HOPE
HIV Online Provider Education

Update on Novel Antiretroviral Agents and HIV and Covid-19

Rajesh T. Gandhi, MD

Massachusetts General Hospital

Professor of Medicine, Harvard Medical School

Boston, Massachusetts

Disclosure: Dr Gandhi has served on a scientific advisory board for Merck & Co, Inc. (Updated 2/1/20)

Acknowledgments: Delaney Taylor and Efe Airewele for assistance

What is the Future of ART?

Why we need new ART

Why we need new ART

New Drugs

How we will use new drugs

How we will use new drugs

But we're going to try!

Why we need new ART

- >30 drugs for treating people with HIV: high rates of viral suppression, low rates of toxicity

- Current regimens have limitations:
  - Weight gain, drug interactions
  - Daily oral dosing: challenge for some of the most vulnerable people
  - Limited information on safety during pregnancy
  - High costs, especially in US

Why we need new ART: Examples

People doing Well on ART	25 yo F. Virologically suppressed on single pill combination. Wants to take fewer medicines: worried about what they will do to her “over the long term”
People Struggling with Daily Oral ART	45 yo M. Swallowing difficulties, depression. On-again, off-again virologic suppression.
People with Multi-drug Resistant HIV	55 yo M with HIV since 1990s. Has been on multiple regimens. Now has virus resistant to all available classes.

Desiderata: “Things Wanted or Needed”

Need	People doing Well on ART	People Struggling with Daily Oral ART	People with Multi-drug Resistant HIV
Fewer drugs	✓	✓	--
Less toxicity	✓	✓	✓
Reduced Dosing Frequency	✓	✓✓✓	--
High Barrier to Resistance	✓	✓✓✓	--
Active against drug resistant HIV	--	--	✓✓✓
Less Visibility/Reduced Stigma	✓	✓✓✓	✓
Safety During Pregnancy	✓	✓	✓
Lower Cost/Better Access	✓	✓	✓

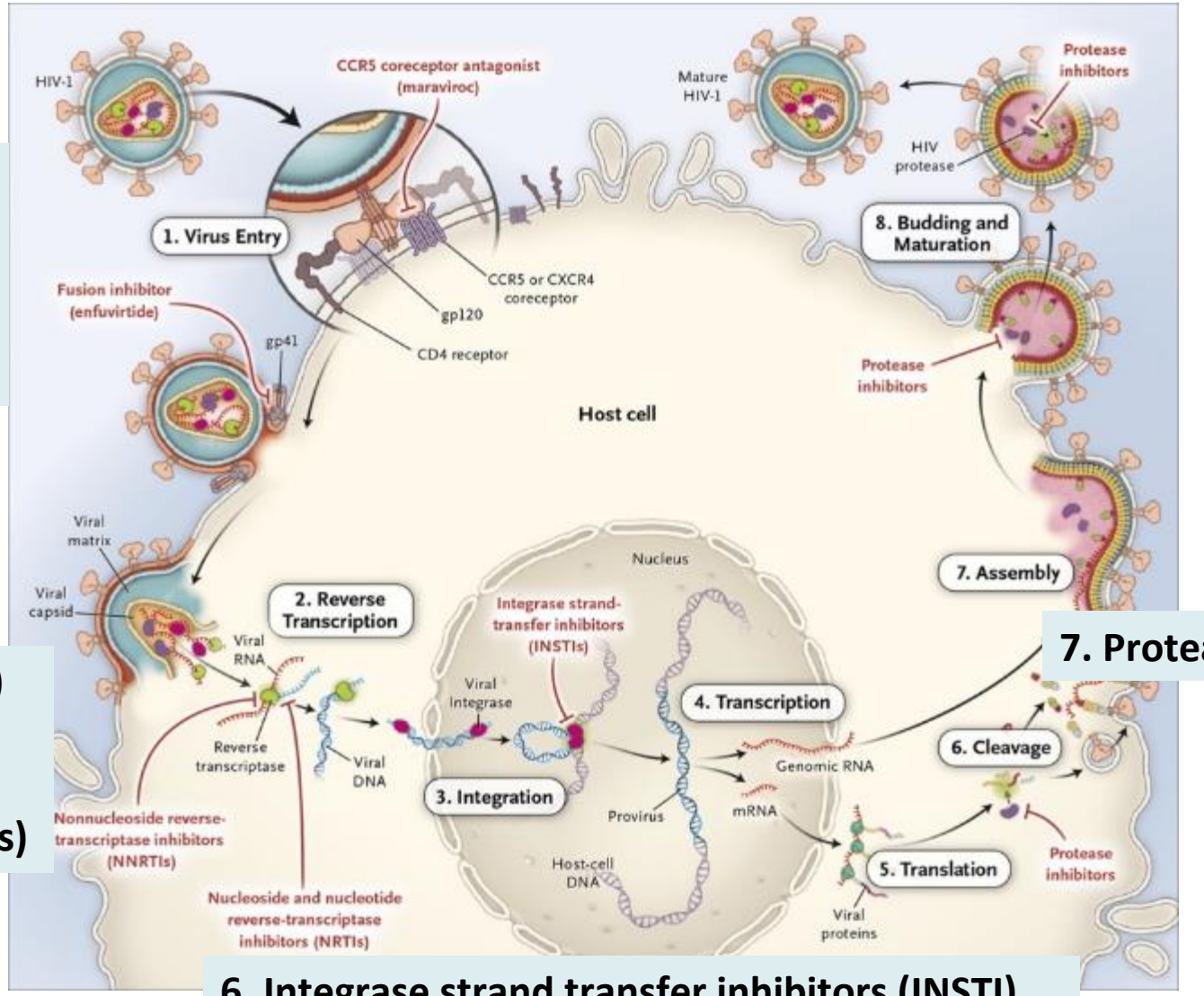
Major Classes (n=7) of Current Antiretroviral Medications

Entry inhibitors:

1. **Attachment inhibitor**
2. **CCR5 Antagonist**
3. **Fusion inhibitor**

Reverse Transcriptase Inh. (RTI)

4. **Nucleoside RTI (NRTIs)**
5. **Nonnucleoside RTI (NNRTIs)**



7. Protease inhibitors (PI)

6. Integrase strand transfer inhibitors (INSTI)

Gandhi M, Gandhi RT. N Engl J Med 2014;371:248-259.

