RESOLVED:
TENOFOVIR IS NO MAS!

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Professor of Medicine
Division of Liver Diseases
Director Institute for Liver Medicine
The paradox of HBV evolution as revealed from a 16th century mummy

Zoe Patterson Ross¹, Jennifer Klunk², Gino Fornaciari³, Valentina Giuffra³, Sebastian Duchêne⁴, Ana T. Duggan², Debi Poinar², Mark W. Douglas⁵, John-Sebastian Eden¹, Edward C. Holmes¹*, Hendrik N. Poinar²,⁶,⁷*
In Ancient Skeletons, Scientists Discover a Modern Foe: Hepatitis B
From 15 sets of skeletal remains, researchers have recovered DNA from the oldest viruses known to have infected humans — and have resurrected some strains in the laboratory.
The viruses were all strains of hepatitis B. Two teams of researchers independently discovered its DNA in 15 ancient skeletons, the oldest a farmer who lived 7,000 years ago in what is now Germany.

The older the virus, the newer the drug needs to be!
Plasma Tenofovir Exposure Following Administration of TDF vs TAF with Third Agents

In Combination with FTC/TDF (Historical Data)1-8

In Combination with FTC/TAF9-11

TAF 25 mg plus a boosted PI results in 80% lower tenofovir exposures than E/C/F/TDF, as well as TDF 300 mg plus the same boosted third agent.

Projected* tenofovir exposures with FTC/TAF 200/25 mg

*Projected TFV exposures were estimated from FTC/TAF 10 mg from study GS-US-311-1089 with ATV+RTV, LPV/r, and DRV+RTV, GS-US-311-1388 with ATV+COBI as separate components5, and GS-US-292-0102 with DRV/c as a STR6; TFV exposures at FTC/TAF 25 mg was estimated by linear scaling of TFV exposures from TAF 10 mg 7 given as E/C/F/TDF; 8 given as E/C/F/TAF 10 mg; RPV, EFV, and DTG with FTC/TAF 25 mg from Study GS-US-311-1089

TFV
HEPATOCYTE

TFV
RENAL TUBULAR CELL

TFV
PLASMA

OAT 1 & 3

TFV
RENAL TUBULAR CELL

OAT 1 & 3

TFV

TFV → TFV-DP

HBV

GI TRACT

DIANION

TFV (tenofovir)

ESTER

TDF (tenofovir disoproxil fumarate) 300 mg

AMIDATE

TAF (tenofovir alafenamide) 25 mg

short plasma half-life

~90% LOWER PLASMA TFV

TAF – A Novel Prodrug of Tenofovir

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TDF = 0.4 minutes, TAF = 90 minutes.


Background and Aim

- Tenofvir (TFV) disoproxil fumarate (TDF) is associated with decreases in hip and spine bone mineral density (BMD) in HIV and CHB patients\(^1,2\)

- **Tenofvir alafenamide (TAF)**
  - New TFV prodrug; greater plasma stability than TDF
  - Enhances delivery of active drug (TFV-diphosphate) to hepatocytes
  - Reduces circulating levels of TFV relative to TDF\(^3\)
  - Improved bone safety has been demonstrated in CHB patients\(^4,5\)

- **Study Aim**
  - To explore factors associated with changes in BMD over 48 weeks in CHB patients treated with TAF compared with TDF

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TAF HBV Phase 3 Program

Two phase 3, randomized, double-blind studies

Inclusion criteria
- HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females)

Primary endpoint (non-inferiority margin of 10%):
- HBV DNA <29 IU/mL at Week 48

Key secondary safety endpoints
- Bone mineral density and renal parameters at Week 48

Amendment to extend double-blind to Week 144 and open-label phase to Week 384 (Year 8) is currently underway

Non-inferiority margin of 10%

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Study 108
HBeAg- (N=425)

Study 110
HBeAg+ (N=873)

TAF 25mg

TDF 300mg

Open-label

TAF 25 mg
Similar and non-inferior rates of virologic suppression with TAF and TDF at Week 48

- No resistance detected in either treatment group
Study 110: Phase 3 CHB Study: TAF vs TDF

**HBV DNA Response at 48 Weeks**

- Similar and non-inferior rates of virologic suppression with TAF and TDF at Week 48
- No resistance detected in either treatment group

