CROI 2021:
Top Ten for Clinicians

Josep M Llibre, MD, PhD
Enfermedades Infecciosas
Hospital Universitari Germans Trias
Badalona, Barcelona
@DrBike7
1. Rifapentine & Moxifloxacin 4M (2HPZM+2HPM) beat classic 6M RHZE in pulmonary TB in PLWH.
3. NADIA: DRVr non-inferior to DTG in 2ND line (1ST salvage) in Africa.
4. Lenacavapir in salvage ART: record VL decay in HTE with MDR.
5. Islatravir multiple dosing possibilities for PrEP and ART... and new partner.
6. mRNA vaccines come to SHIV in macaques... with significant success.
7. One dose mRNA vaccine sufficient in COVID-experienced.
8. Blaze-1: Bamlanivimab + etesivimab: significant improvement in mild-mod ambulatory COVID.
10. Molnupiravir, oral: No culturable SARS-CoV-2 at 5 days.
Rifapentine +/- Moxifloxacin for Pulmonary TBC in PLWH (S31/A5349)

- Intl, randomized (1:1:1), phase 3, open-label, non-inferiority. HIV+ allowed if CD4 >100 cells, only EFV.
- Microbiol confirmed, *M. tuberculosis* susceptible. ITT-E, M≠F (lost to FU, pregnancy, violent, TB reinfection, deaths excluded).
- 2,516 randomized, 214 (8%) were HIV+ (median CD4+ 344 cells/mm$^3$; on EFV-based ART at enrollment 53%).
- 73% cavitary disease. Median BMI 19 kg/m$^2$.
Unfavourable outcomes (n(%)) in primary assessable analysis pop: TB disease-free survival 12 months after randomization.

- More people in the Control arm do not complete 95% of the TBC treatment.

Rifapentine-Moxifloxacin (2HPZM/2HPM) regimen represents a major milestone in the pursuit of shorter TB treatment regimens for PLWH
Study Design

Open-Label Prospective Cohort Study in the Paris Region

- HIV-negative high risk adults
- Inconsistent Condom use
- eGFR ≥ 50 mL/mn
- HbsAg negative if On Demand

n = 3,067
MSM 98.5%
Chemsex use 14%

Participants opted for either Daily or On Demand PrEP and could switch regimen

- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- STI screening at physician’s discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

http://prevenir.anrs.fr/

May 3rd 2017

TDF/FTC
Daily

~50% each along the study period

TDF/FTC
On Demand

September 30, 2020

n = 3,067
MSM 98.5%
Chemsex use 14%

JM Molina. CROI 2021; #148
Global HIV Incidence: 0.11/100 PY (95% CI: 0.04-0.23) (6 cases; all them PrEP stopped. 1/6 M184V)

Mean Follow-up of 22.1 months and 5633 Person-Years
Rate of study discontinuation: 14.4/100 PY

Treatment Options

- **TDF/FTC Daily**

<table>
<thead>
<tr>
<th>IRR (95%CI)</th>
<th>0.99</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.13-7.38)</td>
<td></td>
</tr>
</tbody>
</table>

- **TDF/FTC On Demand**

<table>
<thead>
<tr>
<th>IRR (95%CI)</th>
<th>0.99</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.13-7.38)</td>
<td></td>
</tr>
</tbody>
</table>

High and identical efficacy of daily and on-demand PrEP.
Good safety profile with both dosing regimens.
High retention rate.
High rate of bacterial STIs, watch out hep C.

**RCT (n=52)** with Doxycycline 100 mg/daily x 48 weeks in HIVneg MSM with prior syphilis demonstrates: 82% reduction in STIs with no *Chlamydia* (p=0.001) and Syphilis (p=0.98). No impact on gonorrea.
DISCO Multicenter study (n=500) ongoing.

- Any STD 75 per 100 PY (32 during COVID lockdown).
- 43 cases of viral hepatitis diagnosed in 41 participants: 39 HCV (0.69 per 100 PY).
- Lower drug-related AEs with daily PrEP (8 vs 12 per 100 PY, p<0.05); GI, no diff in kidney toxicity.

JM Molina. CROI 2021; #148

T Grennan, CROI 2021, #709
Oral Abstract-02  HIV TREATMENT AND PREVENTION: NEW OPPORTUNITIES TO OPTIMIZE DRUG DOSING, ADHERENCE, AND ANTIRETROVIRAL THERAPY
11:15 AM - 1:15 PM EST
NADIA Trial: DRV/r vs DTG and TDF vs ZDV in 1\textsuperscript{ST} salvage (2\textsuperscript{ND} Line) in Africa.

