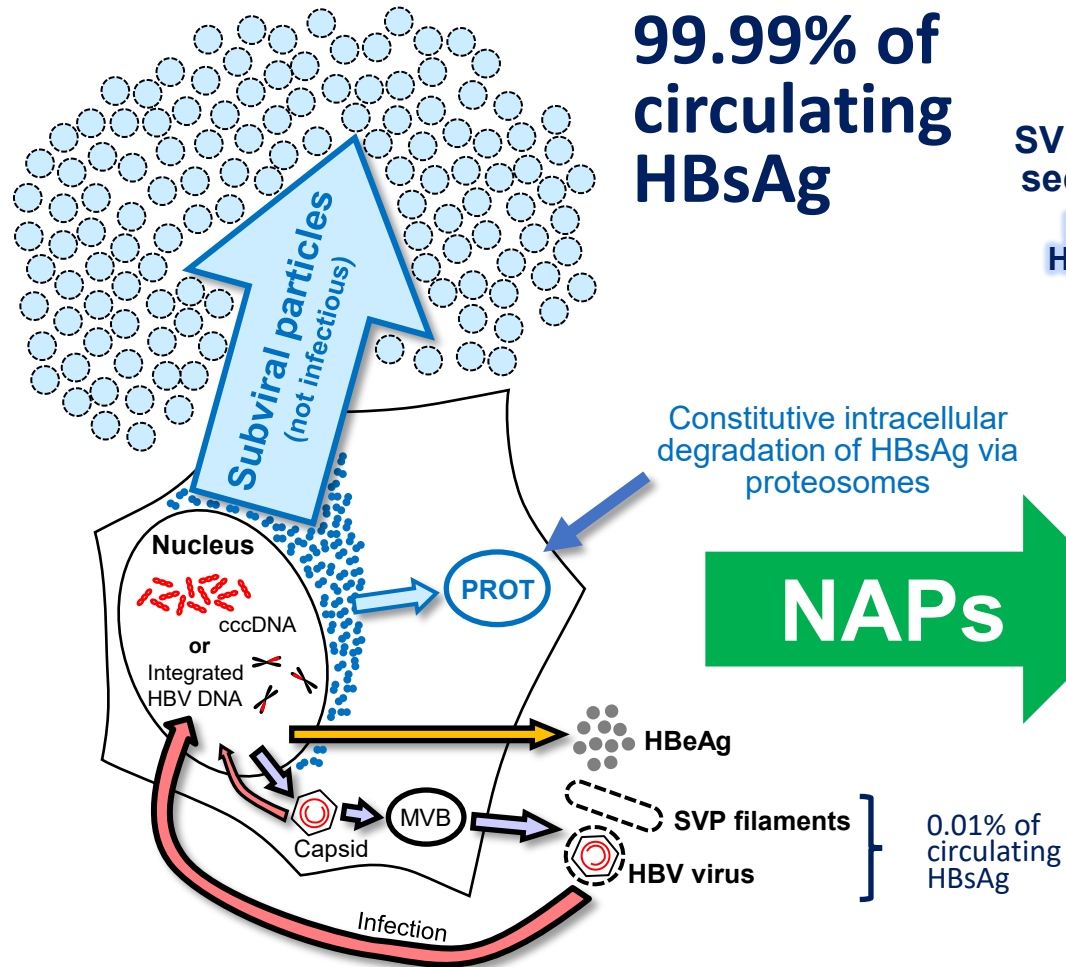
Experimental endpoint analysis during NAP-based therapy

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Chief Scientific Officer
Replicor Inc.