New Drugs in Development

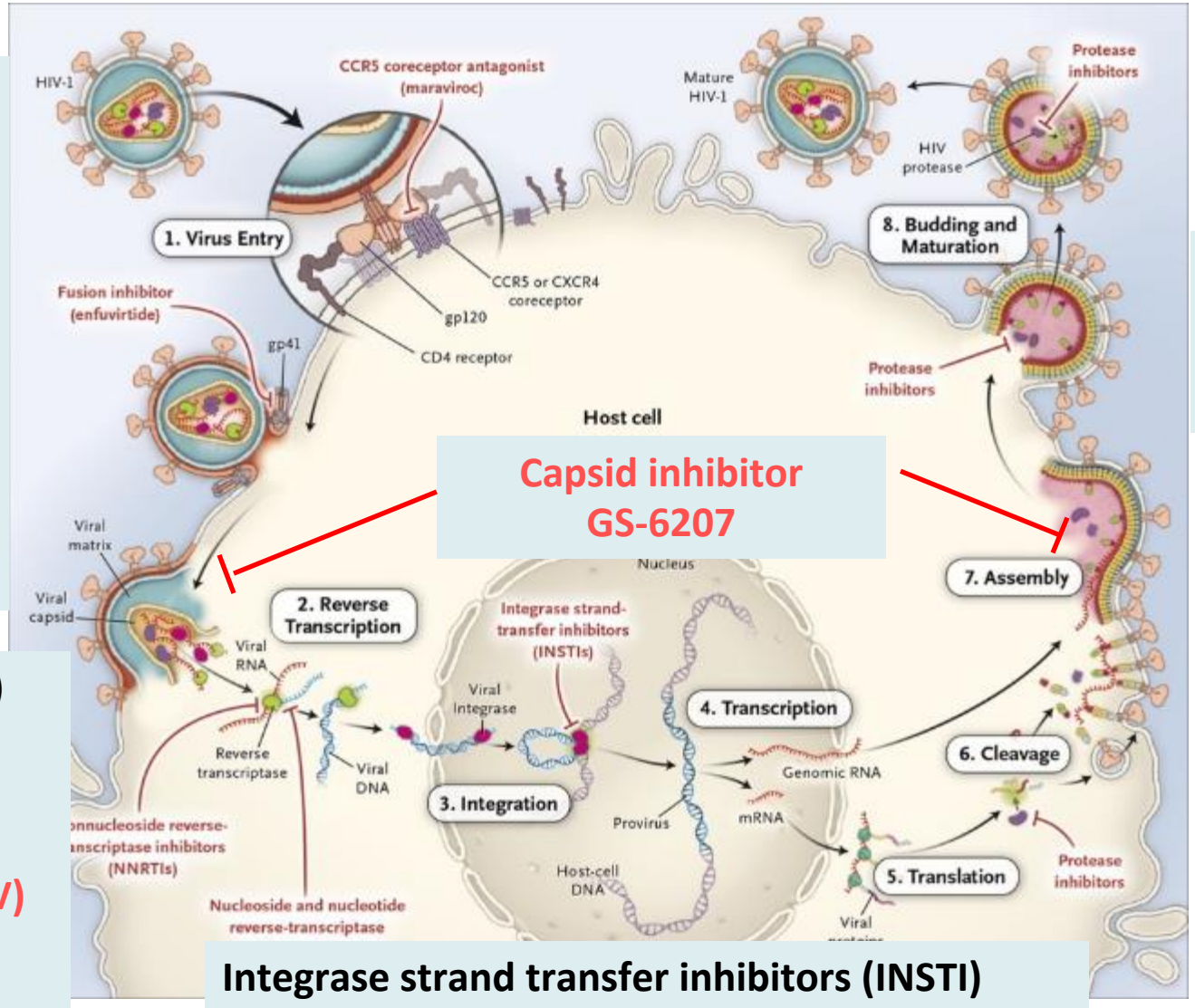
Entry inhibitors:

- Attachment inhibitor:
  - Fostemsavir
  - UB-421
- CCR5 Antagonist:
  - Leronlimab
- Fusion Inh.: Albuvirtide
- Multisite: Combinectin
- Broadly neutralizing Abs

Reverse Transcriptase Inh. (RTI)

Nucleoside RTI (NRTIs)

- Nonnucleoside RTI (NNRTIs)
  - Long-acting rilpivirine (RPV)
  - Elsulfavirine
- Nucleoside RT translocation inhibitor: Islatravir



Integrase strand transfer inhibitors (INSTI)

- Long-acting cabotegravir (CAB)

Maturation inhibitor

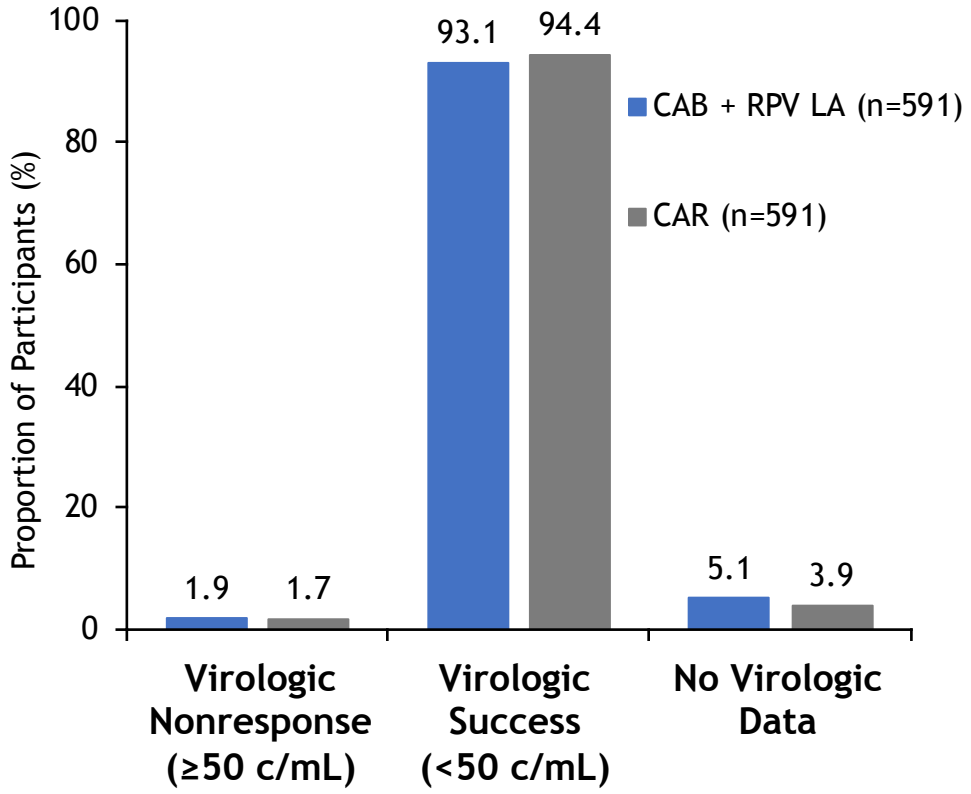
- GSK3640254 (non-boosted)

Gandhi M, Gandhi RT. NEJM 2014;371:248-259.

