Repurposing old drugs for new diseases

Causal inference during a pandemic

Miguel Hernán

CAUSALab
A Center to Learn What Works

HARVARD
T.H. CHAN
SCHOOL OF PUBLIC HEALTH

Suppose a new virus starts infecting humans…

… and many people get sick and die

- What do we do?
  - In the long term, we develop new drugs (and vaccines)
  - In the short-term, we try drugs we already have for other diseases

- Repurposing of existing drugs
  - Which ones?
  - How do we determine what works?

The easier question:
How do we determine what works?

- We design and carry out randomized trials
  - To evaluate effectiveness of the repurposed drugs for the new disease

The harder question:

- **How do we decide** which drugs go into randomized trials?
  - There are thousands of compounds
  - We cannot possibly study all of them via randomized trials

The most important question:

- **Who decides** which drugs go into randomized trials?

Traditional approach to decide which existing drugs will be studied in randomized trials

- We build evidence from different sources
  - in silico studies, in vitro studies, animal studies
- If evidence looks promising
  - launch Phase 1-2 trials to evaluate toxicity

- But what if we also have observational data in human populations?
  - Common situation for drugs used before the new disease appears
  - If promising, can we go directly to Phase 3 trials to evaluate effectiveness and safety?

- What did we do for COVID-19?

COVID-19: a disease with 2 phases

1. Viral infection
   - moderate to mild or no symptoms
   - when viral replication declines, symptoms subside
   - potential benefit of **antivirals** that block viral replication

2. Inflammatory response
   - in a subset of patients, even after viral replication declines
   - severe symptoms, including acute respiratory distress
   - potential benefit of **anti-inflammatory** drugs
     - dexamethasone, tocilizumab

Examples from the years 2020-2022: antivirals

- 2 existing drugs that were used by few persons in 2020
  - Remdesivir: safety profile not well known
  - Hydroxychloroquine: safety profile well known
- 1 existing drug that was not in use in 2020
  - Molnupiravir: safety profile unknown
- 1 existing drug that was used by many persons in 2020
  - Tenofovir: safety profile well known

Repurposing REMDESIVIR against COVID-19

- Developed by Gilead, studied as treatment for Ebola
- Nucleotide prodrug
  - its active metabolite interferes with viral RNA-dependent RNA polymerase
- Intravenous administration

- May 1, 2020: FDA issues an Emergency Use Authorization
  - for treatment in adults and children hospitalized with COVID-19
- Priced at more than $3,100 per treatment course

Remdesivir: Key randomized trials in hospitalized patients (before Delta variant)

- ACTT-1: shorter recovery time, mortality RR: 0.73
  - Feb-Apr 2020, N=1062 (*N Eng J Med* 2020; preliminary report: May 22)
- Solidarity: mortality RR: 0.95
  - March-October 2020, N=5451 (*N Eng J Med* 2021)
- DisCoVeRy: no clinical benefit, mortality RR: 0.93
  - March 2020-January 2021, N=1308 (*Lancet Infect Dis* 2022)
- CATCO – Canada: mortality RR: 0.83
  - August 2020-April 2021, N=1252 (*CMAJ* 2022)

Findings compatible with modest effect on mortality
FDA Emergency Use Authorization based on first trial

Why did remdesivir make it into randomized trials? WHO said so in March 2020

- Scientific Advisory Group recommends remdesivir and lopinavir/ritonavir
- SOLIDARITY trial launched with 4 active treatment arms
  - Remdesivir
  - Lopinavir/ritonavir
  - Hydroxychloroquine
  - Interferon

Sentence about team: Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua.

Why was remdesivir considered for immediate evaluation? WHO's Scientific Advisory Committee said:

> 1. Among the different therapeutic options, Remdesivir was considered a first priority, based on the broad antiviral spectrum, the in vitro and in vivo data available including against coronaviruses and the extensive clinical safety database (used in the Ebola epidemic in DRC).

- In vitro activity against SARS-CoV-2
  - remdesivir and chloroquine inhibit SARS-CoV-2 (Wang et al. *Cell Res* 2020; 30: 269-71; letter to the editor, published online Feb 4, 2020)
- In vivo activity against other coronaviruses
  - effective against infection with MERS-CoV and SARS-CoV in animal models

Choosing dugs for repurposing as COVID-19 treatment wasn't an easy task

- Humbling exercise
  - Lopinavir didn't work
  - Interferon didn't work
  - Hydroxychloroquine didn't work
  - Remdesivir had a modest effect

- Two main problems
  - Not much data relevant to SARS-CoV-2 data were available
  - Antivirals may not work well in persons with advanced disease
    - e.g., in hospitalized patients

Early treatment of viral infections (Ebola, influenza, HIV) improves clinical outcomes and reduces mortality

- Clinical benefit of remdesivir in **rhesus macaques** infected with SARS-CoV-2 and treated 12 hours later
  - Williamson et al. *Nature* 2020; first reported April 2020
- Randomized trial in **non-hospitalized humans** with COVID-19
  - PINETREE: September 2020 - April 2021, <50% of planned enrolment
  - N=562 high-risk individuals (*N Eng J Med* 2021)
- Hazard ratio of hospitalization: 0.13 (95% CI 0.03 to 0.59)

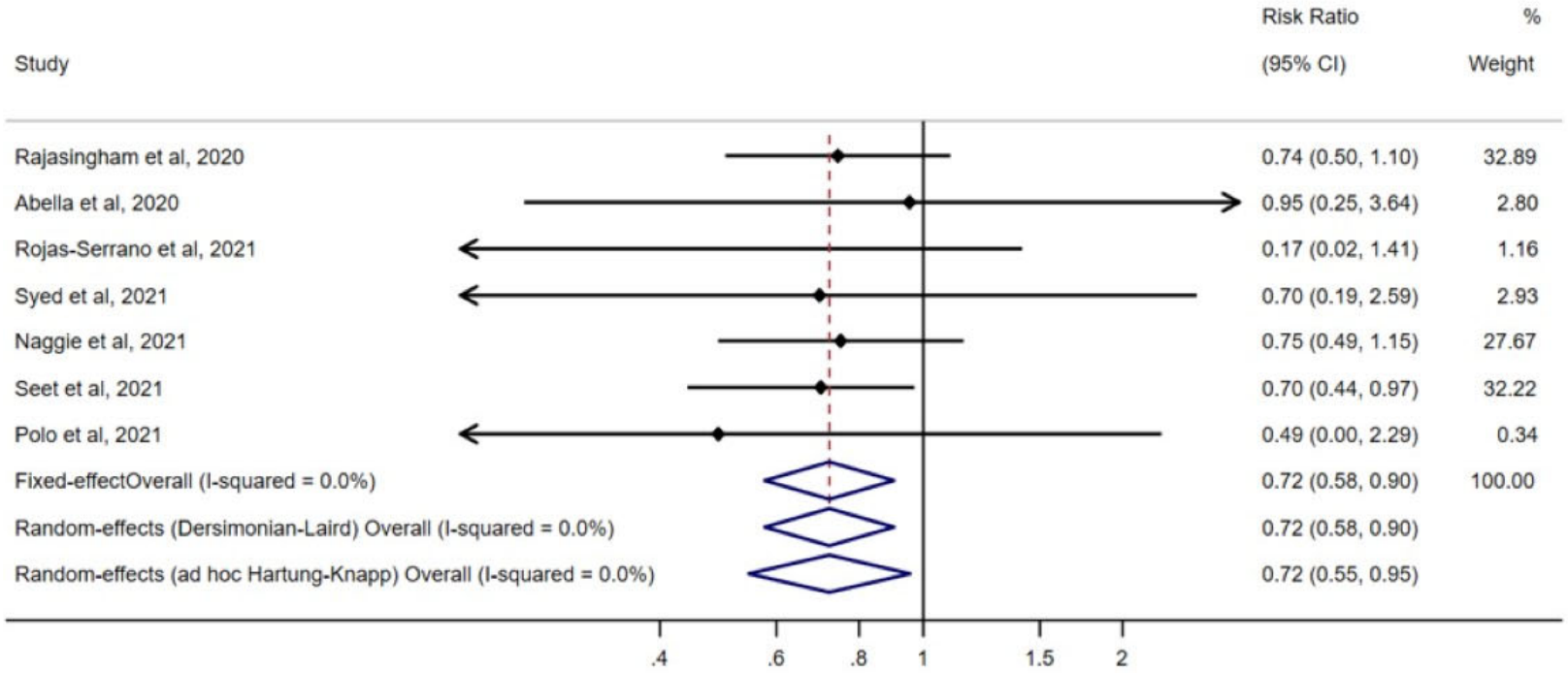
BINGO! (though expensive and intravenous)

Repurposing hydroxychloroquine (HCQ) against COVID-19

- HCQ doesn't work for treatment of hospitalized COVID-19 patients
  - Multiple randomized trials
  - Case closed

- But does it work for the prevention of COVID-19 as pre-exposure or post-exposure prophylaxis?
  - Several randomized trials
  - How about a meta-analysis?