Antiviral effects of NAPs

Primary barrier to functional cure



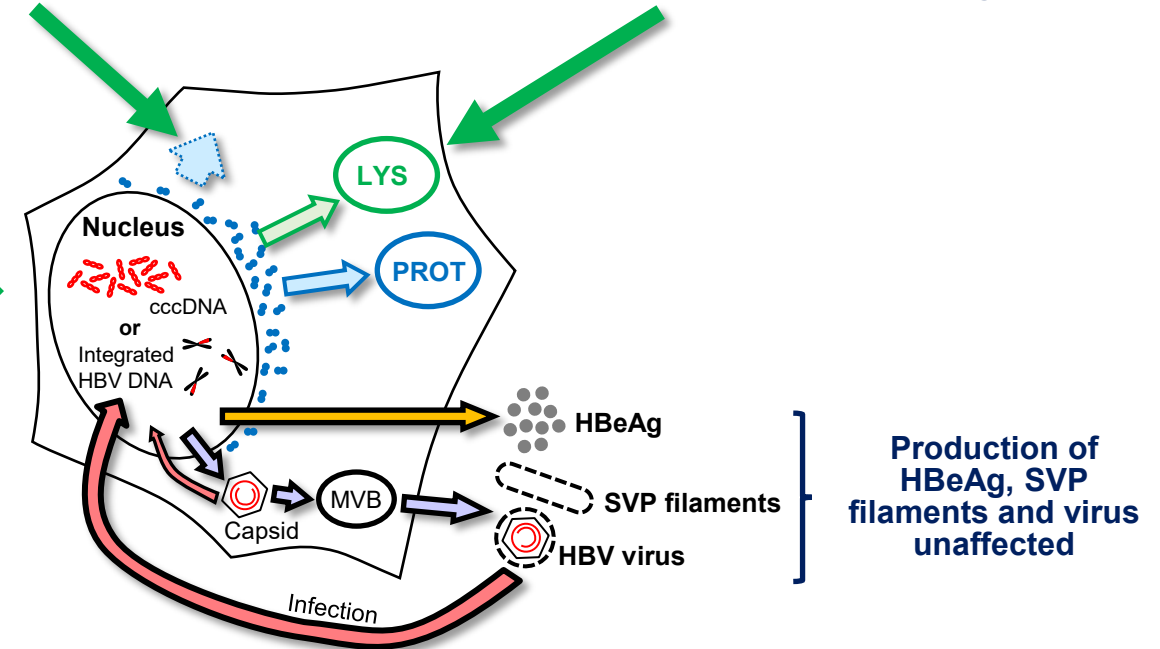
NAPs permit host mediated clearance of SVP and restoration of immune control of HBV infection

