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BHIVA 'Best of CROI' feedback webinars 2023

Hepatitis, TB, and SARS CoV-2

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Conflict of Interest

In relation to this presentation I declare that I have no conflict of interest

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Hepatitis

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TARGET-3D

- Open-label, single-arm pilot of 4W glecaprevir-pibrentasvir for recent HCV (<12 months)
- The primary endpoint: sustained virological response 12W post-treatment (SVR12)
- Twenty three participants with estimated duration of HCV of 7W
  - 96% men, median age 46 years
  - 70% (n=16) with HIV
  - 57% (n=13) had ever injected drugs
  - 35% (n=8) had recent reinfection
- SVR12: 78% ITT, 82% PP, 100% in n=15 with HCV-RNA <6.5$\log_{10}$
- 4 cases of relapse
- Safe & well-tolerated but lower efficacy than observed with longer therapy (6W+)

Martinello et al. Abs #194. CROI 2023, Seattle USA

ALLIANCE: multivariable analysis W48 results

- 243 adults with HIV-1/HBV randomised 1:1 to B/F/TAF or DTG+F/TDF (blinded)

- HIV-RNA <50 copies/mL: B/F/TAF noninferior to DTG+F/TDF
- HBV-DNA <29 IU/mL: BFTAF superior to DTG+F/TDF

  Avihingsanon et al., AIDS 2022

- MVA evaluated predictors of HBV DNA<29 IU/mL:
  - HBeAg-
  - HBV DNA < 8 log
  - ALT >ULN
  - Rx w B/F/TAF

Avihingsanon et al. Abs #116. CROI 2023, Seattle USA

PAGE-B

- The PAGE-B risk score, based on age, sex and platelets, is recommended for the prediction of HCC among individuals with HBV monoinfection
  - it has not been evaluated in PWH, or in Black populations

- External validation of PAGE-B in people with HIV/HBV coinfection in Europe using data from four European cohorts (Swiss HIV Cohort Study, EuroSIDA, ATHENA and Aquitaine)

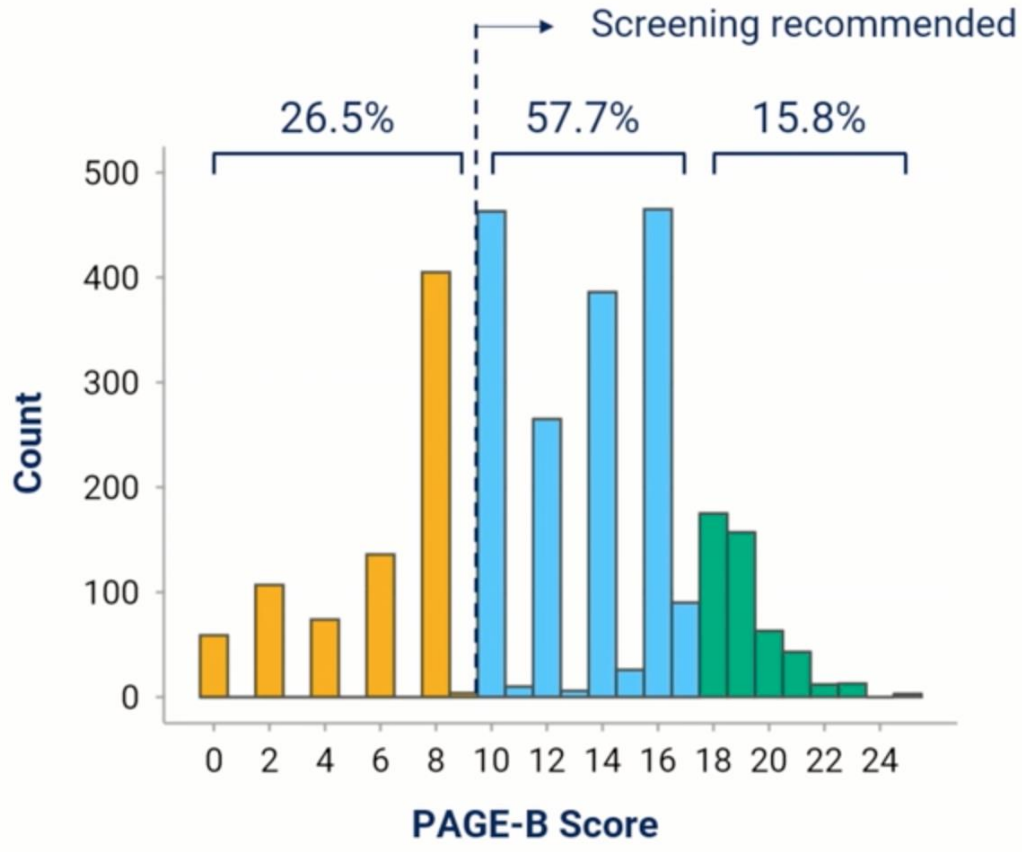
- 2,963 individuals with HIV/HBV coinfection were included