7 randomized trials of HCQ for pre-exposure prophylaxis of COVID-19



- Risk ratio of COVID-19 for HCQ vs. no HCQ: 0.72
  - Garcia-Albeniz et al. (*European Journal of Epidemiology* 2022; first version medRxiv 2020)

But we thought HCQ didn't work. What happened?

- First published studies were for post-exposure prophylaxis
- Small, noninformative trials were interpreted as "no effect"
  - No "statistical significance" = no effect for researchers and media
- Example: Abella et al. *JAMA Int Med* (September 2020)
  - "no significant difference [for] hydroxychloroquine compared with placebo (4 of 64 [6.3%] vs 4 of 61 [6.6%]; P > .99)"
  - Risk ratio: 0.95 (95% CI: 0.24, 3.64)

Penn Medicine News

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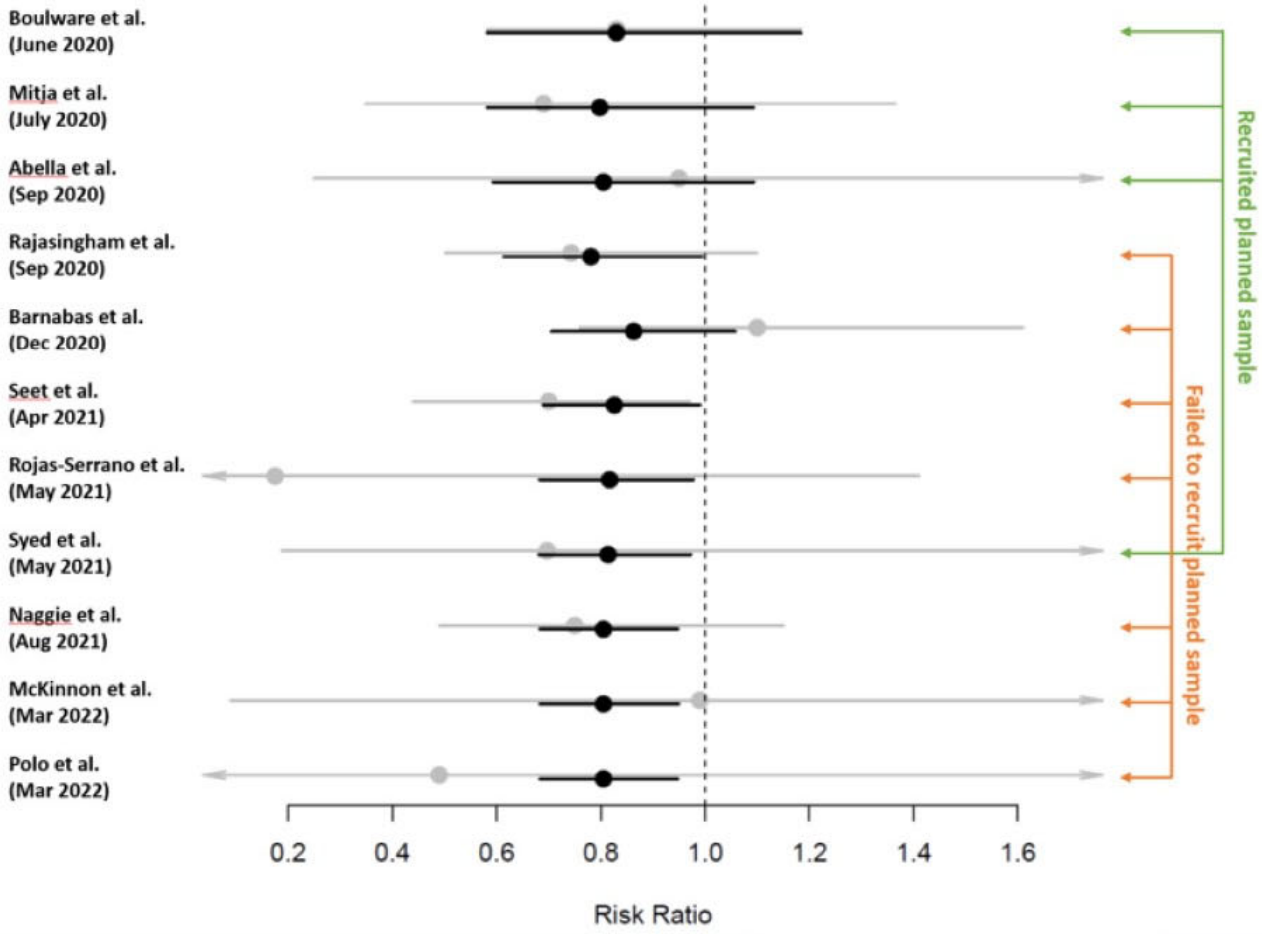
News Release

Hydroxychloroquine No More Effective Than Placebo in Preventing COVID-19

Penn clinical trial shows health care workers in contact with COVID-19 patients who took hydroxychloroquine daily did not reduce their rate of infection

September 30, 2020

No wonder HCQ trials for COVID-19 prophylaxis couldn't recruit their planned sample size



Repurposing MOLNUPIRAVIR against COVID-19

- When the pandemic began, molnupiravir was in pre-clinical development for the treatment of seasonal influenza
- Commercialized by Merck

- Prodrug of a ribonucleoside analog that inhibits replication of RNA viruses by mutagenesis
  - the RNA polymerase escapes proofreading and synthesizes mutated RNA
- Oral administration

Building the evidence towards randomized trials of molnupiravir

- In vitro activity
  - April 20, 2020: molnupiravir inhibits SARS-CoV-2 in human airway epithelial cell cultures (Sheahan et al. Sci Transl Med 2020)
  - [January 2022: Merck announces activity against Omicron variant]
- In vivo activity
  - December 3, 2020: molnupiravir blocks SARS-CoV-2 transmission in ferrets (Cox et al. *Nat Microbiol* 2021)
- Phase 2 Randomized trials
  - Launched in October 2020 by Merck

Randomized trials of molnupiravir

- MOVe-IN: 304 hospitalized patients
  - No clinical benefit (Arribas et al. *NEJM Evidence* 2021)
  - April 2021: don't proceed to Phase 3
- MOVe-OUT (phase 3): 1408 nonhospitalized individuals
  - October 1, 2021: preliminary results (Bernal et al. *N Eng J Med* 2022)
    - molnupiravir reduced the risk of hospitalization or death by approximately **50%**
  - October 19, 2021: Bill & Melinda Gates Foundation commits $120 million
    - to provide access to molnupiravir in lower-income countries
  - November 4, 2021: authorization granted in the UK
  - December 16, 2021: final results
    - molnupiravir reduced the risk of hospitalization or death by approximately **30%**
  - December 23, 2021: FDA issued an Emergency Use Authorization

Molnupiravir developed by a non-profit at Emory University
Funded by $29 million from U.S. government

- March 23, 2020: Emory sells exclusive license to Ridgeback Therapeutics to do randomized trials
  - Undisclosed $ amount
- Early April, 2020: Ridgeback Therapeutics asks U.S. government for $100 million to fund randomized trials
  - Federal government rejects request
- May 26, 2020: Ridgeback sells worldwide rights to Merck
  - Undisclosed $ amount
- June 9, 2021: U.S. government will pay 1.2 billion to Merck if molnupiravir receives FDA's emergency use authorization
  - 1.7 million 5-day treatment courses at $712 per course
  - Conservative estimate of production costs: $18 per course

Why did the U.S. government rejected the funding of randomized trials of molnupiravir? Safety concerns

- Molnupiravir is a mutagenic agent
  - Could contribute to the emergence of SARS-CoV-2 variants
  - Could be incorporated into the host DNA and cause mutations, especially in rapidly dividing human tissues including fetuses
  - Reproductive toxicity in animal studies
  - Structurally related compounds had been previously abandoned

- FDA: low risk for genotoxicity because given only 5 days, but
  - Merck needs to monitor the emergence of variants
  - not authorized for patients under 18 years of age

So what information used the FDA to approve molnupiravir? A single randomized trial with 1443 patients

- Viral sequences in half of the sample
  - delta 58.1%, mu 20.5%, 10.7% gamma
- Interim analysis with N=775
  - Reported October 1, 2021
  - HR about 0.5
- Final analysis with N=1443
  - Reported December 2021
  - HR: 0.69 (1.01)
  - which implies that the HR is the second half of participants was ~0.92 (???)