SVP assembly and secretion blocked

Interaction with
HSP40 chaperone
DNAJB12

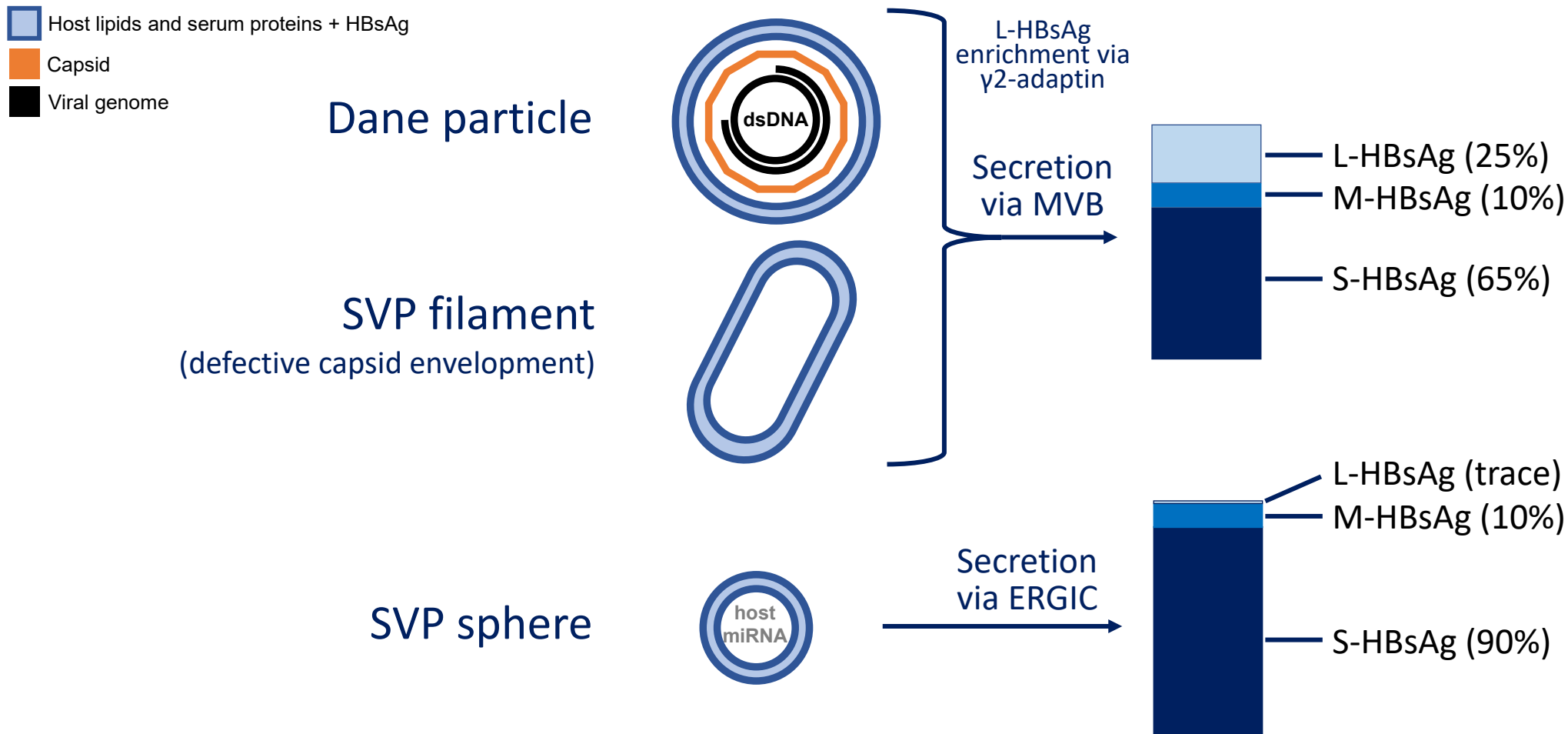
Enhanced degradation of
intracellular HBsAg in lysosomes

Reduced levels of intracellular HBsAg



HBsAg isoform content in various secreted HBV particles

Vaillant ACS Inf Dis 2020 Dec 10



Selective targeting of SVP will result in selective decline in S-HBsAg

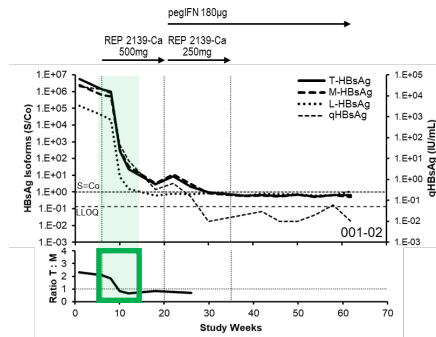
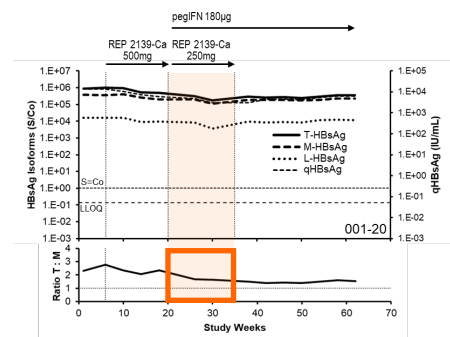
REP 301 / 401: Validating the NAP mechanism in the clinic

Change in S-HBsAg content: change in ratio of total HBsAg (S+M+L) : preS2 (M+L) over time

Weak HBsAg response

Strong HBsAg response

REP 301
(HBV / HDV)