- Within a median follow-up of 9.6 years, 68 individuals developed HCC
  - PAGE-B cut-off of < 10 had a negative predictive value of 99.4% for HCC within 5 years, and the HCC risk of a score < 12 remained below the commonly accepted screening threshold

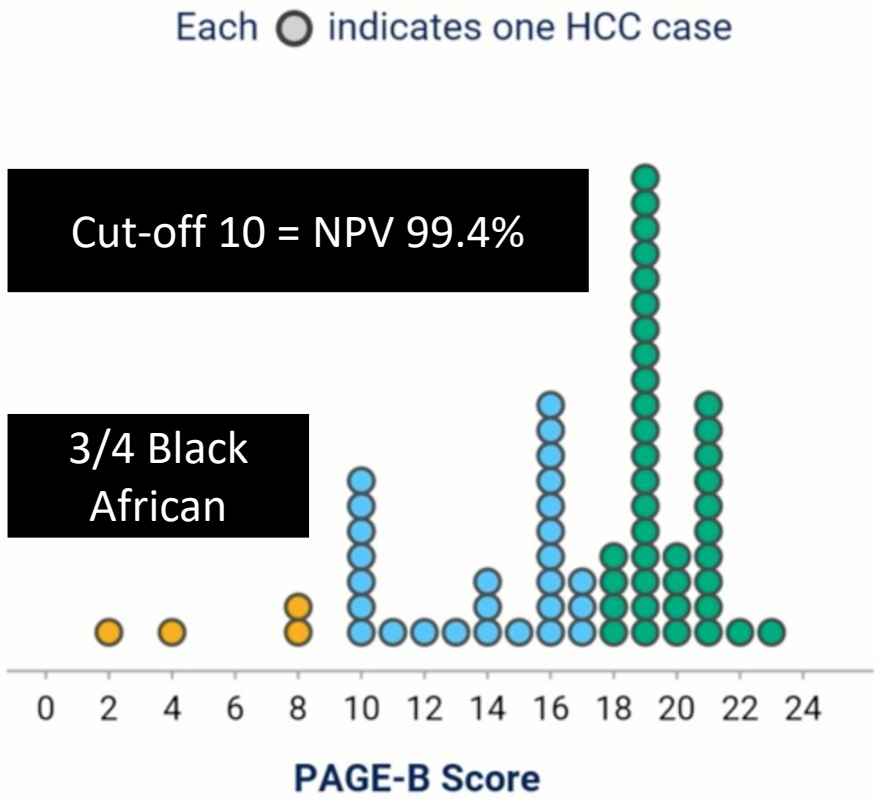
Surial et al. Abs #117. CROI 2023, Seattle USA

PAGE-B & HCC in 2963 people with HIV+HBV

Data from 4 large European cohorts, median FU 9.6 years



Median FUP 9.6 years (4.9 - 13.3)