NIH: COVID-19 Treatment Guidelines for High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19 (January 19, 2021)

- Women should abstain from sex or use reliable contraception for up to 4 days after receiving molnupiravir
- Men who are sexually active with individuals of childbearing potential should abstain from sex or use a reliable method of contraception **for at least 3 months** after receiving molnupiravir

- Molnupiravir: oral, moderately effective, expensive antiviral with safety profile to be determined

Last nail in molnupiravir's coffin? PANORAMIC trial (2022)

- Open-label, adaptive, multi-arm, platform, randomized trial
  - aged ≥50 or ≥18 years with comorbidities
  - ≤5 days with confirmed COVID-19 in the community
- Risk of hospitalization/death
  - 0.8% in the molnupiravir group (800mg twice daily for 5 days)
  - 0·8% in usual care group
    - adjusted odds ratio 1.06 (95% credible interval 0·80 – 1·40)
  - Butler et al. (preprint 2022, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4237902

Repurposing TENOFOVIR against COVID-19?

- Used as treatment for HIV and chronic Hepatitis B infection (HBV), and as pre-exposure prophylaxis for HIV for over 20 years
  - For HIV, given with emtricitabine (FTC)
- After activation into its triphosphate form, it interferes with viral RNA-dependent RNA polymerase
- Oral administration, safe even during pregnancy
- 2 prodrugs of tenofovir (both developed by Gilead)
  - Tenofovir disoproxil fumarate (TDF) - generic
    - greater intracellular availability in most tissues
  - Tenofovir alafenamide fumarate (TAF) - proprietary
    - preferential distribution in lymphoid tissues

Why consider tenofovir in the first place?

- Tenofovir was proposed as treatment for SARS-CoV-1 infection

- Clinical observation at the start of the pandemic:
  - Persons with HIV and adequate virological control didn't appear to have a greater risk of serious COVID-19
  - In a Madrid hospital that uses mostly TDF/FTC as treatment for people with HIV

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Early evidence for tenofovir (2020)

In vitro studies

- Mixed results

- Active against SARS-CoV-2 in some studies, depending on experimental conditions
  - Jockusch et al. *J Proteome Research* 2020 (first posted April)
  - Clososki et al. *J Braz Chem Soc* 2020 (May)
  - Sun. bioRxiv 2020 (November)
- Inactive against SARS-CoV-2 in other studies
  - Abstract presented at the European Clinical AIDS Society, October 2021
    - Feng et al. (Gilead)

In vivo studies

- Ferrets were treated with antivirals
  - TDF/FTC, lopinavir/ritonavir, HCQ
  - Park et al. *mBio* 2020 (May)
- The TDF/FTC group showed a reduction in overall clinical scores and a shorter duration of clinical symptoms
- "These results suggest that [TDF/FTC] may be the most likely candidate to reduce clinical symptoms, of SARS-CoV-2-infected hosts"

Human studies

- Observational studies in individuals already receiving TDF/FTC for
  - treatment of HIV-positive individuals
  - prophylaxis of HIV infection (PrEP)

- These studies were not possible for remdesivir and molnupiravir

Spanish HIV/COVID-19 Collaboration

- Observational study of 77,590 HIV-positive persons receiving antiretrovirals
  - >100 investigators, HIV clinics in 60 Spanish hospitals
    - del Amo et al. *Ann Int Med* 2020 and *Epidemiology* 2020

ORIGINAL RESEARCH

Annals of Internal Medicine

Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy

A Cohort Study

Julia del Amo, MD, PhD; Rosa Polo, MD, PhD; Santiago Moreno, MD, PhD; Asunción Díaz, MD, PhD; Esteban Martínez, MD, PhD; José Ramón Arribas, MD, PhD; Inma Jarrín, PhD; and Miguel A. Hernán, MD, DrPH; for The Spanish HIV/COVID-19 Collaboration*

Spanish HIV/COVID-19 Collaboration

- Lower risk of hospitalization in TDF/FTC users

NRTI Backbone	Estimated Persons at Risk[a]	COVID-19 Hospital Admission	
		N	Rate Ratio (95% CI)
TAF/FTC	25,571	52	1 (ref.)
TDF/FTC	12,395	13	0.53 (0.29–0.97)
ABC/3TC	20,105	47	1.0 (0.69–1.5)
Other regimes[b]	19,520	39	0.89 (0.59–1.4)

Spanish HIV/COVID-19 Collaboration

- Perhaps TDF/FTC are healthier than others?
  - Confounding by comorbidity?
  - No data on comorbidity so adjustment not possible

- Sensitivity Analysis 1: Younger than 60 years
  - low prevalence of comorbidities, little confounding
  - Rate ratio of COVID-19 hospitalization
    - 0.55 (95% CI 0.29–1.04)
    - for TDF/FTC compared with TAF/FTC

Spanish HIV/COVID-19 Collaboration

- Sensitivity Analysis 2: Compare risk of COVID-19 hospitalization between hospitals which used
  - >70% of tenofovir as TDF/FTC vs.
  - >70% of tenofovir as TAF/FTC
- Distribution of comorbidities across hospitals is similar
  - differences in risk between hospitals not explained by individual-level differences in comorbidities
  - little confounding, huge misclassification
- Rate ratio: 0.80 (95% CI: 0.41–1.56)

Western Cape Province, South Africa

- Observational study of 3978 HIV-positive individuals with COVID-19
  - medRxiv 2020 (first reported July)
- Lower risk of death in TDF/FTC users
  - among those on antiretroviral therapy
- Mortality hazard ratio
  - 0.42 (95% CI 0.22, 0.78)
  - for TDF/FTC vs. abacavir/zidovudine
  - Adjusted for sex, age, **comorbidities** (including kidney disease) and viral suppression

PrEP users in Madrid

- Observational study in HIV/STI clinic for PrEP
  - Ayerdi et al. *Open Forum Infectious Diseases* 2020
- 60 individuals on TDF/FTC and 15 on TAF/FTC with positive IgG serology
- Risk of COVID-19 symptoms
  - Risk ratio 0.73 (95% CI: 0.49, 1.07)
  - for TDF/FTC vs. TAF/FTC

A nice progression for causal inference

- In vitro studies
- In vivo studies
- Human (observational) studies

- Also, TDF/FTC is a cheap generic drug
  - with excellent safety profile for use over several months
  - even in pregnancy
- Next step: Randomized trials?
  - A strong case had been built for TDF/FTC
  - Not much weaker than for, say, remdesivir or molnupiravir

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Randomized trials (2020/21)

Randomized trials of TDF/FTC for COVID-19

- PANCOVID (Spain): treatment of hospitalized patients
  - No clinical benefit
  - Preliminary results reported at CROI 2022
- Pilot study (France): treatment of nonhospitalized patients
  - 30 patients on TDF/FTC, 30 standard of care
  - TDF/FTC group had faster clearance of nasopharyngeal viral burden
    - Parienti et al. eClinicalMedicine 2021 (August)
- EPICOS (Spain and Latin America): pre-exposure prophylaxis
    - Polo et al. *Microbiology and Infection* 2022

EPICOS randomized trial
Double-blind, placebo-controlled design

- Treatment strategies
  - TDF/FTC plus HCQ
  - TDF/FTC plus HCQ placebo
  - HCQ plus TDF/FTC placebo
  - TDF/FTC placebo plus HCQ placebo
    - TDF/FTC: single pill with 245mg of TDF and 200 mg of FTC once a day.
    - HCQ: 200 mg once a day
- Outcome: symptomatic COVID-19