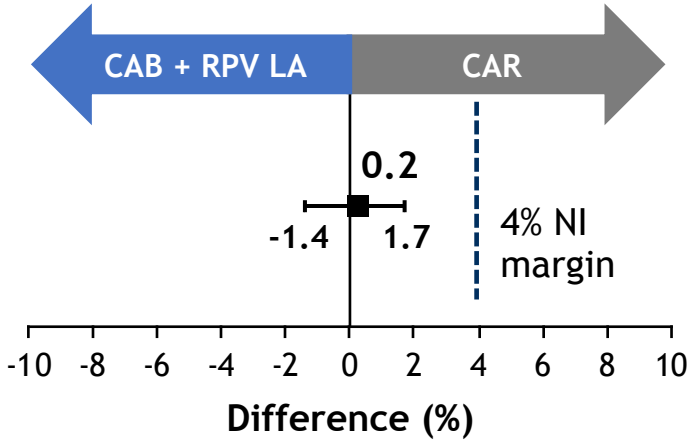
Monthly LA Cabotegravir/Rilpivirine in PWH with Suppressed HIV RNA: ATLAS/FLAIR Week 48 Pooled Results

Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, available in long-acting nanosuspension formulations that can be given by injection

Virologic outcomes



Adjusted treatment difference (95% CI)*



Primary Endpoint:

LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

Week 96 FLAIR: monthly LA CAB/RPV non-inferior to oral DTG/ABC/3TC. No confirmed virologic failures in LA arm from Wk 48 to 96

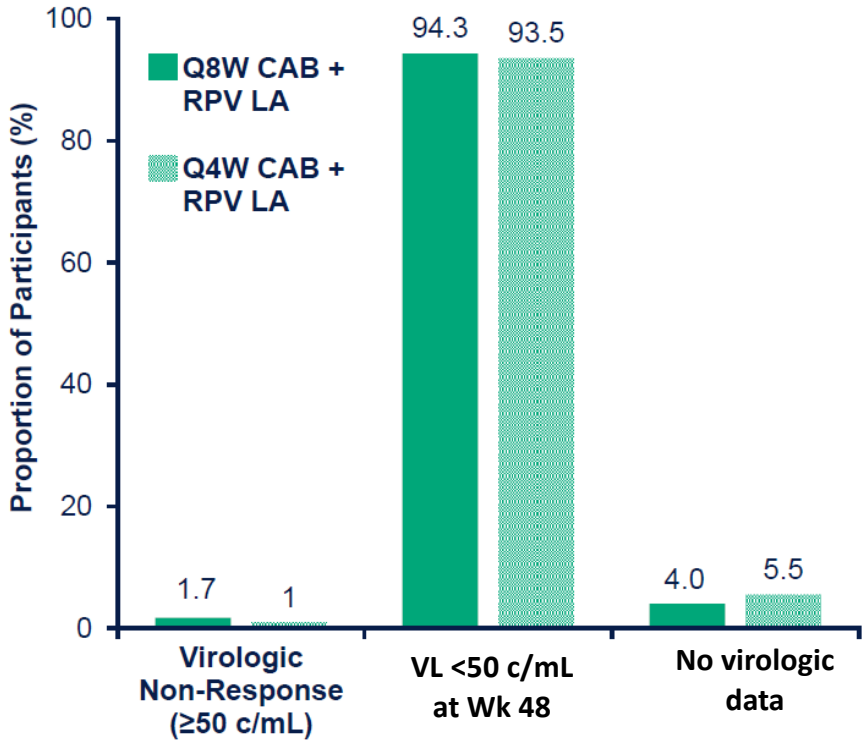
Orkin C et al, CROI 2020, #482

*Adjusted for sex and baseline third agent class.
CAR, current antiretroviral; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority;

Overton E, IAS 2019 MOPEB257; Swindells S et al, NEJM 2020; Orkin C et al, NEJM, 2020

ATLAS-2M

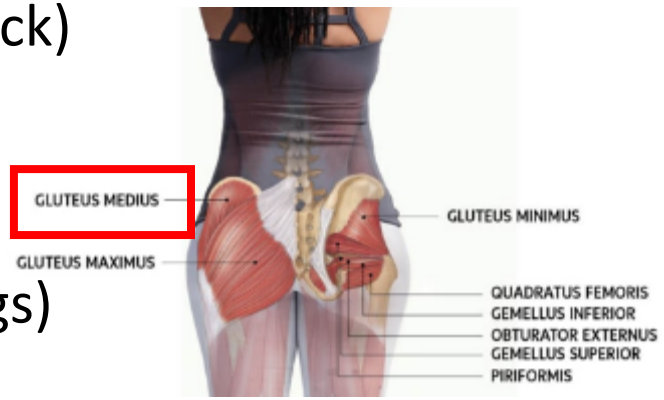
- Phase 3 open-label trial in people with HIV suppressed on CAB/RPV LA every 4 weeks (n=391) or oral ART (n=654)
  - Candidates excluded if history of virologic failure or INSTI or NNRTI resistance (except K103N)
- Randomized 1:1 to CAB/RPV LA every 4 weeks or every 8 weeks
- CAB/RPV Q8W non-inferior to Q4W: 1.7% vs. 1.0% VL >50 c/mL at wk 48
- >90% of participants preferred Q8W dosing over their previous regimen



Overton E et al, CROI 2020, #34

LA CAB/RPV: Practical Considerations and Questions

- Injections given into gluteus medius (upper outer quadrant of buttock)
  - Need private space: how will we set up clinics to deliver the drugs?
  - Alternative spaces: Pharmacies? Home healthcare?
- RPV LA requires cold chain (consideration in resource limited settings)
- Is 4-week oral lead-in needed? What about direct to inject?
- Can CAB/RPV be used in someone who is viremic?
  - Case: person with bowel resection; not able to absorb oral ART; suppressed on IM CAB/RPV
- Long PK tail (48 wk or longer) after stopping drugs. Will missed doses → resistance?
- How will we remind people to come in for visits? Might pharmacies play a role?
- Will CAB/RPV be useful in people who have difficulty with adherence? ACTG A5359
- What will the cost of the drugs be? Will the cost of administration be reimbursed?