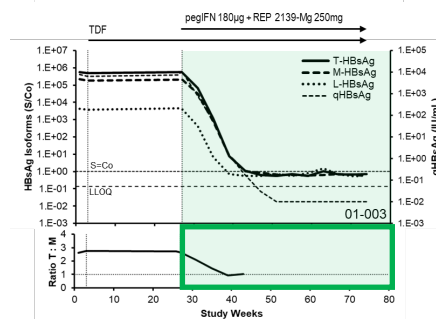
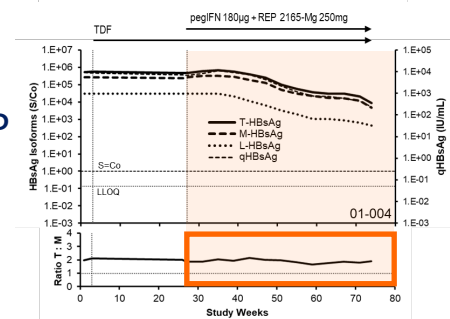


Weak HBsAg declines not accompanied by selective decline in S-HBsAg

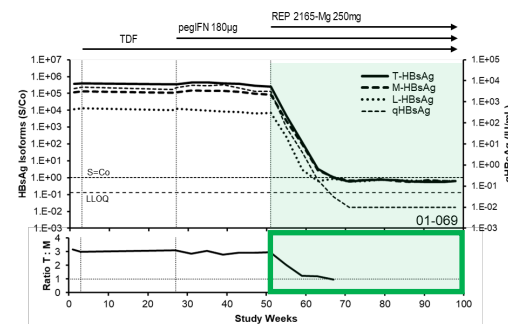
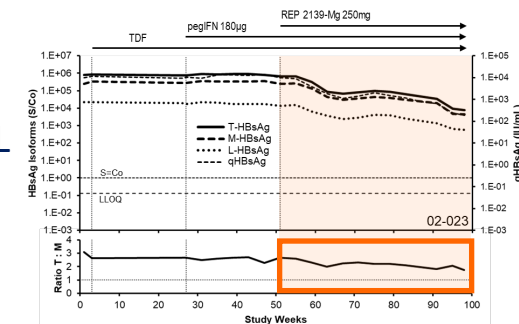
Strong HBsAg declines with NAPs are accompanied by selective decline of S-HBsAg

REP 401
(HBV)