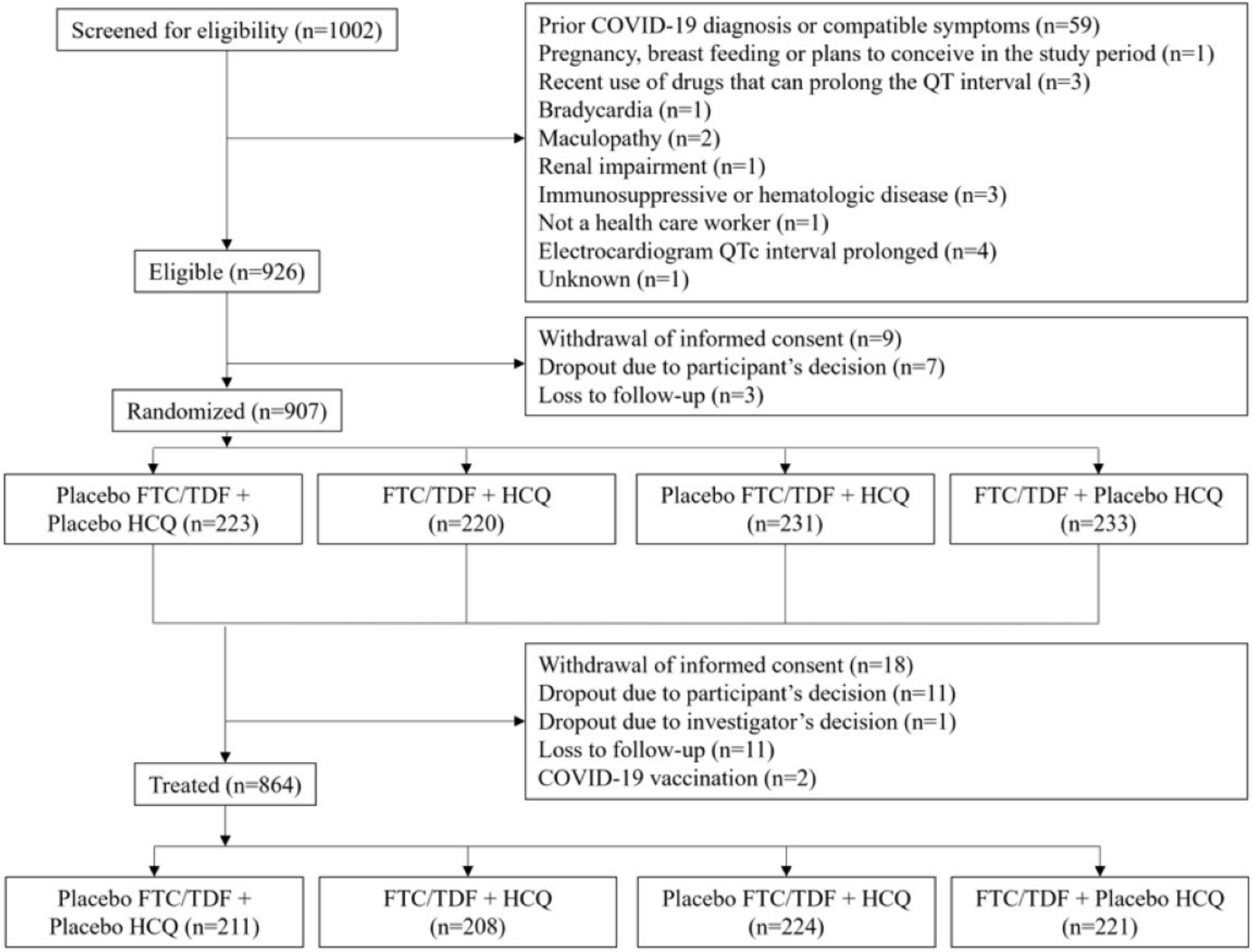
EPICOS randomized trial
Planned sample size: 4000 healthcare workers

Recruitment started:

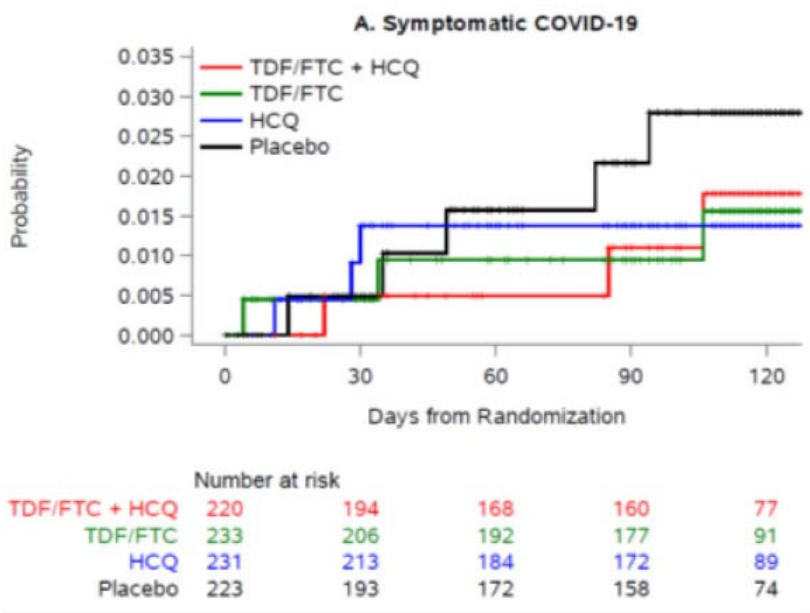
- April 2020 in Spain
- October 2020 in Bolivia
- March 2021 in Venezuela

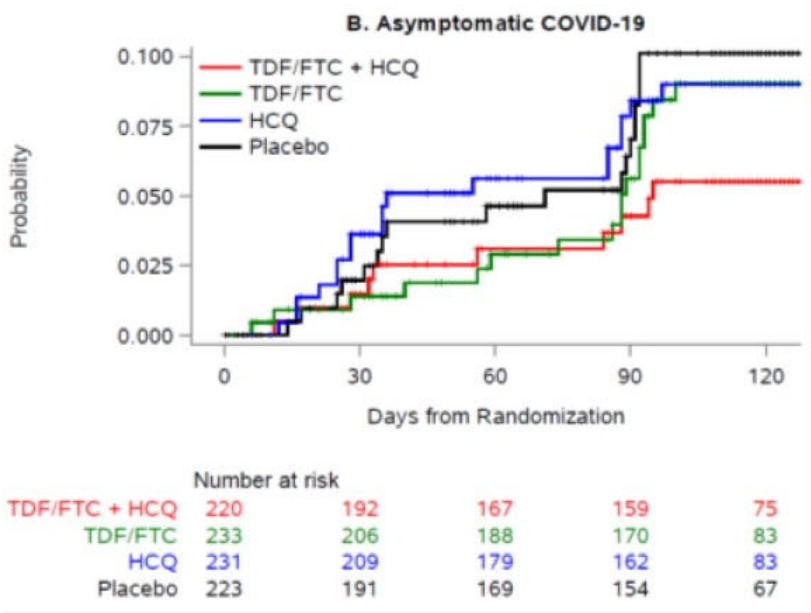
Final sample size: <1000

- Why join a trial in which you can be assigned to HCQ?
- By the end of 2020, health care workers start to be vaccinated

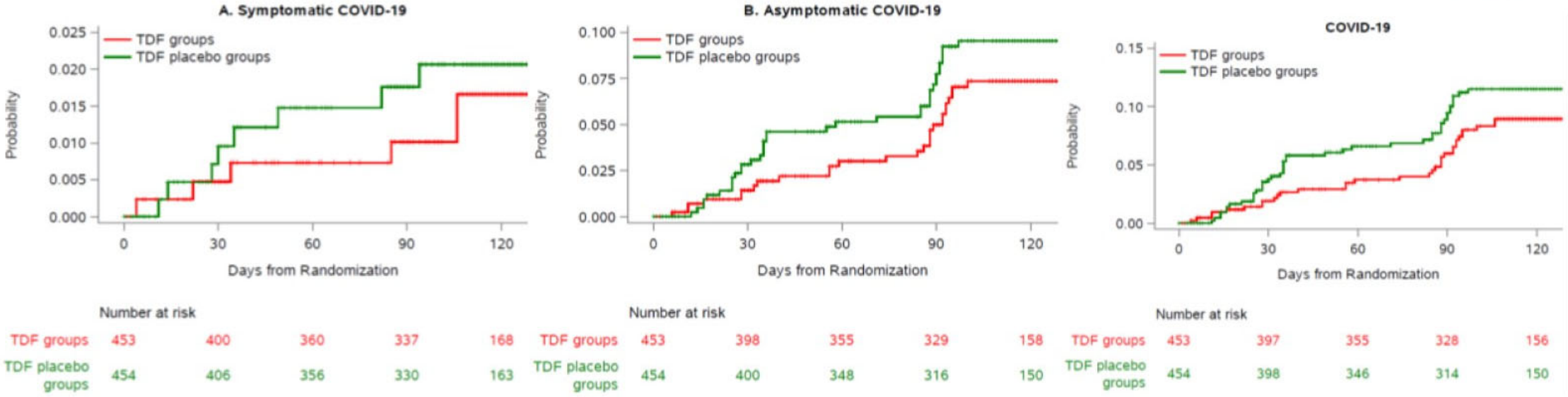

Screened for eligibility (n=1002)
Prior COVID-19 diagnosis or compatible symptoms (n=59)
Pregnancy, breast feeding or plans to conceive in the study period (n=1)
Recent use of drugs that can prolong the QT interval (n=3)
Bradycardia (n=1)
Maculopathy (n=2)
Renal impairment (n=1)
Immunosuppressive or hematologic disease (n=3)
Not a health care worker (n=1)
Electrocardiogram QTc interval prolonged (n=4)
Unknown (n=1)
Eligible (n=926)
Withdrawal of informed consent (n=9)
Dropout due to participant's decision (n=7)
Loss to follow-up (n=3)
Randomized (n=907)
Placebo FTC/TDF + Placebo HCQ (n=223)
FTC/TDF + HCQ (n=220)
Placebo FTC/TDF + HCQ (n=231)
FTC/TDF + Placebo HCQ (n=233)
Withdrawal of informed consent (n=18)
Dropout due to participant's decision (n=11)
Dropout due to investigator's decision (n=1)
Loss to follow-up (n=11)
COVID-19 vaccination (n=2)
Treated (n=864)
Placebo FTC/TDF + Placebo HCQ (n=211)
FTC/TDF + HCQ (n=208)
Placebo FTC/TDF + HCQ (n=224)
FTC/TDF + Placebo HCQ (n=221)