Orkin C, IAS 2019 TUSY0403; Landovitz, R, HIV R4P, Madrid, 2018. Abstract #OA15.06LB; Saman R, EACS 2019

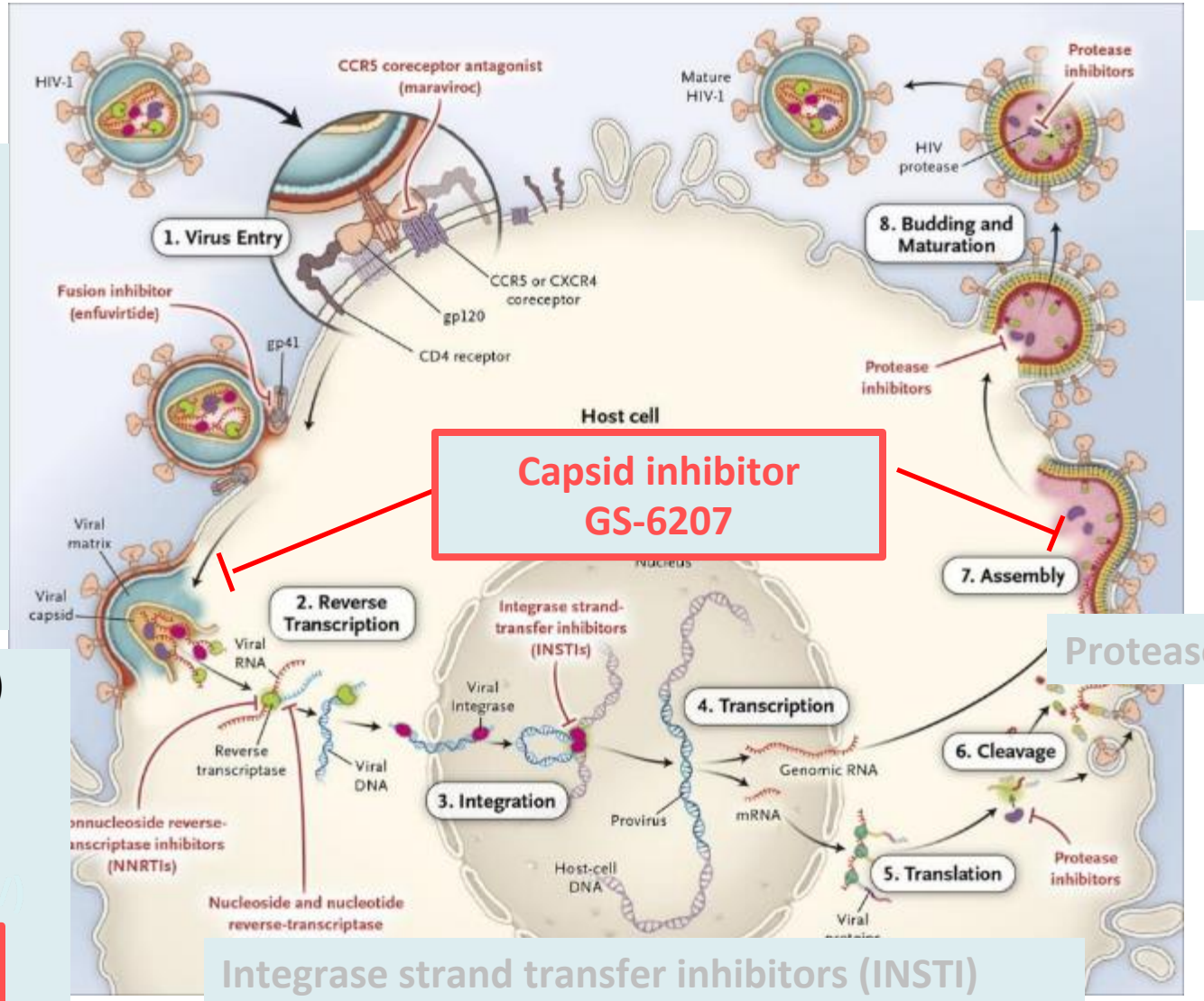
New Drugs

Entry inhibitors:

- Fusion Inh.: Albuvirtide
- CCR5 Antagonist:
  - Leronlimab
- Attachment inhibitor:
  - Fostemsavir
  - UB-421
- Broadly neutralizing Abs

Reverse Transcriptase Inh. (RTI)

- Nucleoside RTI (NRTIs)
- Nonnucleoside RTI (NNRTIs)
  - Long-acting rilpivirine (RPV)
- **Nucleoside RT translocation inhibitor: Islatravir**



Capsid inhibitor
GS-6207

Maturation inhibitors

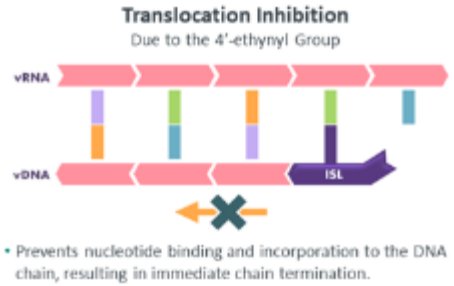
Protease inhibitors (PI)

Integrase strand transfer inhibitors (INSTI)

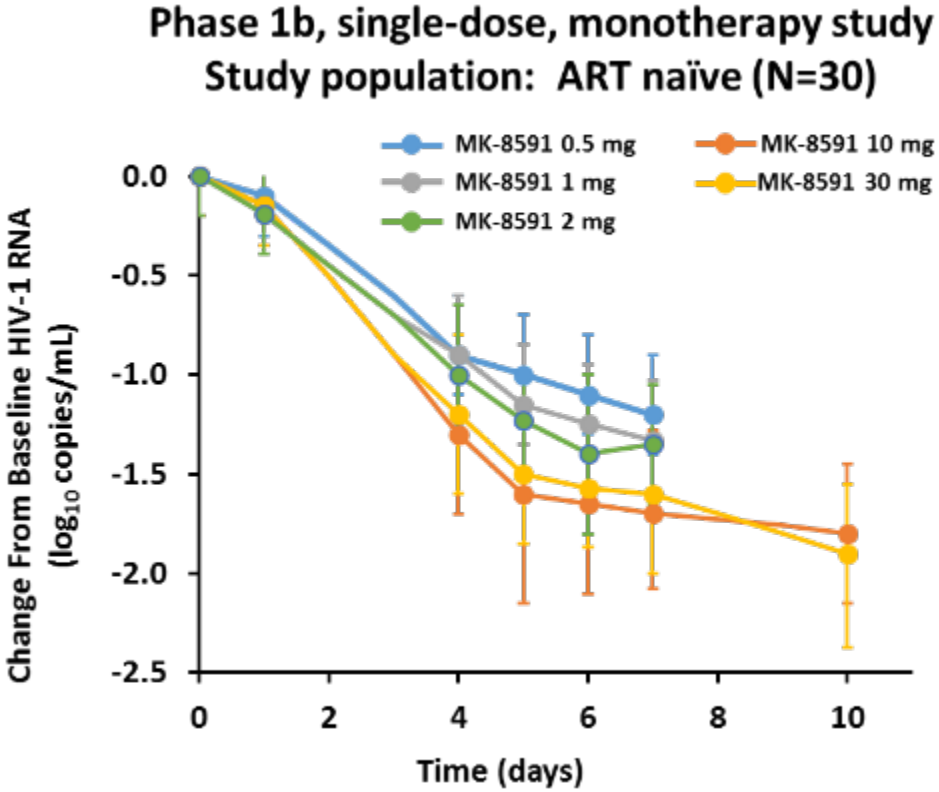
- Long-acting cabotegravir (CAB)

Gandhi M, Gandhi RT. N Engl J Med 2014;371:248-259.