EXP



CTL

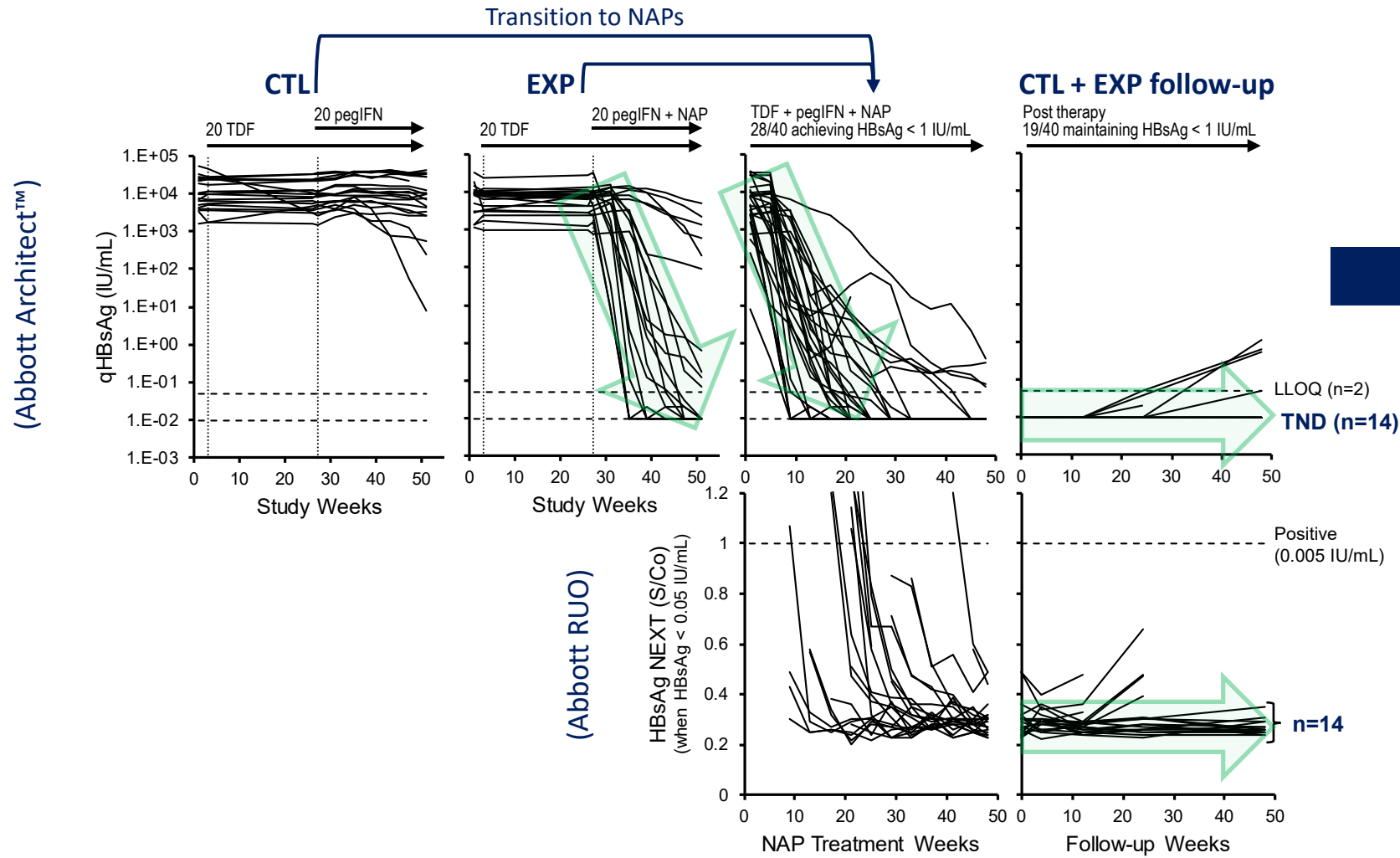


Correlation between selective S-HBsAg clearance during therapy and qHBsAg response

| qHBsAg response during therapy (decline from baseline) | Total | Selective S-HBsAg decline | p-value |
|--|-------|---------------------------|---------|
| < 2 log ₁₀ IU/mL | 10 | 1 | < 0.01 |
| > 2 log ₁₀ IU/mL | 42 | 39 | |

Strong HBsAg decline with introduction of NAP therapy is accompanied by selective clearance of SVP