Eligible patients:
On TDF+3TC/FTC+NNRTI regimen for ≥ 6m with \textit{treatment failure} defined as:
VL ≥ 1000 copies/ml at screening AND
EITHER: VL ≥ 1000 copies/ml on test taken < 6m (& ≥4wks) prior to screening
OR: VL ≥ 1000 copies/ml on confirmatory test taken ≥4wks after screening

2 x 2 factorial randomisation

RANDOMISATION 1

N=464

DTG (n=235)

DRV/r (800/100mg od) n=229

RANDOMISATION 2

TDF + 3TC

ZDV* + 3TC

TDF + 3TC

ZDV* + 3TC

Follow up for 96 weeks

Primary outcome: Viral load < 400 copies/ml at week 48 (!)

- 7 sites in Uganda, Kenya, Zimbabwe (July-Dec 2019).
- HIV VL and CD4 monitoring at 24 and 48 weeks.
- Batched GRT on stored BL samples (results blinded).
- ITT; δ for non-inf: 12%.
- Died prior to week 48: 5 (1.1%), Lost-to-FU: 1 (0.2%).
- Scheduled visits attended: > 99%.
- Median CD4 194 cells/mm\textsuperscript{3}, VL >100.000 28%.
- M184V/I 86%; K65R/N 50%.

\textsuperscript{1} Paton. CROI 2021, #94.
NADIA Trial: DRV/r vs DTG and TDF vs ZDV in 1\textsuperscript{ST} salvage (2\textsuperscript{ND} Line) in Africa.

Efficacy outcomes (VL < 50 c/mL, ITT; secondary outcome):

**DTG vs DRV/r:** 80.9% vs 79.5% (1.4; 95%CI -5.9 to 8.6). Non-inf confirmed (δ 12%).
- With CD4 <200 cells: 89.6% vs 95.6% (-6.0; -12.5, +0.6).
- No active (0) NRTIs: 92.4% vs 93.7%.
- D/C due to AEs: 0.9% vs 1.3%.
- VL rebound ≥ 1000 c/ml (confirmed) with ≥1 major DRM: 4 DTG (1.7%; 1 intermediate, 3 high-level) vs 0 DRV/r.

**TDF vs ZDV:** 80.7% vs 79.7%; 1.0 (0.6 to 8.3). Non-inf confirmed (δ 12%).
- With K65R/N present: 94.0% vs 96.0%.
- With M184V/I: 94.0% vs 92.0%.

**DTG was not superior to DRV/r in efficacy or safety in 2\textsuperscript{ND} line.**
- DTG resistance (2%) can occur, usually high-level.
- TDF/3TC is non-inferior to switching to ZDV/3TC.
- High rates of VS will all strategies

N Paton. CROI 2021, #94.
Lenacapavir in Phase 2/3 in Heavily ART-experienced PMW

- First-in-class HIV capsid inhibitor, multi-site MOA, highly potent (nano-molar, EC$_{50}$=50 pM) and long-acting.
- No cross-resistance and no observed pre-existing resistance.
- Single SC doses maintained target concentrations for 26 weeks, supporting its use once every 6 months.

Median CD4 150 cells, VL >75,000 c/mL 28%.

*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.

OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).
Lenacapavir in Phase 2/3 in Heavily ART-experienced PMW

In HTE PWH with MDR, LEN showed potent antiviral activity, when added to a failing regimen and led to high rates of virologic suppression.

- 73% VL<50 c/mL at week 26 (ITT M=F), CD4 increase +72 cells/mm³.
- 2 CVF with LEN DRMs (M66I, and M66I + N74D) with high level LEN resistance.
- No safety issues. No SAEs related to study drug or leading to study drug discontinuation.
- ISRs common (46%), mostly grade 1.

S Segal-Maurer. CROI 2021. #127.
Islatravir LA, multiple dosing possibilities for PrEP and ART

- First-in-class nucleoside transcriptase translocation inhibitor.
- Intracellular $t_{1/2}$ of ISL-TP: 190 hours (8 days).
- High potency, amenable for LA formulations.

- Predicted IQ >17
- IQ>5 associated with antiviral efficacy against wt and M184V HIV in PrEP
- Adequate tissue distribution (rectal, cervical, vaginal).
- Dose selected for phase 3 studies: 60 mg oral monthly:
- IMPOWER-022 (Women) and 023 (MSM) vs TDF/TAF.

Next generation radiopaque implants. Implanted in non-dominant upper arm.

60 mg oral monthly, population PK

56 mg reformulated implant projected to release adequate ISL-TP for >52 weeks

Potential for once-yearly SC PrEP

Se presenta en sociedad la pareja de Islatravir: MK-8507 (NNRTI). $T_{1/2}$ 70 horas (3 días).