Islatravir (MK-8591)



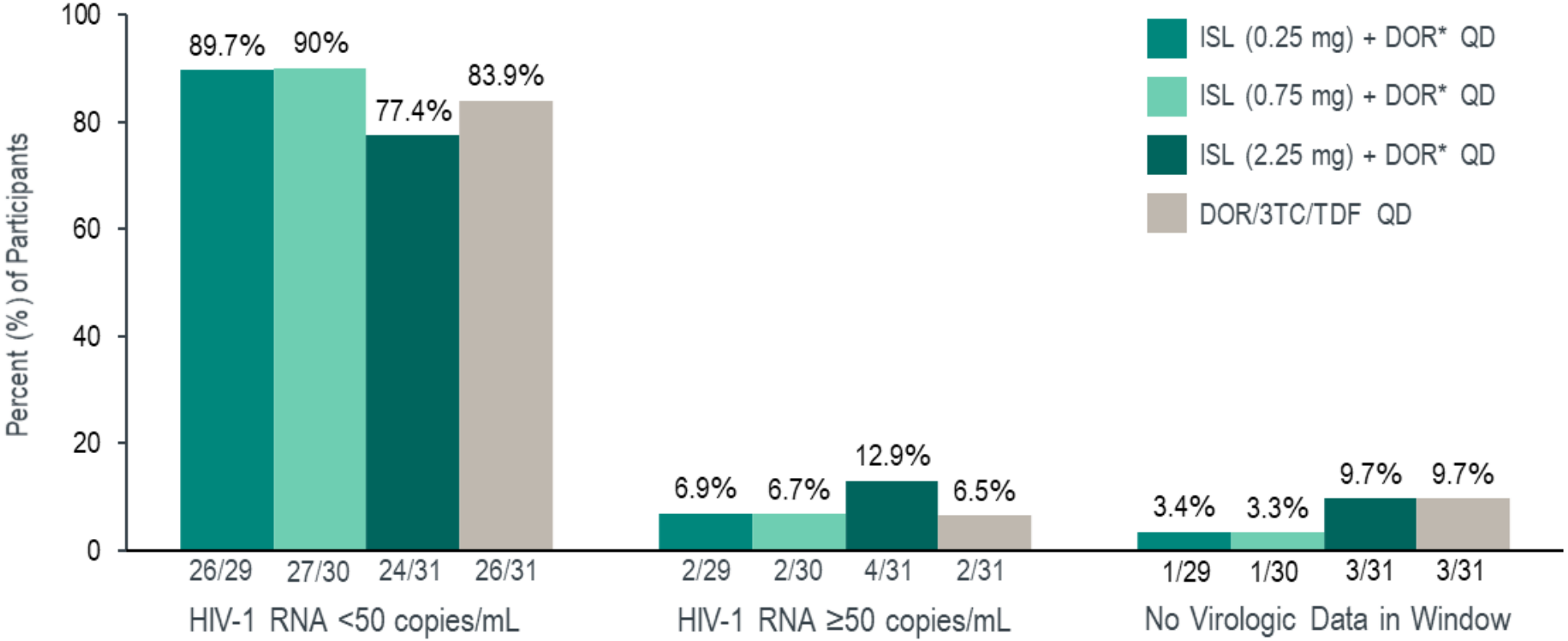
- Nucleoside RT translocation inhibitor (NRTTI)
- Potent at low doses: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days
- High barrier to resistance
- Long intracellular half-life (78-120 h)
  - Potential for once daily, once weekly or less frequent dosing



Grobler et al CROI 2017 #435; Matthews et al IAS 2017 #TUPDB0202LB; Schurmann et al, Lancet HIV, 2020

Phase 2b study for treatment: DRIVE2Simplify: ISL + DOR vs. DOR/3TC/TDF

Participants initially received ISL+DOR+3TC; then switched to ISL+DOR during week 24-48 after achieving virologic suppression. Week 48 virologic outcomes (FDA Snapshot)



Islatravir (ISL)

- **Phase 3 trials of ISL/DOR (0.75 mg/100 mg):**
  - Switch studies: from BIC/FTC/TAF (n=578)[1] or other 2- or 3-drug regimen (n=578)[2]
  - Highly treatment-experienced participants (at least 3 class resistance) (n=100)[3]
  - Treatment naïve participants: DOR/ISL vs. BIC/FTC/TAF (n=680)[4]

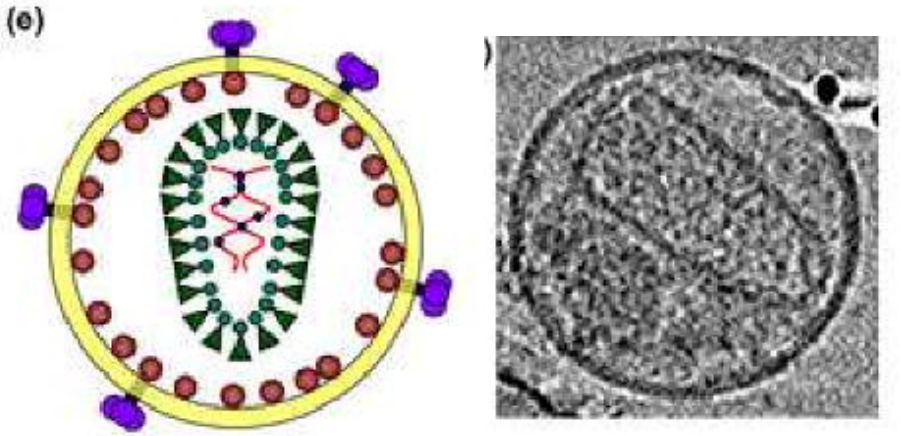
<u>Future possibilities:</u>

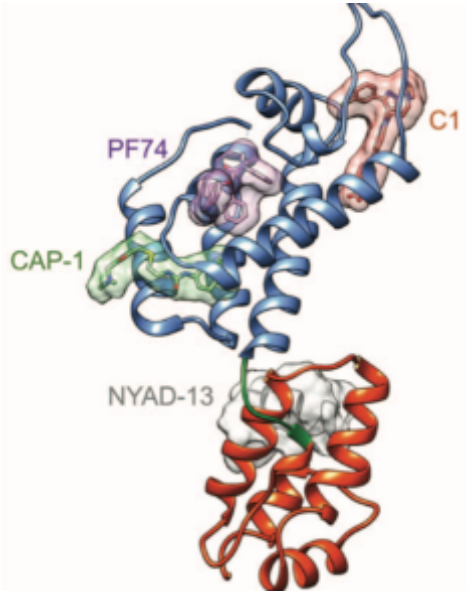
- In SIV model, weekly oral ISL provided effective post-exposure prophylaxis[5]
- May have applications for PrEP
  - Phase 2 trial in people at low risk of HIV: once monthly oral (60, 120 mg)[6]
  - Promising PK results with ISL implant[7]