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**HBV DNA <29 IU/mL (%)**

- Treatment difference -3.6% (-9.8, +2.6); p=0.25

**Log<sub>10</sub> HBV DNA Change**

- TAF: 64% (Wk 48)
- TDF: 67% (Wk 48)
ALT Normalization at 48 Weeks

TAF showed statistically significant increased ALT normalization rates utilizing AASLD ALT criteria

Central Laboratory

Study 108

- TAF: P = 0.076
- TDF: 83%, 75%

AASLD

- P < 0.001
- TAF: 50%
- TDF: 32%

Study 110

- TAF: P = 0.18
- TDF: 72%, 67%

- P = 0.014
- TAF: 45%
- TDF: 36%

Central lab upper limit of normal (ULN): males ≤43 U/L, females ≤34 U/L (≥69 y, males ≤35 U/L, females ≤32 U/L); AASLD ULN: males ≤30 U/L, females ≤19 U/L.

Buti EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF
Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

**Results: Renal Safety**

![Graph showing mean (SD) change in eGFR\textsubscript{CG} at different study weeks with TAF and TDF treatments.]

- **TAF**
  - n=866
  - Change in sCr, mg/dL: 0.010 (0.11)
- **TDF**
  - n=432
  - Change in sCr, mg/dL: 0.024 (0.10)

<table>
<thead>
<tr>
<th></th>
<th>TAF</th>
<th>TDF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in sCr, mg/dL</td>
<td>0.010 (0.11)</td>
<td>0.024 (0.10)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Subjects receiving TAF experienced significantly less change in eGFR\textsubscript{CG} and sCr at Week 48 compared to TDF.

Continuous data are expressed as mean (SD)
sCr, serum creatinine; eGFR\textsubscript{CG}, creatinine clearance by Cockcroft-Gault
Buti EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12
Gilead Sciences, Data on File
Results: Quantitative Proteinuria at Week 48

Changes in tubular proteinuria were significantly lower with TAF compared to TDF
Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Results: BMD Changes at Week 48

Higher proportion of TAF patients had significantly less or no BMD decrease compared to TDF patients

*All categories
- Buti, EASL 2016, Oral GS06
- Chan, EASL 2016, Oral GS12
Mean Changes in BMD Through Week 72

- TAF treatment resulted in smaller decline in Hip and Spine BMD compared to TDF.

- Values from the ANOVA model including treatment as a fixed effect.
Safety And Efficacy At 1 Year After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide In Chronic HBV Patients With Risk Factors for Bone Disease and Renal Dysfunction With TDF Use

<table>
<thead>
<tr>
<th>Baseline Condition</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>&gt;60 y*</td>
</tr>
<tr>
<td>Bone diseases</td>
<td>Osteoporosis by hip and/or spine T-score*</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>CKD Stage ≥2 (BL eGFR&lt;sub&gt;CG&lt;/sub&gt; &lt; 90 mL/min)†</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Urine albumin:creatinine &gt;30 mg/g*</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Serum phosphate &lt;2.5 mg/dL*</td>
</tr>
<tr>
<td>Obesity</td>
<td>Body mass index ≥30 kg/m²</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Hypertension, diabetes mellitus, CV disease, or hyperlipidemia</td>
</tr>
</tbody>
</table>

*Risk factors for TDF use in EASL HBV guidelines 2017; †eGFR <60 mL/min/1.73m² used in EASL HBV guidelines.

BL, baseline; CKD, chronic kidney disease.
Study Design

- Two Phase 3, randomized, double-blind, active-controlled trials
  - Study 108 (N=425): HBeAg-negative patients
  - Study 110 (N=873): HBeAg-positive patients
- Key inclusion criteria (both studies)
  - HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males) >38 U/L (females); eGFR$_{CG}$ ≥50 mL/min
- 2:1 randomization
  - Stratified by HBV DNA level and treatment status (naïve/experienced)

ALT, alanine aminotransferase; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault method; HBeAg, hepatitis B e antigen.
**Study Design**