Symptomatic COVID-19	Cases / n	14-week risk (95% CI), %	Risk difference (95% CI), %	Risk ratio (95% CI)
TDF/FTC + HCQ	3 / 220	1.10 (0 - 2.55)	-1.70 (-4.41 to 1.09)	0.39 (0-1.98)
TDF/FTC	3 / 233	0.94 (0 - 2.63)	-1.85 (-4.43 to 1.16)	0.34 (0-2.06)
HCQ	3 / 231	1.37 (0 - 3.12)	-1.42 (-4.48 to 1.34)	0.49 (0-2.29)
Placebo	5 / 223	2.79 (0.60-5.22)	Reference	Reference
Asymptomatic COVID-19				
TDF/FTC + HCQ	10 / 220	5.51 (2.25-9.04)	-4.61 (-10.43 to 1.30)	0.54 (0.21-1.19)
TDF/FTC	17 / 233	8.44 (4.70-12.6)	-1.68 (-7.72 to 4.26)	0.83 (0.45-1.66)
HCQ	18 / 231	9.01 (5.37-13.3)	-1.11 (-7.06 to 5.16)	0.89 (0.49-1.91)
Placebo	18 / 223	10.1 (5.49-14.5)	Reference	Reference





Symptomatic COVID-19	Cases / n	14-week risk (95% CI), %	Risk difference (95% CI), %	Risk ratio (95% CI)
TDF-containing groups	6 / 453	1.02 (0.24-2.16)	-1.05 (-2.69 to 0.65)	0.49 (0.09-1.70)
Groups without TDF	8 / 454	2.07 (0.78-3.36)	Reference	Reference
Asymptomatic COVID-19				
TDF-containing groups	27 / 453	7.05 (4.24-9.57)	-2.50 (-6.68 to 1.43)	0.74 (0.43-1.21)
Groups without TDF	36 / 454	9.55 (6.43-12.41)	Reference	Reference
COVID-19				
TDF-containing groups	33 / 453	8.01 (5.33-10.93)	-3.51 (-7.56 to 0.81)	0.70 (0.43-1.10)
Groups without TDF	44 / 454	11.52 (7.94-14.63)	Reference	Reference



EPICOS randomized trial
Suggestive but inconclusive

- Compatible with a protective effect of TDF/FTC and HCQ, but very imprecise estimates
- TDF/FTC was safe, with most adverse events being mild

- The HCQ debacle interfered with recruitment
  - Misinterpreting "lack of statistical significance" as "no effect" prevented the quantification of the effect

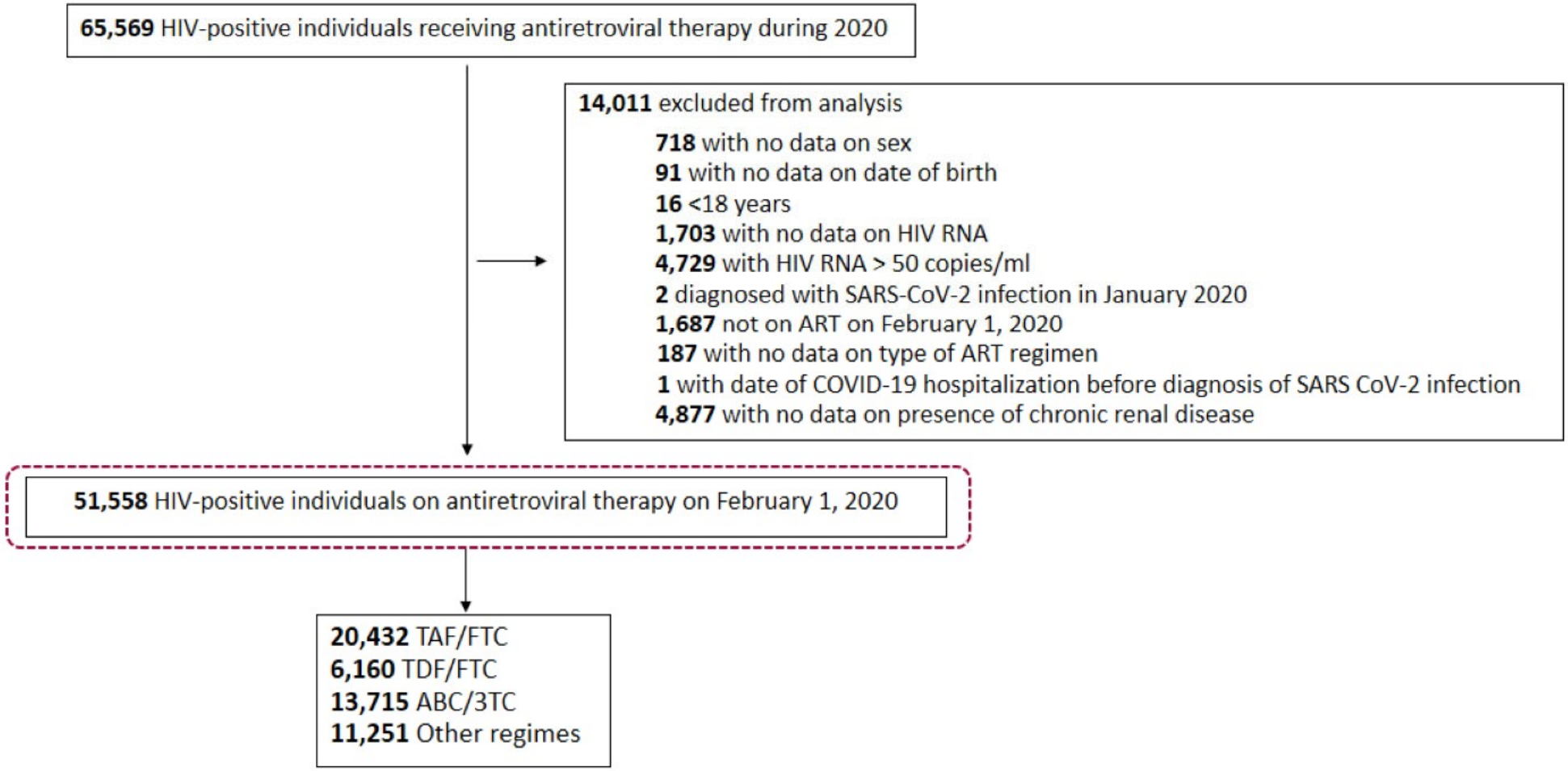
3

Observational studies (2021/22)

CoVIHd Collaboration

- Individuals with HIV on antiretroviral therapy and with adequate virological control in 2020
- Attending HIV clinics in 69 hospitals in Spain
- Funded by NIH
  - del Amo et al. *AIDS* 2022