[1]NCT04223791; [2]NCT04223778; [3]NCT04233216; [4]NCT04233879; [5]Markowitz M, CROI 2020, #89LB; [6]NCT04003103; [7]Matthews R, IAS 2019, TUAC0401LB

HIV Capsid and Capsid Inhibitors

- Capsid core: conical structure that encapsulates HIV genome and viral proteins (RT, integrase)
- Composed of multiple capsid protein subunits
- After virion enters cell, capsid core undergoes step-wise disassembly
  - Required for reverse transcription, subsequent steps
  - Host proteins (TRIM-5α, MxB) bind capsid, inhibit infection
- Late in HIV lifecycle, capsid proteins assemble and mature into the capsid core's final conical shape
- Capsid inhibitors bind distinct sites on capsid subunits

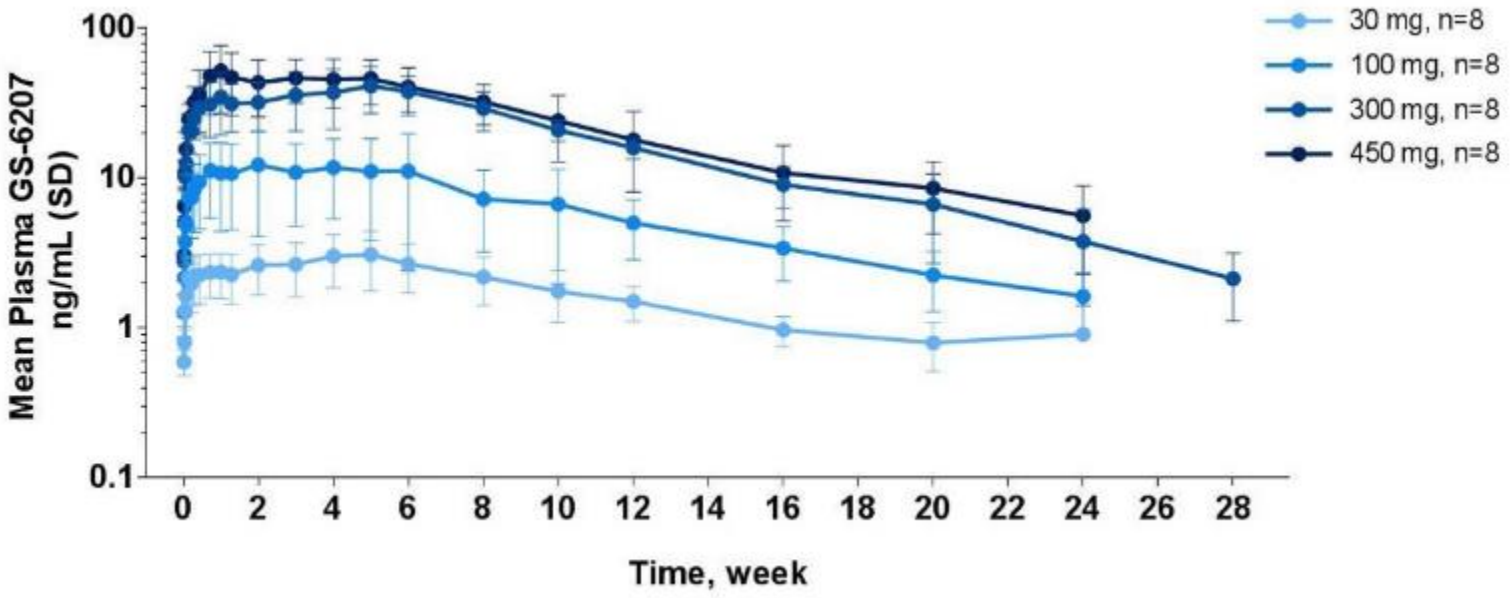




Ganser-Pornillos BK, Yeager M, Sundquist WI, Curr Opin Struct Biol, 2008; Campbell E and Hope T, Nat Rev Micro, 2015; Carnes SK et al, Curr Opin HIV AIDS, 2016

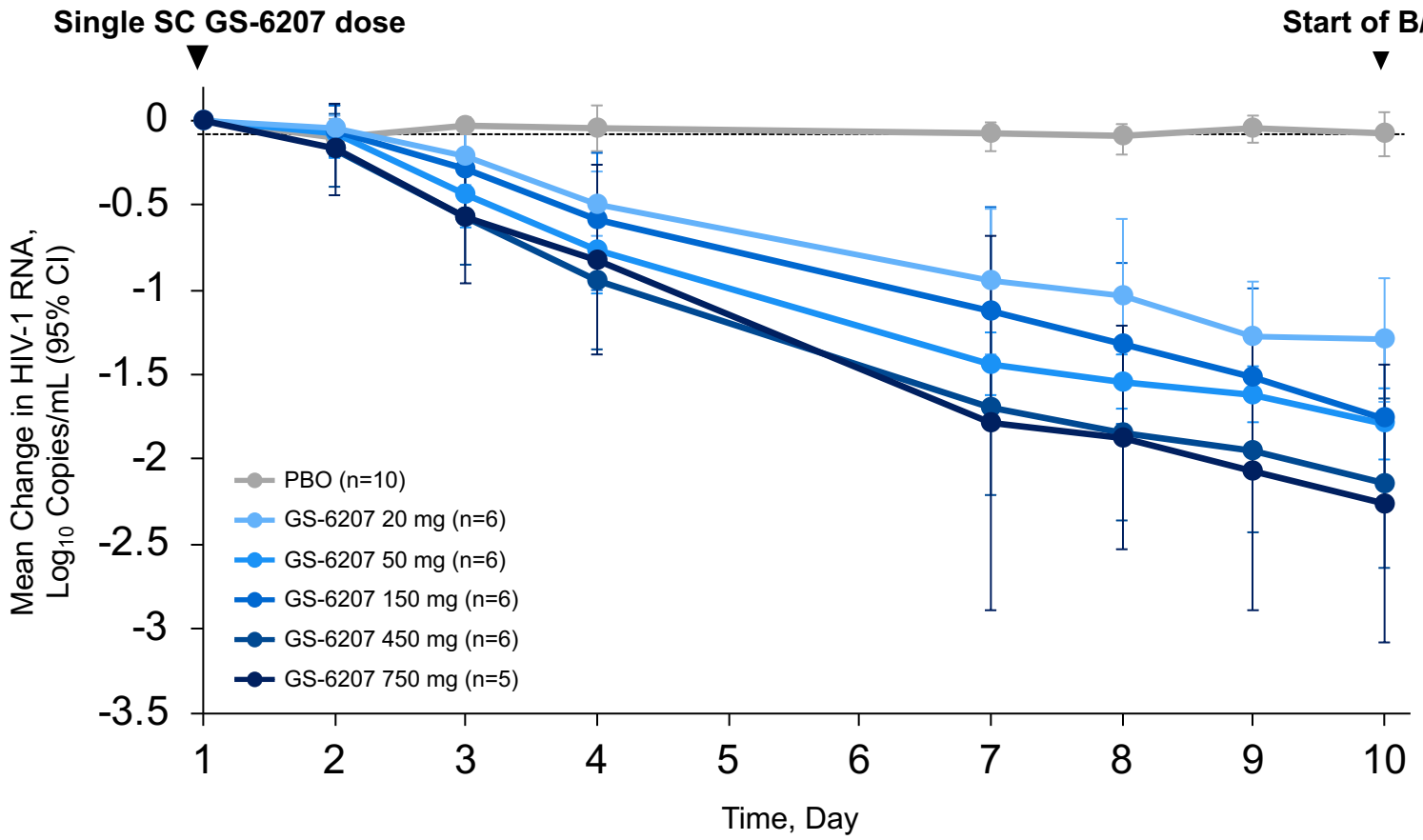
GS-6207 (Capsid Inhibitor)