REP 401: NAPs dramatically improve rates of HBsAg loss



14/40 functional cure

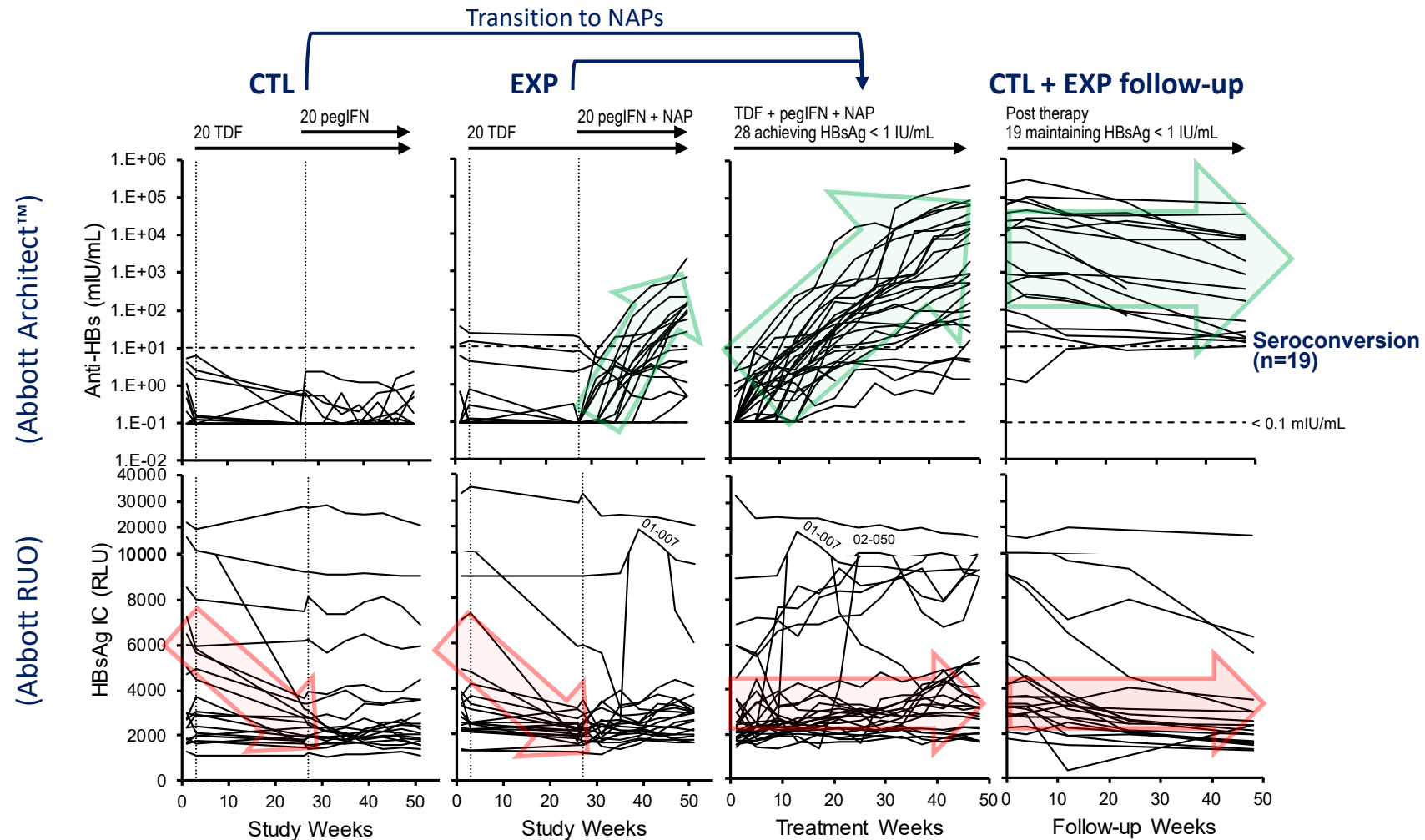
HBsAg < 0.05 IU/mL
HBV DNA TND
Normal ALT

15/40 partial cure

HBV DNA < 2000 IU/mL
Normal ALT

HBsAg clearance during therapy
is profound!
< 0.005 IU/mL
Maintained with functional cure

REP 401: HBsAg seroconversion and its role in HBsAg clearance



HBsAg seroconversion

- Occurs during therapy in all participants with partial and functional cure
- Maintained 14/14 participants with functional cure
- Lost in 10/15 participants with partial cure