68 HCCs (IR 2.58 per 1000 PY, CI 2.03 - 3.27)

Surial et al. Abs #117. CROI 2023, Seattle USA

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Tuberculosis

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SimpliciTB

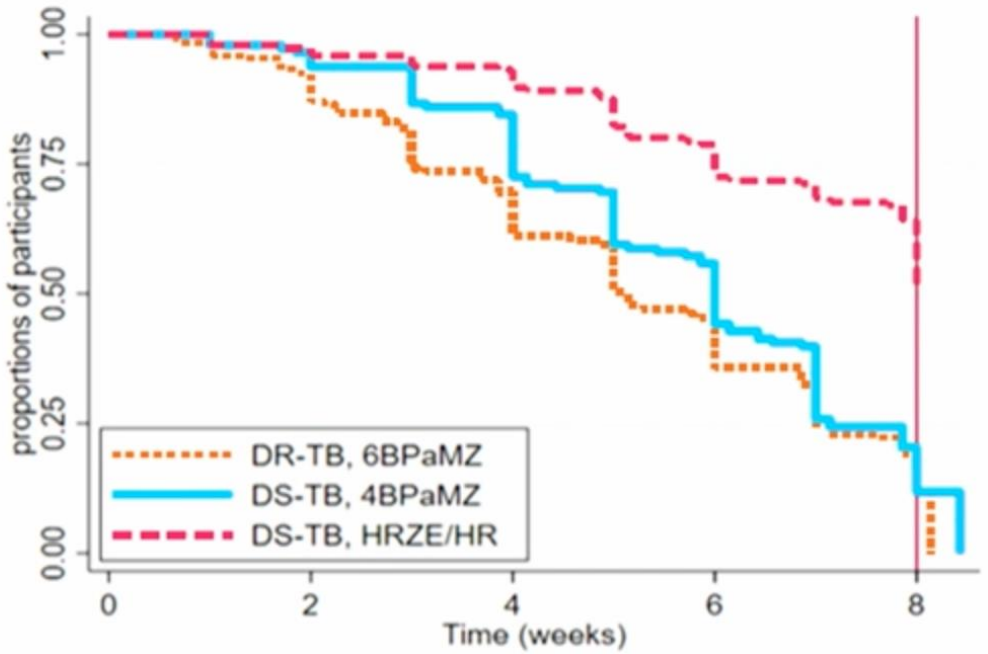
- Open-label safety and efficacy study:
  - 303 DS-TB participants randomized 1:1 to 4-months bedaquiline-pretomanid-moxifloxacin-pyrazinamide (BPaMZ) vs 6-months HRZE
  - 152 DR-TB participants given 6-months BPaMZ

- Primary efficacy endpoint was time to culture negative status through 8 weeks; a key secondary endpoint was relapse-free cure at week 52

Cevik et al. Abs #109. CROI 2023, Seattle USA

Primary Efficacy Endpoint
Time To Culture Negative Status By 8 Weeks (MITT)

SIMPLICITB



Number at risk					
DR-TB, 6BPaMZ	133	122	90	57	24
DS-TB, 4BPaMZ	145	139	119	77	26
DS-TB, HRZE/HR	148	143	136	114	93

HAZARD RATIO

4BPaMZ is superior
Culture negative by 8 weeks is more likely with BPAMZ

*2.17-3.96 (95%CI)

PROPORTION OF PTS CULTURE NEGATIVE AT WEEK 8

Drug-Sensitive TB

Drug-Resistant TB

Conclusions

SIMPLICITB

- A 4-month regimen of BPaMZ demonstrated superior time to culture negativity over 8 weeks in DS-TB patients, compared with HRZE, with a hazard ratio of > 2
  - This provides clinical correlation with the widely used relapsing mouse model, in which BPaMZ is a standard efficacy benchmark
- The trial did not demonstrate non-inferiority for clinical outcomes of BPaMZ compared to HRZE at week 52 in the mITT analysis
  - The per protocol analysis showed that BPaMZ did meet non-inferiority compared to HRZE
  - Treatment withdrawals were primarily related to hepatic enzymes elevations
- The hepatic adverse reactions associated with BPaMZ substantially differed from clinical studies of the BPaL regimen, where liver enzyme elevations were lower and very infrequently resulted in treatment discontinuation

TRUNCATE-TB

- 674 participants with rifampicin-susceptible pulmonary TB randomised to SOC for 24W, or one of four novel 5-drug regimens 8W

Standard Treatment	24w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8w	↑ Rifampicin 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

Paton et al. Abs #113. CROI 2023, Seattle USA

Analysis of regimen efficacy and safety

Efficacy

- Primary outcome: unfavourable outcome
  - Rx failure, relapse, death by W96; not evaluated at W96 & no evidence of cure at last visit
  - Censored (classified as “unassessable”): inadequate initial Rx (did not complete; switched from assigned regimen; missed 7 days by W8; restarted Rx without evidence of TB disease)
- Bayesian analysis*
  - Probability of difference in regimen unfavourable outcome vs standard regimen < 12%
  - Probability that regimen unfavourable outcome proportion < 20%

Safety

- Primary outcome: AEs ≥ Grade 3 during initial strict randomised Rx (+30 days)

*Flat (“uninformative”) prior distribution; Laptook et al JAM (2017) DOI: 10.1001/jama.2017.14972

Primary endpoint: unfavourable outcome

Rx failure, relapse, death by W96, not evaluated W96, no cure at last visit

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD (N=184)	8 weeks BDQ/LZD (N=189)
Unfavourable outcome – no (%)	7 (3.9%)	46 (25.0%)	26 (13.8%)
Treatment failure at switch to standard Rx	0 (0.0)	0 (0.0)	1 (0.5)
Treatment failure at end of treatment	0 (0.0)	0 (0.0)	1 (0.5)
Confirmed relapse	4 (2.2)	39 (21.2)	20 (10.6)
Un-confirmed relapse	0 (0.0)	0 (0.0)	3 (1.6)
Death by W96, possible TB-related cause	2 (1.1)	5 (2.7)	0 (0.0)
Did not attend W96, lacks evidence of cure at last attended visit	1 (0.6)	2 (1.1)	1 (0.5)
Unassessable outcome	6 (3.3)	29 (15.8)	16 (8.5)