- Picomolar activity against HIV in vitro
- Retains activity against HIV mutants resistant to other HIV classes
- Subcutaneous (SC) injection: sustained levels for >24 wk
- Oral formulation: median half-life 11-13 days



Yant SR et al, Nat Med, 2019
Yant et al, CROI 2019, abstract 480; Sager et al CROI 2019 abstract 141; Begley R et al CROI 2020 # 470

GS-6207 (Capsid Inhibitor): Antiviral activity after single subcutaneous dose in people with HIV



Mean change in HIV RNA:
-1.3 to 2.3 $\log_{10}$ c/mL over 10 days[1]

- Phase 2/3 study in heavily treatment experienced PWH (CAPELLA)
  - GS-6207 oral lead-in followed by SC injections (900 mg, 2 x 1.5 mL) every 6 mo + OBR
- Phase 2 trial in treatment naïve PWH (CALIBRATE)
- GS-6207 is also being developed for PrEP

OBR: optimized background regimen

[1]Daar E CROI 2020 # 469; Daar E IAS 2019 LBPEB13; Daar E EACS 2019 PE3/17
[2]clinical trials.gov: NCT04150068; NCT04143594

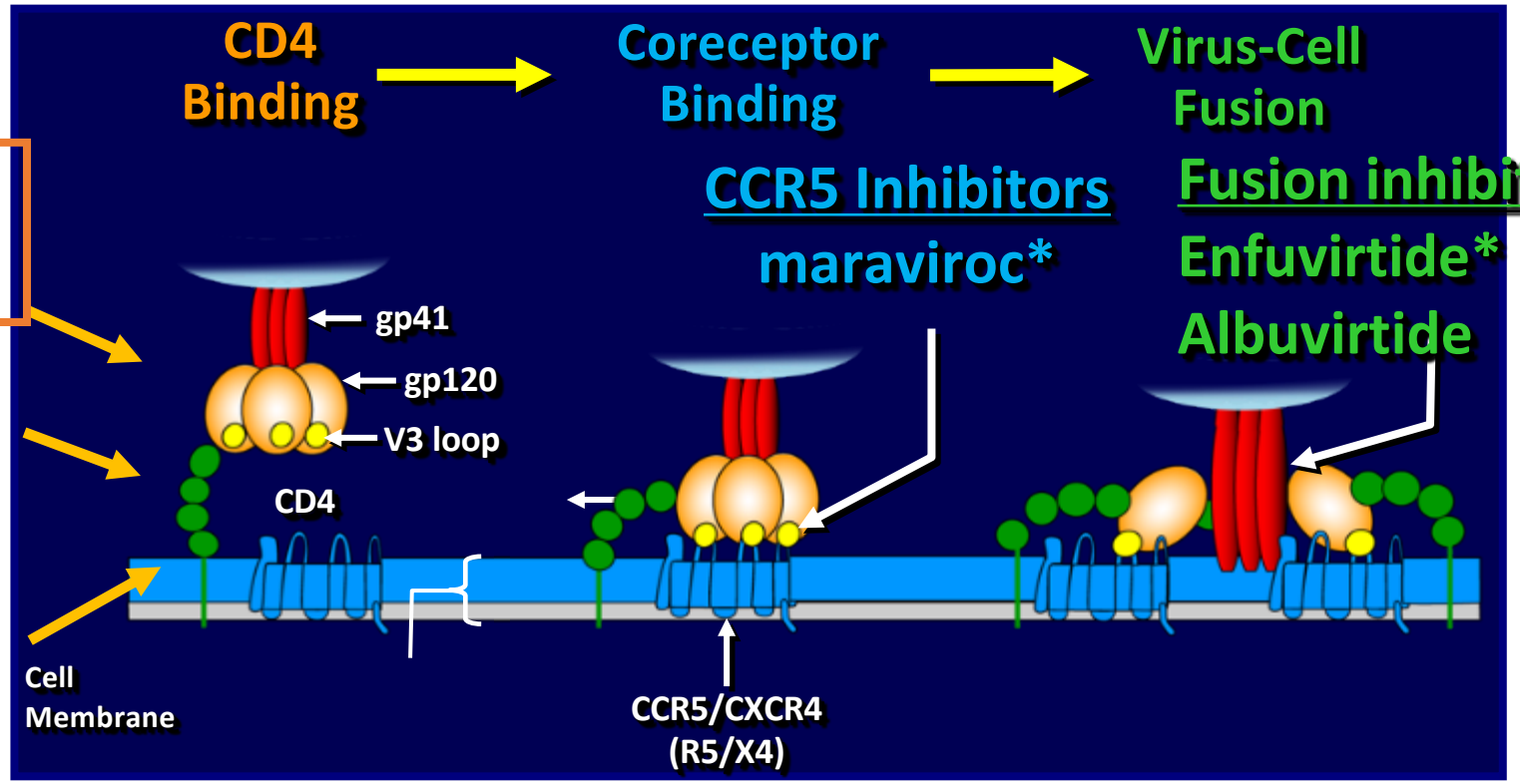
HIV Entry Inhibitors

Leronlimab
(PRO 140)[Y]

Fostemsavir

Ibalizumab*[Y]

UB-421[Y]