HBsAg seroconversion during therapy does not predict functional cure

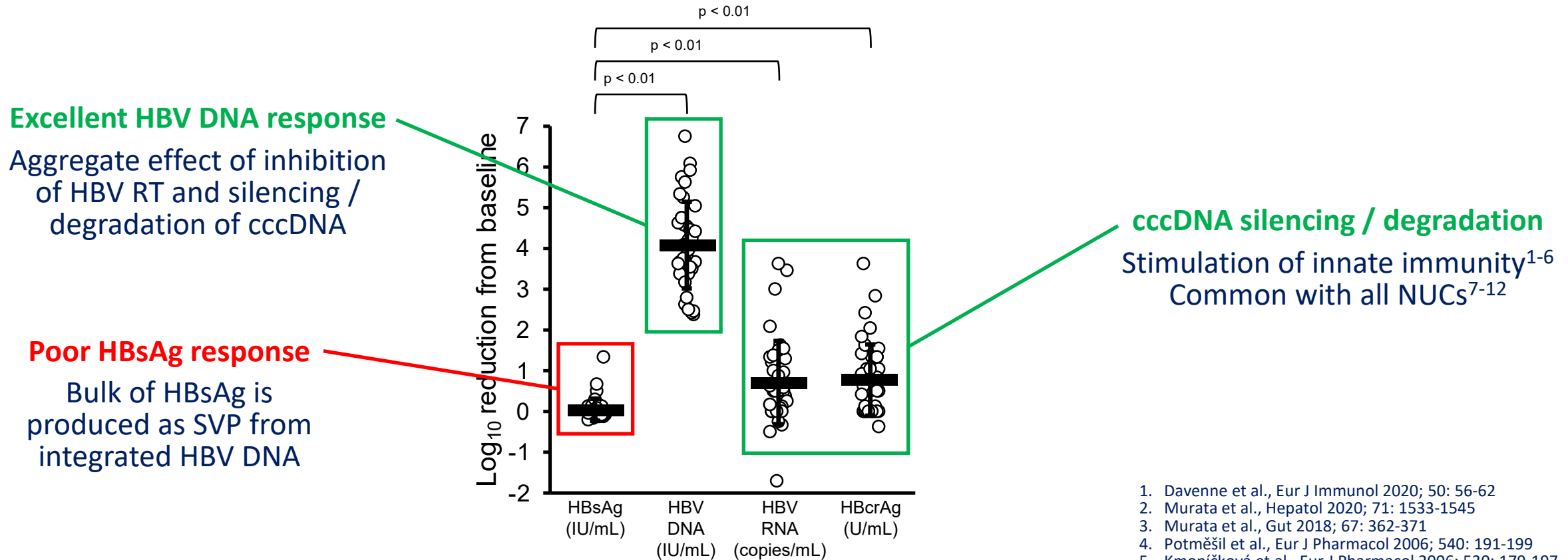
HBsAg immunocomplexes

- Decline during TDF in 36/40 participants
- Increases are absent despite profound seroconversion in 34/40 participants
- Immunocomplexes remain low during follow-up in all participants with functional cure
- **HBsAg clearance is anti-HBs independent**
- **Persistent HBsAg < 0.005 IU/mL with functional cure signals absence of HBsAg production**

Indicates removal of integrated HBV DNA and silencing of cccDNA

REP 401: Bifunctional nature of TDF monotherapy

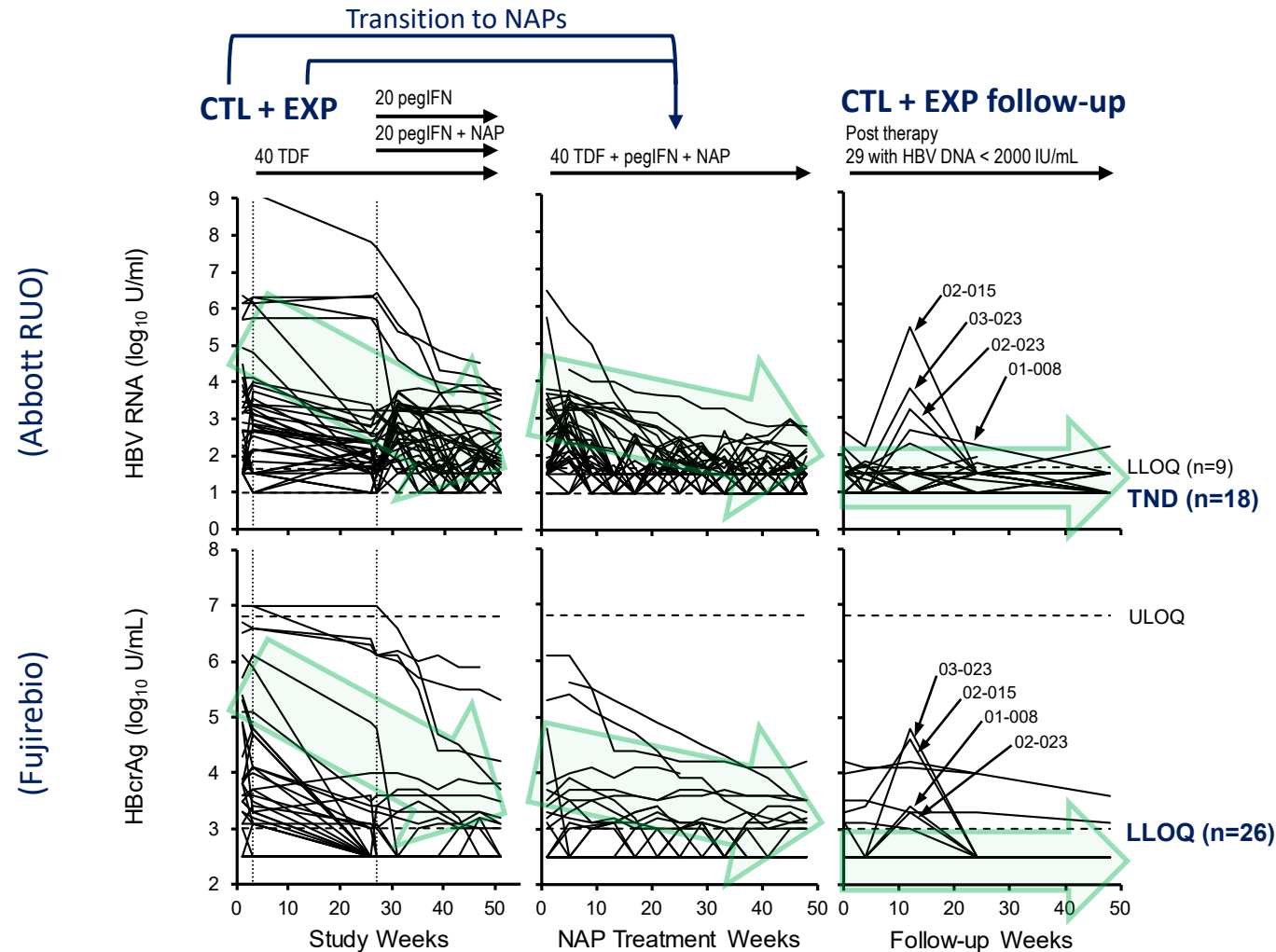
Virologic response to 24 weeks lead-in TDF monotherapy in the REP 401 study