Conclusions

Regimen efficacy

- Unfavourable outcome more frequent with 8wk regimens than 24wk standard regimen, as expected
- Difference modest with 5-drug BDQ/LZD regimen (high probability <12%); excess relapses can be managed within the TRUNCATE strategy*
- Biomarkers can identify subgroups with low probability of achieving target relapse rate (< 20%) with 8wk regimen. Refining criteria for treatment extension may improve strategy outcomes further.

Regimen safety

- Regimens were safe overall (severe Aes and serious AEs uncommon)
- Toxicity burden from linezolid appeared manageable
- BDQ resistance in two (1.1%) is a caution; needs monitoring in other studies

* Paton N, Cousins C, Suresh C et al. NEJM published online 20 Feb 2023: DOI: 10.1056/NEJMoa2212537

TRUNCATE-TB

- Unfavourable outcome was more frequent with 8-week regimens than the 24-week regimen, as expected

- However, with the BDQ/LZD regimen the excess was modest and likely can be reduced further by adjusting criteria for treatment extension by subgroup; the regimen was safe

- An 8-week initial treatment duration appears to be a feasible target for most people with TB, with the excess of unfavourable outcomes manageable within the TRUNCATE strategy

Paton et al. Abs #113. CROI 2023, Seattle USA

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SARS CoV-2

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Ensitrelvir

- Protease inhibitor approved in Japan under emergency regulations
- Phase 3 results presented from ambulatory low-risk cases of COVID
- Demonstrated a significant reduction in the time to resolution of 5 typical symptoms of COVID-19
  - stuffy or runny nose, sore throat, cough, feeling hot/feverish, low energy or tiredness
- Robust antiviral effects and good tolerability
- In this placebo-controlled trial, treated pts had a significantly reduced likelihood of reporting symptoms of PACS at 3 and 6 months
  - Strong argument for Rx in low-risk cases

Uehara et al. Abs #166. CROI 2023, Seattle USA

SARS IFN

- **Single dose sc pegIFN lambda (n=931) vs placebo (n=1018)**
  - Significantly decreased clinical events in IFN arm

- **Orally inhaled IFN ß1a**
  - n=221 outpatients with mild-moderate COVID-19
  - Exogenous interferon beta has broad-spectrum antiviral activity
  - Safe and well tolerated
  - No impact on SARS-CoV-2 RNA levels in nasopharynx
  - No impact on time to improvement of COVID-19 symptoms
  - Non-statistically significant decrease in hospitalisations (1 vs. 7 placebo) - warrants further investigation in a phase 3 clinical trial?

Glenn et al. Abs #167. CROI 2023, Seattle USA
Fischer et al. Abs #169. CROI 2023, Seattle USA

Metformin

- In a published phase 3, RCT of outpatient COVID-19 therapy, yielded:
  - 42% reduction in ER visits/hospitalizations/deaths by day 14
  - 58% reduction in hospitalizations/death by day 28
  - 42% reduction in Long Covid through 10 months
- This analysis presented the results of viral load sampling in that clinical trial
- Metformin lowered SARS-CoV-2 viral load
- The magnitude of antiviral effect was similar to nirmatrelvir at day 5; greater than nirmatrelvir at day 10
- Metformin induced greater VL decline than placebo - also important secondary endpoints (hospitalization and ER visits), diagnoses of Long Covid
- Metformin is safe, inexpensive, widely available, and has few contraindications