Study population



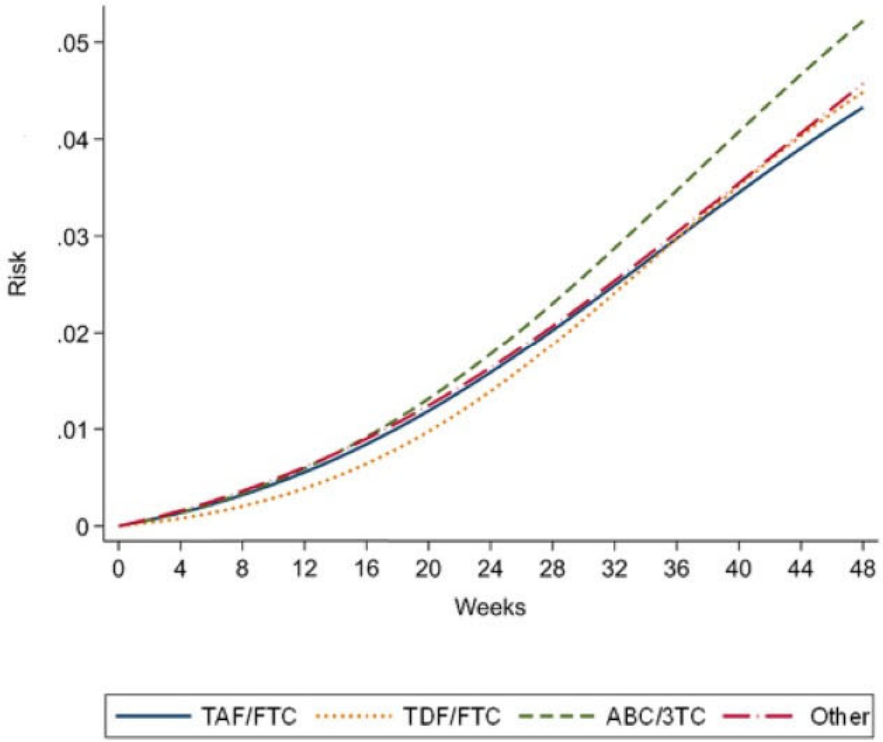
Baseline characteristics

CoVIHd

	TAF/FTC N = 20,432 (39.6%)	TDF/FTC N = 6,160 (11.9%)	ABC/3TC N = 13,715 (26.6%)	Other regimes N = 11,251 (21.8%)
Hypertension [N (%)]				
No	16,804 (82.2)	5,388 (87.5)	10,897 (79.4)	8,469 (75.3)
Yes	3,091 (15.1)	695 (11.3)	2,589 (18.9)	2,564 (22.8)
Unknown	537 (2.6)	77 (1.2)	229 (1.7)	218 (1.9)
Diabetes [N (%)]				
No	18,490 (90.5)	5,707 (92.6)	12,217 (89.1)	9,736 (86.5)
Yes	1,486 (7.3)	380 (6.2)	1,302 (9.5)	1,305 (11.6)
Unknown	456 (2.2)	73 (1.2)	196 (1.4)	210 (1.9)
Chronic renal disease [N (%)]				
No	19,375 (94.8)	5,952 (96.6)	12,570 (91.6)	10,028 (89.1)
Yes	1,057 (5.2)	208 (3.4)	1,145 (8.3)	1,223 (10.9)
Cardiovascular disease [N (%)]				
No	16,628 (81.4)	5,511 (89.5)	11,759 (85.7)	9,568 (85.0)
Yes	1,051 (5.1)	302 (4.9)	773 (5.6)	887 (7.9)
Unknown	2,753 (13.5)	347 (5.6)	1,183 (8.6)	796 (7.1)
Treatment with immunosuppressants or corticosteroids [N (%)				
No	13,631 (66.7)	4,313 (70.0)	8,768 (63.9)	7,805 (69.4)
Yes	174 (0.8)	78 (1.3)	163 (1.2)	142 (1.3)
Unknown	6,627 (32.4)	1,769 (28.7)	4,784 (34.9)	3,304 (29.4)

TDF/FTC group had lower prevalence of hypertension and slightly lower prevalence of diabetes and chronic renal disease

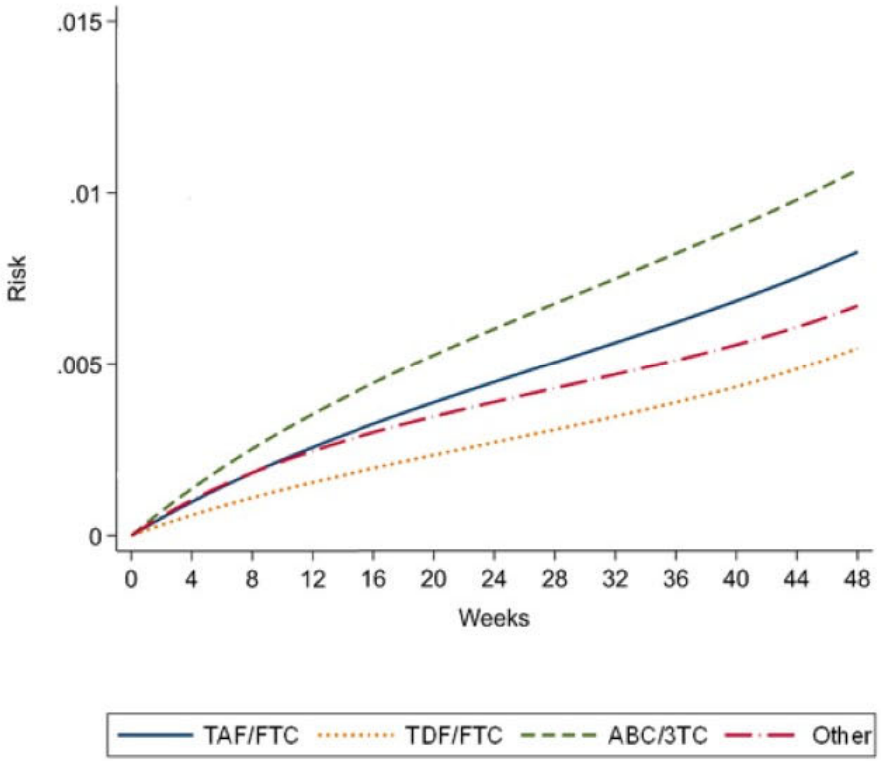
Results – Documented SARS-CoV-2 infection



	No. events	Risks (95%CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)
TAF/FTC	923	4.3 (4.1, 4.6)	0	1.00
TDF/FTC	300	4.5 (3.9, 5.0)	0.16 (-0.48, 0.69)	1.04 (0.89, 1.17)
ABC/3TC	687	5.2 (4.8, 5.6)	0.89 (0.40, 1.34)	1.21 (1.09, 1.33)
Other	492	4.6 (4.1, 5.0)	0.24 (-0.27, 0.77)	1.06 (0.94, 1.18)

** Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4 (<350, 350-500, >500 cells/mm3), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.*

Results –COVID-19 hospitalization

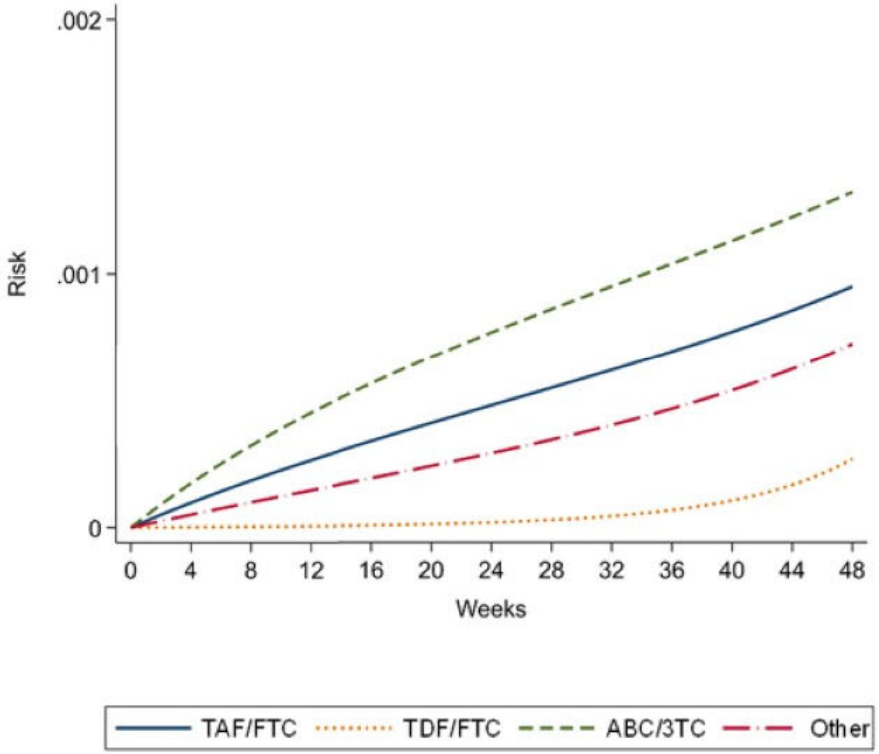


	No. events	Risks (95%CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)
TAF/FTC	157	0.8 (0.7, 1.0)	0	1.00
TDF/FTC	35	0.5 (0.4, 0.7)	-0.28 (-0.52, -0.08)	0.66 (0.43, 0.91)
ABC/3TC	147	1.1 (0.9, 1.2)	0.24 (0.02, 0.45)	1.29 (1.02, 1.58)
Other	86	0.7 (0.5, 0.8)	-0.16 (-0.34, 0.04)	0.81 (0.62, 1.05)

** Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4 (<350, 350-500, >500 cells/mm3), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.*