1. Davenne et al., Eur J Immunol 2020; 50: 56-62
2. Murata et al., Hepatol 2020; 71: 1533-1545
3. Murata et al., Gut 2018; 67: 362-371
4. Potměšil et al., Eur J Pharmacol 2006; 540: 191-199
5. Kmoníčková et al., Eur J Pharmacol 2006; 530: 179-197
6. Dahari et al., Hepatology 2020; Nov 13
7. Carey et al., Hepatol. 2020 72: 42-57
8. Bommel et al., Hepatology 2015; 61: 66-76
9. Lai et al., J Hepatology 2017; 66: 275-281
10. Van Campenhout et al., Clin Microbiol Inf 2016; 22: 571.e6
11. Liu et al., Alimentary Pharmacol Therap 2020; 52: 692-700
12. Suslov et al. J Heptaol 2021; 74: 794-800

REP 401: Role of cccDNA silencing in achieving functional cure

cccDNA activity measured via HBV RNA and HBcrAg



Steady decline in cccDNA during therapy

- Similar in the presence / absence of NAPs.
- Similar in all outcome groups
(Rebound, partial cure or functional cure)
- cccDNA activity detected in partial cure and functional cure groups at the end of therapy

Inactivation of cccDNA does not predict outcome

Strong silencing of cccDNA during follow-up

- Self resolving flare in cccDNA activity consistent with viral flare (HBV DNA) in 4 participants
- HBV RNA TND and HBcrAg < LLOQ persistently maintained off-therapy in all participants establishing functional cure

Summary

Selective inhibition of SVP assembly by NAPs observed *in vitro* and *in vivo* is occurring with NAPs in the clinic

HBsAg clearance is mostly anti-HBs independent and HBsAg seroconversion does not predict functional cure

Functional cure is predicted by strong host mediated transaminase flares with HBsAg < 1 IU/mL

Bazinet et al., J Viral Hep. 2021; 5: 817-825

HBsAg loss off therapy is maintained in the absence of antibody mediated clearance (HBsAg IC)

Indicates silencing of cccDNA and removal of integrated HBV DNA during NAP-based therapy

cccDNA inactivation is progressive with TDF monotherapy and NAP-based therapy

But complete silencing during therapy is accompanied by viral rebound in the absence of HBsAg loss

Establishment of functional cure maintains persistent silencing of cccDNA