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- 2:1 randomization
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*Study has been amended to extend the double blind to Week 144 and open-label to Week 384 (Year 8).
## Results: Baseline Demographics and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No TDF Risk Factors</th>
<th>≥1 TDF Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAF → TAF n=177</td>
<td>TDF → TAF n=79</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>33 (19–56)</td>
<td>36 (18–56)</td>
</tr>
<tr>
<td>Age &gt;60 y, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>53 (30)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>140 (79)</td>
<td>60 (76)</td>
</tr>
<tr>
<td>Nucleos(t)idine experienced, n (%)</td>
<td>48 (27)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>HBeAg-, n (%)</td>
<td>46 (26)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>HBV genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>15 (9)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>B</td>
<td>34 (19)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>C</td>
<td>86 (49)</td>
<td>35 (44)</td>
</tr>
<tr>
<td>D</td>
<td>41 (23)</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Median HBV DNA, log_{10} IU/mL (Q1, Q3)</td>
<td>7.7 (5.9, 8.3)</td>
<td>7.5 (6.1, 8.2)</td>
</tr>
<tr>
<td>Median ALT, U/L (Q1, Q3)</td>
<td>83 (57, 128)</td>
<td>88 (53, 132)</td>
</tr>
<tr>
<td>Median eGFR_{CG}, mL/min (Q1, Q3)</td>
<td>112 (103, 127)</td>
<td>113 (101, 136)</td>
</tr>
<tr>
<td>eGFR_{CG} &lt;90 mL/min, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Osteoporosis BMD Status (T-score &lt;-2.5), n (%)</td>
<td>Hip</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spine</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>23 (13)</td>
<td>18 (18)</td>
</tr>
</tbody>
</table>

*BMD, bone mineral density; Q, quartile.
Results: HBV DNA <29 IU/mL in Patients with ≥1 TDF Risk Factor

- **TAF → TAF**
  - 96 weeks: 166/183 (91%)
  - 144 weeks: 162/183 (89%)

- **TDF → TAF**
  - 96 weeks: 89/101 (88%)
  - 144 weeks: 85/101 (84%)

- Viral suppression was maintained in CHB patients that switched from TDF to TAF at week 96
Results: HBV DNA <29 IU/mL in Patients with ≥1 TDF Risk Factor

- Viral suppression was maintained in CHB patients that switched from TDF to TAF at week 96
- No mutations associated with resistance to TAF or TDF (sequence and phenotypic analysis) were detected
Results: Changes in Spine Bone Mineral Density (BMD)

No TDF Risk Factors

≥1 TDF Risk Factor
Conclusions

- The majority of patients on treatment at Week 96 had at least one risk factor for TDF toxicity at baseline.

- Among CHB patients with TDF risk factors, switching from TDF to TAF treatment is associated with:
  - Maintenance of viral suppression
  - Improvement in bone and renal safety parameters

- Longer-term follow-up is required to determine the clinical relevance of these findings.
High HBV and HIV Suppression With Treatment of HIV/HBV Coinfection in B/F/TAF Studies

Jürgen K. Rockstroh,1 Paul E. Sax,2 Eric S. Daar,3 Sharon Walmsley,4 Kim Workowski,6 Chloe Orkin,6 Jose R. Arribas,7 Edwin DeJesus,8 David Wohl,9 Jean-Michel Molina,10 David Plontkowski,11 Xuelian Wei,11 Hal Martin,11 Andrew Cheng,11 Erin Quirk11

1Universitätsklinikum Bonn, Germany; 2Brigham and Women’s Hospital, Boston, MA; 3Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA; 4Toronto General Hospital, Toronto, Ontario, Canada; 5Emory University, Atlanta, GA; 6Barts Health NHS Trust, The Royal London Hospital, Barts Health NHS Trust, London, UK; 7Hospital Universitario La Paz, Madrid, Spain; 8Orlando Immunology Center, Orlando, FL; 9University of North Carolina at Chapel Hill; 10Hôpital Saint-Louis, Paris, France; 11Gilead Sciences, Inc., Foster City, CA

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**Treatment-Naive Study Designs**

- **Study 1489**
  - Treatment-Naive Adults
  - HIV-1 RNA ≥500 copies/mL
  - eGFR ≥50 mL/min
  - HLA B*5701 negative
  - Active HBV excluded