Results –COVID-19 ICU admission

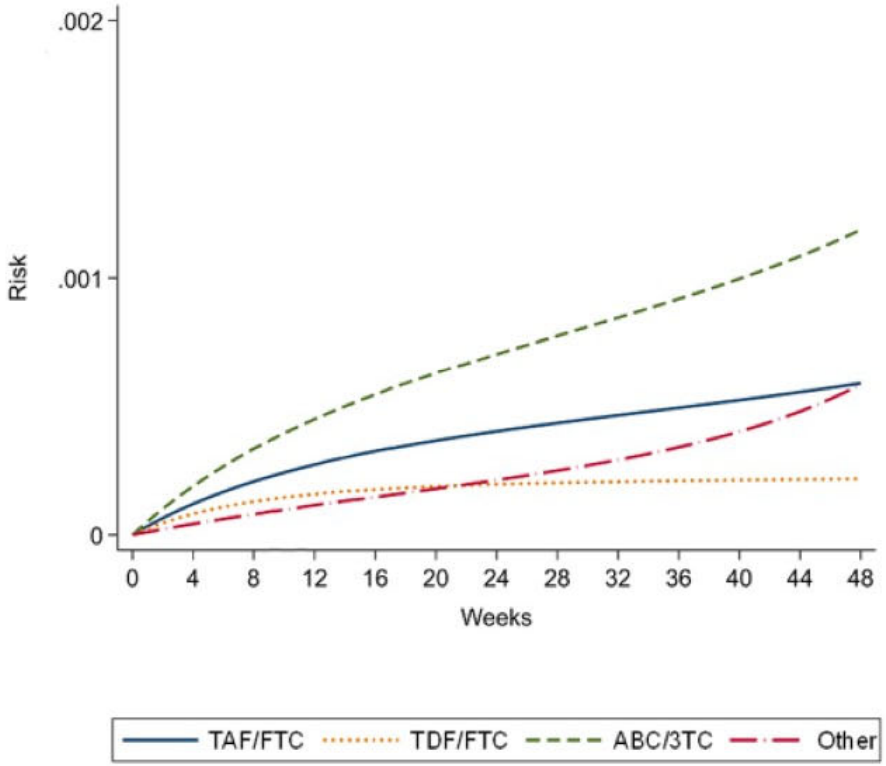
CoVIHd



	No. events	Risks (95%CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)
TAF/FTC	17	0.09 (0.05, 0.14)	0	1.00
TDF/FTC	2	0.03 (0.01, 0.08)	-0.07 (-0.12, -0.004)	0.28 (0.11, 0.90)
ABC/3TC	18	0.13 (0.08, 0.19)	0.04 (-0.03, 0.12)	1.39 (0.70, 2.80)
Other	8	0.07 (0.02, 0.12)	-0.02 (-0.09, 0.04)	0.76 (0.23, 1.77)

** Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4 (<350, 350-500, >500 cells/mm3), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.*

Results –COVID-19 death

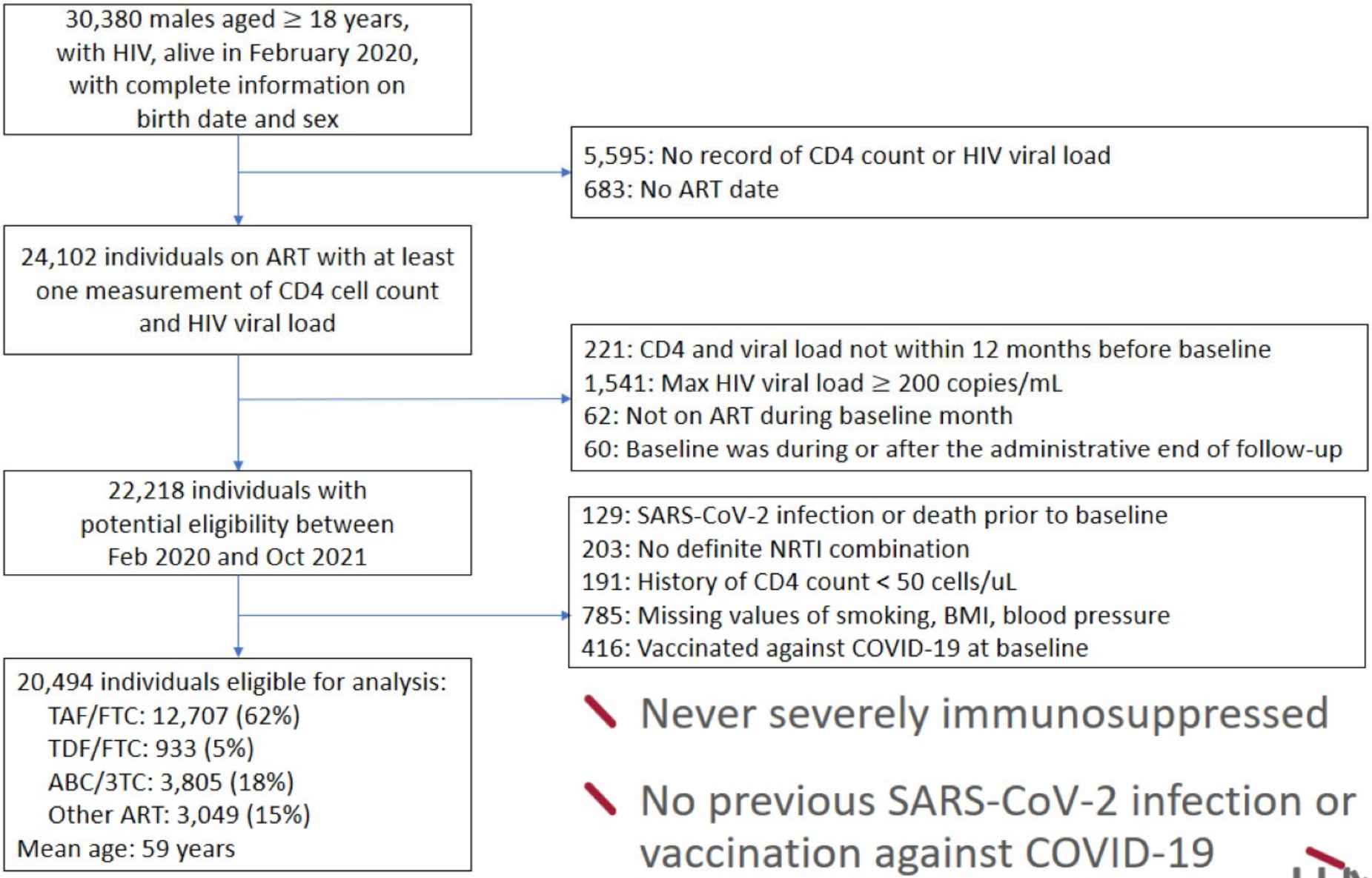


	No. events	Risks (95%CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)
TAF/FTC	9	0.06 (0.02, 0.11)	0	1.00
TDF/FTC	1	0.02 (0.02, 0.09)	-0.04 (-0.07, -0.03)	0.37 (0.23, 1.90)
ABC/3TC	18	0.12 (0.07, 0.18)	0.06 (-0.01, 0.12)	2.02 (0.88, 6.12)
Other	9	0.06 (0.02, 0.11)	0 (-0.06, 0.06)	0.99 (0.34, 2.61)

** Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4 (<350, 350-500, >500 cells/mm3), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.*

Veterans Aging Cohort Study – VACS

- U.S. veterans currently in care at nine VA medical centers
  - HIV-positive cohort is predominantly male
  - Medical records include detailed data on comorbidities
- Risk of COVID-19 outcomes by antiretroviral therapy regime
  - TDF/FTC
  - TAF/FTC
  - ABC/3TC (abacavir/lamivudine)
  - Other
- Funded by NIH
  - Li et al. *AIDS* 2022


30,380 males aged ≥ 18 years, with HIV, alive in February 2020, with complete information on birth date and sex
5,595: No record of CD4 count or HIV viral load
683: No ART date
24,102 individuals on ART with at least one measurement of CD4 cell count and HIV viral load
221: CD4 and viral load not within 12 months before baseline
1,541: Max HIV viral load ≥ 200 copies/mL
62: Not on ART during baseline month
60: Baseline was during or after the administrative end of follow-up
22,218 individuals with potential eligibility between Feb 2020 and Oct 2021
129: SARS-CoV-2 infection or death prior to baseline
203: No definite NRTI combination
191: History of CD4 count < 50 cells/uL
785: Missing values of smoking, BMI, blood pressure
416: Vaccinated against COVID-19 at baseline
20,494 individuals eligible for analysis:
TAF/FTC: 12,707 (62%)
TDF/FTC: 933 (5%)
ABC/3TC: 3,805 (18%)
Other ART: 3,049 (15%)
Mean age: 59 years
Never severely immunosuppressed
No previous SARS-CoV-2 infection or vaccination against COVID-19

Baseline characteristics similar across groups, except

	TDF/FTC N=933 (5%)	TAF/FTC N=12707 (62%)	ABC/3TC N=3805 (18%)	Other ART N=3049 (15%)
Chronic kidney disease (CKD)	4.5%	8.2%	14.3%	15.3%
eGFR < 60 mL/min	9.2%	18.0%	28.4%	28.7%