80 mg MK-8507 QW probably taken forward + 20 mg QW ISL.
An Env/Gag VLP mRNA vaccine induced significant protection from SHIV infection

### Design of the Study

**Animals:** Rhesus macaques (*M. mulatta*), juvenile males

**Immunogens:** mRNA (HIV-1 Env, SIV Gag), 200-400 µg/animal by IM injection

**Study groups:**
- **Arm 1 (n=3):** Clade-B priming (WITO Env+Gag), clades A+C boosts (BG505+DU422+Gag) + final protein boosts (SOSIP.664 trimers)
- **Arm 2 (n=4):** Clade-B priming (WITO+Gag), clades A+C boosts (BG505+DU422+Gag)
- **Arm 3 (n=7):** Naïve controls (added at challenge phase)

**Challenge:** *In vivo*-titrated SHIV-AD8, 13 weekly low-dose 10 TCID<sub>50</sub> by rectal inoculation
An Env/Gag VLP mRNA vaccine induced significant protection from SHIV infection

- Lipid nanoparticles that include small lengths of a nucleic acid that deliver instructions for making proteins.
- mRNA vaccines allow sustained *in vivo* expression of native endogenous proteins (identical to real-life infection) with no distracting epitopes.
- Early and strong induction of neutralizing Abs.

An Env/Gag VLP mRNA vaccine induced significant (but partial) protection from infection with a difficult-to-neutralize heterologous SHIV in macaques.

P Zhang. CROI 2021, #86.
1. Rifapentine & Moxifloxacin 4M (2HPZM+2 HPM) beat classic 6M RHZE in pulmonary TB in PLWH.


3. NADIA: DRVr non-inferior to DTG in 2\textsuperscript{ND} line (1\textsuperscript{ST} salvage) in Africa.

4. Lenacavapir in salvage ART: record VL decay in HTE with MDR.

5. Islatravir multiple dosing possibilities for PrEP and ART… and new partner.

6. mRNA vaccines come to SHIV in macaques… with significant success.

7. One dose mRNA vaccine sufficient in COVID-experienced.

8. Blaze-1: Bamlanivimab + etesivimab: significant improvement in mild-mod ambulatory COVID.


10. Molnupiravir, oral: No culturable SARS-CoV-2 at 5 days.
One dose of mRNA vaccine sufficient in COVID-experienced (Pfizer/BNT). HCWs

• Large scale RCTs excluded subjects with prior diagnosis of COVID.
• The magnitude, quality and durability of response to vaccination is unknown in subjects with prior SARS-CoV-2 infection.

N=20

Neutralizing titers against new variants

ELISA for anti-S1 IgG antibodies

MI Samanovic-Golden. CKUI 2021, #119.
A single dose of mRNA vaccine in SARS-CoV-2 experienced subjects induced similar or higher Ab responses (total, neutralizing and avidity) than 2 doses in SARS-CoV-2 naive subjects.

Titers were not boosted by second dose.

Cellular immune responses after one dose showed a similar pattern.
ELI-Lilly/NIAID/AbCellera (BLAZE-1)

Bamlanivimab + etesivimab in high-risk ambulatory COVID-19

- Fully human nmAb IgG1, binds to SARS-CoV-2 RBD (Spike).
- N=1035 Mild (77%)-mod (23%) COVID-19 <3 days of RT-PCR+ and ≥1 comorbidity. Median duration of symptoms: 4 days.

### PHASE 2 PORTION

- **Bamlanivimab Monotherapy**
  - 7000 mg (N = 101)
  - 2800 mg (N = 107)
  - 700 mg (N = 101)
  - Placebo (N = 100)

- **Bamlanivimab + Etesivimab**
  - 2800 mg + 2800 mg (N = 109)

**Primary Endpoint:** Virology
**Population:** Mild-to-Moderate COVID-19

### PHASE 3 PORTION (Higher Risk Population)

- **Bamlanivimab + Etesivimab IV (1 hour infusion)**
  - 2800 mg + 2800 mg (N = 518)
  - Placebo (N = 517)

- **700 mg + 1400 mg (N = 500)**
  - Placebo (N ~ 250)

**Primary Endpoint:** Hospitalization or Death Through Day 29
**Population:** Mild-to-Moderate COVID-19 with Risk Factor(s)

**VL decay vs pbo:**
- P = 0.70
- P = 0.02
- P = 0.38

M Dougan. CROI 2021, #122.
**Deaths**: 10 (1.9%; 9 COVID-related) vs 0, pbo vs mAb. \(P < 0.001\)

• Significantly faster symptom resolution.