Bramante et al. Abs #170. CROI 2023, Seattle USA

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Mpox

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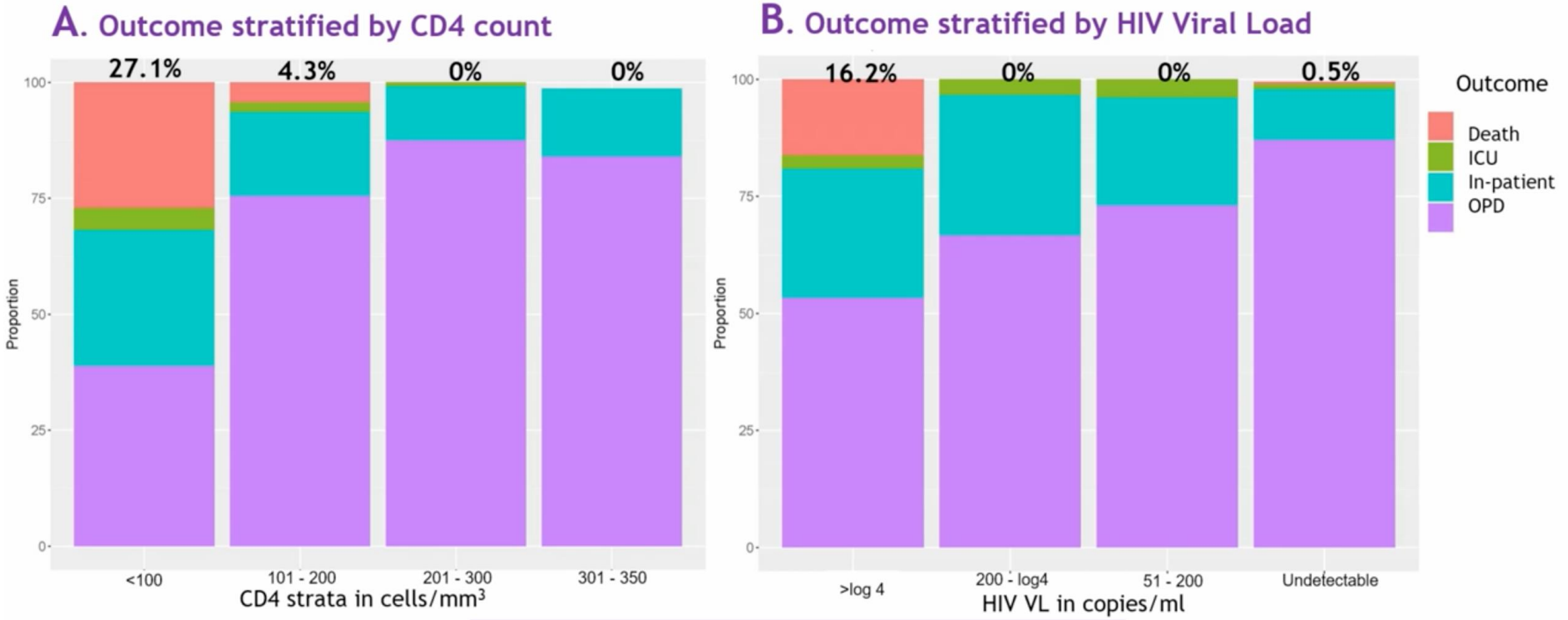
Mpox in immunosuppressed people with HIV

- N=382 with confirmed mpox and CD4<350 and/or CDC-C
- Complications correlated with CD4

Outcome stratified by CD4 count and VL



Legend: % mortality rate

Mortality CD4 <100	
VL <50	VL > 4 log
7%	29.7%

DEATHS	TOTAL n (%) N = 27/382 (7.1%)
CD4 count (cells/mm3) - median (IQR)	**35 (24-100)**
Deaths with CD4 count >200	**0**
Death rate with CD4 <200	**15% (27/179)**
Death rate with CD4 <100	**27%**
Viral Load (log copies/ml) - median (IQR)	**5 (4-5)**
Complications	
Severe coalescing or necrotising skin lesions	**25 (93%)**
Blood stream or 2^0 bacterial infections	**24 (89%)**
Respiratory symptoms and respiratory failure	**23 (85.0%)**
Rectal complications	21 (78%)
Oropharyngeal	18 (78%)
Ocular	13 (48.%)
CNS	8 (30%)
Cause of death	
Septic shock and multiorgan failure	**20 (74.1%)**
Respiratory failure	4 (14.8%)
Disseminated mpox	2 (7.4%)
Cardiac arrest	1 (3.7%)

IMMUNE RESTITUTION INFLAMMATORY SYNDROME (IRIS)	
ART started or restarted	**85 (22.3%)**
MPOX IRIS suspected	**21 (25.%)**
MPOX to ART - median days (range)	**21 (0-73)**
ART start to worsening of MPOX - days (range)	**14 (3-64)**
IRIS treatment	Steroids 9 NSAIDS 1 Supportive care 10
Deaths	**12/21 (57.1%)**

Implications

- **Mpox is an opportunistic pathogen**
- **Severe necrotising form of mpox is an AIDS-defining condition**
- **International disease classifications (CDC and WHO) should reflect this**
- **Clinical recommendations in CD4< 200:**
  - Vigilance -likelihood of sepsis
  - Consider timing of ART
  - Prioritise for mpox antivirals and preventive vaccines (research needed)
- **Prioritise access to mpox antivirals & vaccines in countries without access**

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