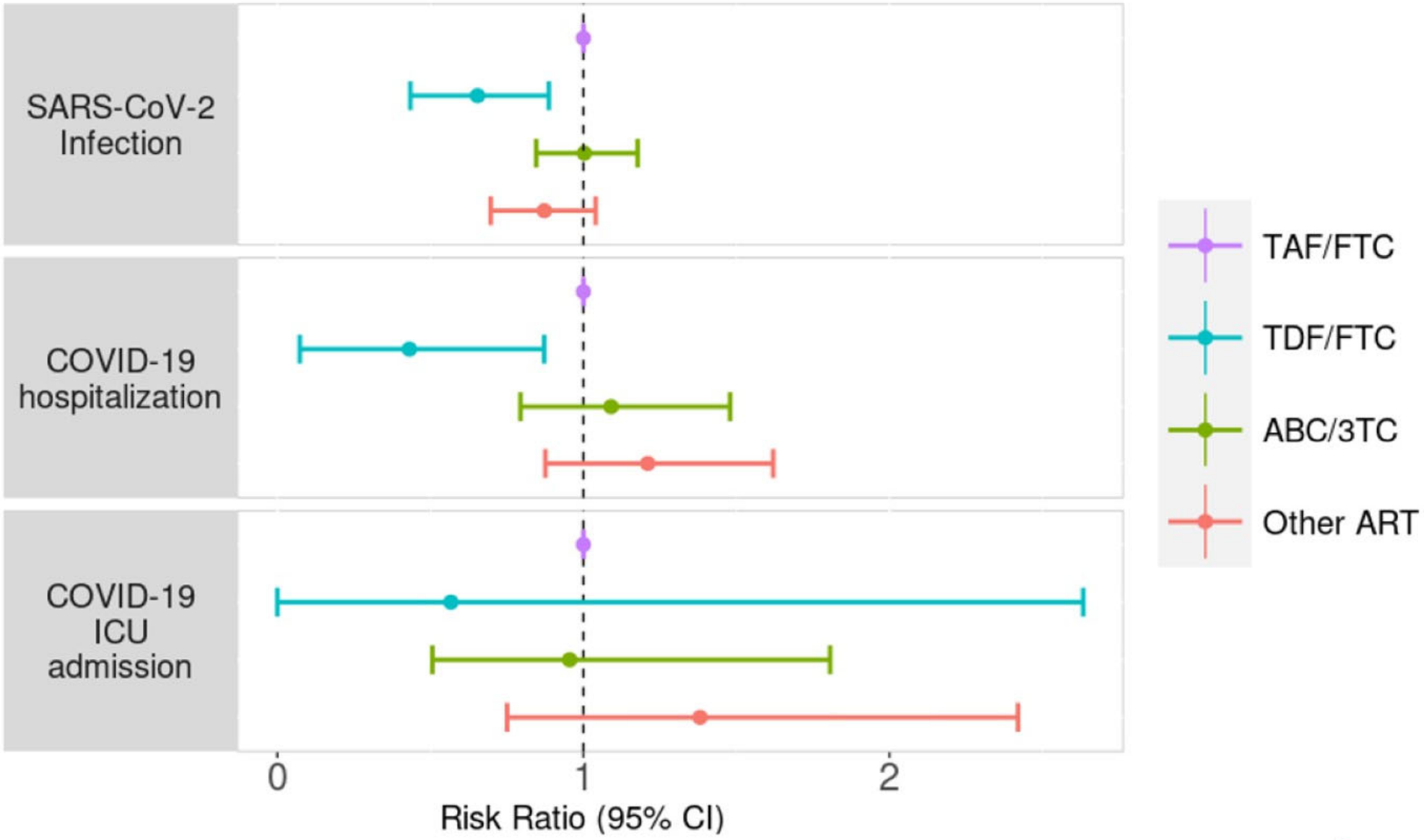
- Individuals in Other ART group were slightly older, had lower CD4 count, higher viral load, and higher % of comorbidities

eGFR: estimated glomerular filtration rate

We estimated the 18-month risk of

- Documented SARS-CoV-2 infection
- Hospitalization, ICU admission, death
  - Within 30 days of the first positive SARS-CoV-2 test

- Standardized by:
  - Age, race/ethnicity, smoking status
  - CD4 count, HIV viral load, max HIV viral load
  - BMI, blood pressure, eGFR
  - Calendar month
  - Hospitalization in previous month, comorbidities (including CKD)


SARS-CoV-2 Infection
COVID-19 hospitalization
COVID-19 ICU admission
0
1
2
Risk Ratio (95% CI)
TAF/FTC
TDF/FTC
ABC/3TC
Other ART

Let's review the situation
How many randomized trials for each antiviral?

- Remdesivir (in vitro and in vivo studies, some safety data)
  - Multiple in hospitalized patients
  - 1 in nonhospitalized patients (Gilead)
- HCQ (in vitro studies, lots of safety data)
  - Multiple
- Molnupiravir (in vitro studies, in vivo studies, safety concerns)
  - 1 in hospitalized patients (Merck)
  - 1 in nonhospitalized patients (Merck) before approval, others later
- TDF/FTC (in vitro and in vivo studies, excellent safety record, **and highly supportive human data from observational studies in humans**
  - 1 in hospitalized patients
  - 1 pre-exposure prophylaxis trial with 25% of planned size (publicly funded)

A single randomized trial was available at the time of emergency approval for both remdesivir and molnupiravir

- Where is the single randomized trial for TDF/FTC in nonhospitalized patients?

Why no randomized trials for tenofovir despite all observational evidence?

- TDF may or may not work for the early treatment of COVID-19
- But TDF is safe and
- the evidence to launch randomized trials for TDF is not weaker, and is arguably stronger, than for other drugs
  - The cost of 1 trial for tenofovir would have been a fraction of money paid for molnupiravir before its effectiveness was shown

Profit motive?

- TDF is an inexpensive generic drug
- Why would a for-profit pharmaceutical company spend money?

- But profit can't be the only explanation to this story
- Nonprofit COVID-19 Therapeutics Accelerator never considered TDF
  - Despite meeting their scoping criteria for new treatments
  - https://www.therapeuticsaccelerator.org/propose-a-treatment-or-study/
- And not only them…

The tenofovir story summarizes all misconceptions about observational data

- Observational studies were just not taken seriously

- "Association is not causation"
- If you think observational studies aren't enough evidence to launch a randomized trial, WHY?
  - What causal model do you have in mind? What alternative explanations?
  - What confounding factor may explain the observational results?

Even the investigators of some observational studies bent over backwards to dismiss their estimates

PISCIS

Methods: We conducted a propensity score-matched analysis in the prospective PISCIS cohort of PLWH ($n = 14\,978$) in Catalonia, Spain. We used adjusted Cox regression models to assess the association between tenofovir and SARS-CoV-2 outcomes.

Results: After propensity score-matching, SARS-CoV-2 diagnosis rates were similar in TAF/FTC versus ABC/3TC recipients (11.6% versus 12.5%, $P = 0.256$); lower among TDF/FTC versus ABC/3TC recipients (9.6% versus 12.8%, $P = 0.021$); and lower among TDF/FTC versus TAF/FTC recipients (9.6% versus 12.1%, $P = 0.012$). In well-adjusted logistic regression models, TAF/FTC was no longer associated with reduced SARS-CoV-2 diagnosis [adjusted odds ratio (aOR) 0.90; 95% confidence interval (CI), 0.78–1.04] or hospitalization (aOR 0.93; 95% CI, 0.60–1.43). When compared with ABC/3TC, TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or hospitalization (aOR 0.51; 95% CI, 0.15–1.70). TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or associated hospitalization (aOR 0.33; 95% CI, 0.10–1.07) compared with TAF/FTC.

Conclusions: TAF/FTC or TDF/FTC were not associated with reduced SARS-CoV-2 diagnosis rates or associated hospitalizations among PLWH. TDF/FTC users had baseline characteristics intrinsically associated with more benign SARS-CoV-2 infection outcomes. Tenofovir exposure should not modify any preventive or therapeutic SARS-CoV-2 infection management.

- Nomah et al. *J Antimicrob Chemother* 2022

Conclusion:
A missed opportunity

- If we had to do things over, would we pour so much money into remdesivir and molnupiravir without simultaneously studying TDF?
- It may now be too late for TDF and COVID-19, but we have learned a lesson for next time:
  - If observational studies yield strong effect estimates for which no alternative explanation is known
  - Let's launch a randomized trial

- Let's educate the decision makers before it happens all over again

Our research is funded by
- National Institute of Allergy and Infectious Diseases
- National Institute of Mental Health
- National Institute of Child Health and Development
- National Cancer Institute
- PCORI – Patient-Centered Outcomes Research Institute
- U.S. Department of Veterans Affairs

Thank you

@_MiguelHernan

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