- **Study 1490**
  - Treatment-Naive Adults
  - HIV-1 RNA ≥500 copies/mL
  - eGFR ≥30 mL/min
  - Active HBV allowed

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**Switch Study Designs**

- **Study 1844**
  - HIV-Suppressed Adults on ABC/3TC/DTG
  - HIV-1 RNA <50 copies/mL
  - eGFR ≥50 mL/min
  - Active HBV excluded

- **Study 1878**
  - HIV-Suppressed Adults on Boosted DRV or ATV + 2 NRTIs
  - HIV-1 RNA <50 copies/mL
  - eGFR ≥50 mL/min
  - Active HBV allowed if suppressed on F/TDF

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**Primary Endpoint**

- ABC/3TC/DTG placebo qd
- B/F/TAF placebo qd
- Extension Phase

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**Week 0**

- n=314
- n=315
- n=320
- n=325

**Primary Endpoint**

- B/F/TAF qd
- ABC/3TC/DTG placebo qd
- DTG + B/F/TAF placebo qd
- DTG + F/TAF placebo qd

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**Week 48**

- Switch to B/F/TAF qd
- ABC/3TC/DTG placebo qd
- Continue ABC/3TC/DTG qd
- Switch to B/F/TAF qd

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**Week 281**

- n=282

**Extension Phase**

- n=281

**Week 287**

- n=290
- n=287
- SBR
Conclusions

- B/F/TAF- and F/TAF-containing regimens produced robust HBV antiviral responses in treatment-naive participants with HIV/HBV coinfection
  - 85% of participants (11/13) achieved HBV DNA <29 IU/mL at Week 48
  - No participant developed HBV resistance to FTC or TAF; the 2 without HBV DNA <29 IU/mL at Week 48 had decreases in HBV DNA from >170,000,000 IU/mL at baseline to <400 IU/mL at Week 48
  - 15% had HBsAg loss and seroconverted to HBsAb-positive status at Week 48
  - 25% of HBeAg-positive participants experienced HBeAg loss at Week 48
  - 100% had HIV-1 RNA <50 copies/mL at Week 48

- B/F/TAF- and F/TDF-containing regimens maintained HIV-1 virologic suppression in HIV/HBV-coinfected participants with HIV-1 suppression at study entry
  - 100% of participants with HBV suppression at baseline had HBV DNA <29 IU/mL at Week 48
  - 1/4 (25%) who were HBeAg positive at baseline had HBeAg conversion at Week 48
  - 100% with Week 48 HIV-1 RNA results had HIV-1 RNA <50 copies/mL at Week 48

- No participant treated with B/F/TAF, or an F/TAF- or F/TDF-containing regimen acquired HBV infection during the studies
  - 1 treated with ABC/3TC/DTG had incident HBV infection with confirmed HBV viremia at Week 48

- The results confirm findings from prior studies of ART with anti-HBV activity in patients with HIV/HBV coinfection:
  - Higher HBsAb seroconversion rates than in chronic HBV mono-infection\(^9\)
  - Not all patients become undetectable after 48 wk in the setting of high HBV DNA at baseline\(^10\)
    • To date, there is no evidence of HBV resistance to F/TAF-containing regimens

- B/F/TAF may be a treatment option for HIV-1–infected patients with HBV coinfection
  - Further studies of HBV treatment and prevention with B/F/TAF and other F/TAF-containing ART regimens are warranted in HIV/HBV-coinfected patients
<table>
<thead>
<tr>
<th>Participants, n/n (%)</th>
<th>Total Randomized to B/F/TAF or DTG + F/TAF With HBV DNA Results at Week 48 n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;29 IU/mL</td>
<td>11/13 (85)</td>
</tr>
<tr>
<td>HBV DNA ≥29 IU/mL</td>
<td>2/13 (15)</td>
</tr>
<tr>
<td>HBsAg conversion</td>
<td>2/12 (17)</td>
</tr>
<tr>
<td>HBeAg conversion</td>
<td>1/4 (25)</td>
</tr>
</tbody>
</table>
Switch to E/C/F/TAF in HIV/HBV co-infected patients demonstrated robust HIV and HBV suppression with favourable effects on liver safety endpoints.

*4/8 patients with available ALT data at W48
†35/60 patients with paired baseline and W48 data