• SAFE.

**Bamlanivimab + etesivimab in high-risk ambulatory COVID-19**

**BLAZE-1 PHASE 3: PRIMARY ENDPOINT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Rate</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>517</td>
<td>36</td>
<td>7.0%</td>
<td>-</td>
</tr>
<tr>
<td>Bamlanivimab 2800 mg + Etesevimab 2800 mg</td>
<td>518</td>
<td>11</td>
<td>2.1%</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

70% reduction vs. placebo

**VIRAL LOAD CHANGE FROM BASELINE**

- \(P < 0.001\)
- \(P < 0.001\)
- \(P < 0.001\)

**BLAZE-1 confirms 70% reduction in hospitalization, significantly faster viral load decrease and symptom ressolution in ambulatory mild-mod COVID with bamlanivimab + etesivimab. No deaths (1.9% v 0)**

M Dougan. CROI 2021, #122.
BLAZE-2: Bamlanivimab in nursing-home settings reporting at least 1 COVID case.

- PREVENTION POPULATION: 966 participants negative at BL for SARS-CoV-2 RT-PCR and serology (666 staff, 300 residents).
- Median age 52 y (residents 76 y). High-risk: 59% and 100.
- Primary endpoint: ≥ mild COVID within 8 weeks.

In US nursing home residents: 5% of cases, 37% of deaths.

Study Design:

1175 participants dosed, 966 (82.2%) comprised the prevention population

<table>
<thead>
<tr>
<th>Evaluation Period</th>
<th>Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deployment &amp; Screening</td>
<td>1:1 Randomization</td>
</tr>
<tr>
<td>N=484</td>
<td>N=482</td>
</tr>
</tbody>
</table>

Confirmed Case at Site

Bamlanivimab 4200 mg

Placebo

To facilitate rapid prophylaxis and treatment of residents and facility staff, participants were enrolled prior to assessment of baseline SARS-CoV-2 status. This allowed for separate prevention and empiric treatment populations.
A single mAb (Bamlanivimab) PrEP significantly prevented COVID-19 and reduced progression in nursing facilities by 72-80%, with no deaths (4 vs 0). Those who acquired COVID-19 with bamlanivimab had lower viral loads and faster viral clearance (spread reduction).

M Cohen. CROI 2021, #121
mAbs for COVID-19 prevention in household contacts

Similar results with phase 3 Casirivimab + Imdevimab mAb (REGEN-CoV cocktail, SC) in COVID PrEP in 409 household contacts (interim analysis): no symptomatic COVID and 50% reduction in PCR+ (low rates overall), strong impact on SARS-CoV-2 VLs.
(REGN-COV2)

• Passive immunization with a subcutaneous dose of the REGEN-COV antibody cocktail:
  - Prevented symptomatic infection in 100% of cases
  - Reduced high viral load infection by 100%
  - Reduced overall infection by 50%
  - Decreased duration of viral RNA detection

MP O'Brien. CROI 2021, #123.
Declaraciones polémicas

Trump promete distribuir gratis un tratamiento experimental contra el covid

El presidente afirma que haber pasado la enfermedad es "una bendición de Dios"

En un video colgado en las redes, se compromete a poner a disposición de todos los estadounidenses y de forma gratuita el Regeneron
Molnupiravir: Time to clearance of infectious SARS-COV-2. Phase 2 (dose-finding)

- Broad range *in-vitro* activity against all CoVs including SARS-CoV-2 REM-resistant mutants.
- Potent ribonucleoside analog: *induces viral error catastrophe* (Emory → Ridgeback → MSD).
- Activity proven in mouse and ferret models for Tx and PrEP with SARS-CoV-2.
- Favourable PK: ORAL. Safe in humans in phase 1.
- N=200 ambulatory symptomatic COVID <7 days.
- NP swabs collected at 3,5,7,14,28 days.
- Molnupiravir 200, 400 or 800 mg ORAL x 5 d.

**Figure 1.** Proportion of overall participants with positive viral culture by RT-PCR (for participants positive at baseline)

- Of 182 subjects with evaluable swabs, 78 (43%) had positive baseline cultures.
- **No culturable SARS-CoV-2 at 5 days with any dose** (n=47): 200 mg (n=11), 400 mg (n=15) or 800 mg (n=26=).
- SAFE (author comment).
- Phase 3 studies underway

1st specific SARS-CoV-2 antiviral
¡MUCHAS GRACIAS!

Josep M Llibre, MD, PhD
Enfermedades Infecciosas
Hospital Universitari Germans Trias
Badalona, Barcelona
@DrBike7