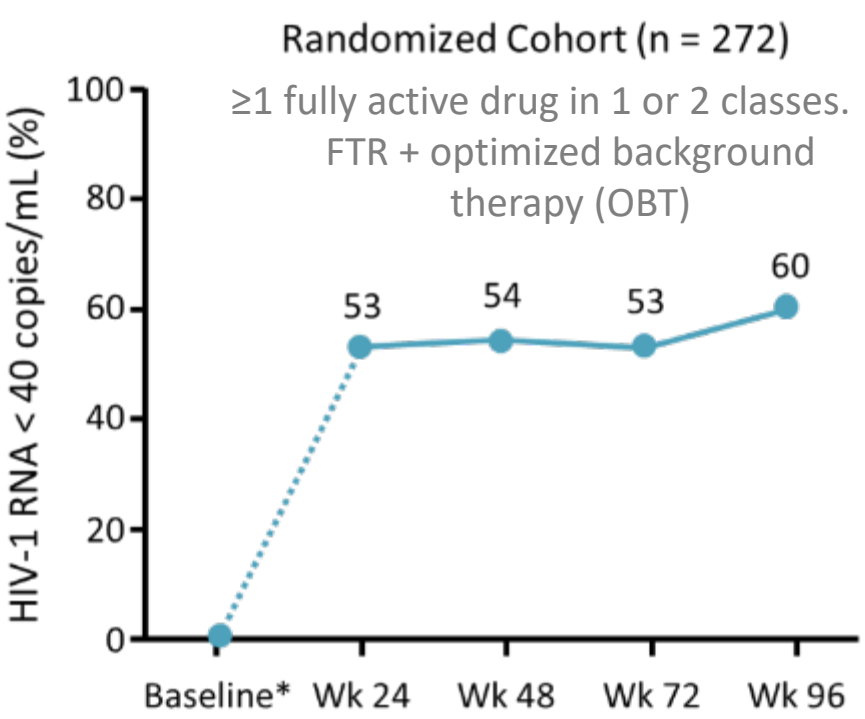


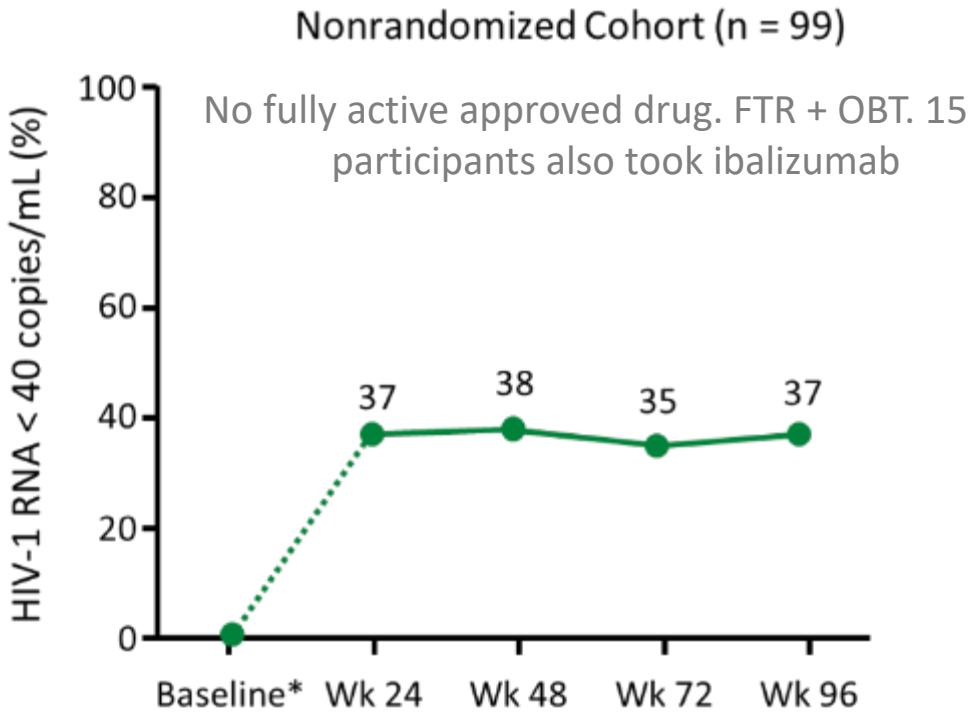
* FDA approved. [Y] Antibody

Slide adapted from one that is courtesy of Trip Gulick, MD;
Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of temsavir: binds to gp120, inhibits HIV attachment to CD4
- Phase 3 trial in heavily treatment experienced participants (BRIGHTE)

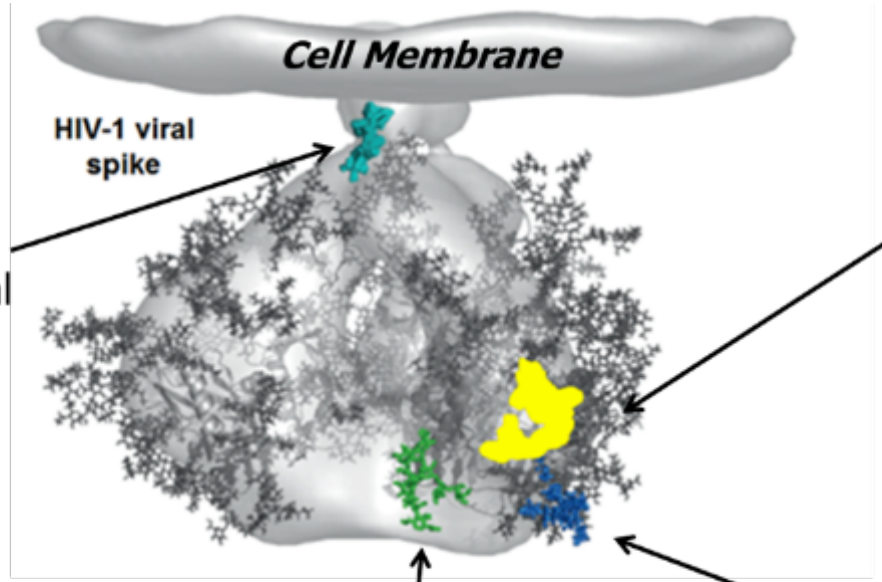




New drug application filed with FDA in Dec 2019 and EMA in Jan 2020. Compassionate access program.

Lataillade, IAS 2019. MOAB0102;
Kozal M et al, NEJM, March 26, 2020

HIV broadly neutralizing antibodies (bNAbs) in Clinical Trials



gp41 MPER:
10E8VLS: no ongoing trial

CD4 Binding Site:
VRC01: Phase 1-2b
VRC01-LS: Phase 1
VRC07-523LS: Phase 1-2
N6LS: Phase 1
3BNC117 and LS: Phase 1-2

SAR441236 - trispecific
VRC01LS/PGDM1400/10E8: Phase 1-2

TMB-Bispecific
ibalizumab/10E8.4: Phase 1

V1V2 Glycan:
CAP256V2LS: Phase 1 soon
PGDM1400 and LS: Phase 1-2

N332 Glycan Supersite:
PGT121: Phase 1-2
PGT121.BIJ414LS: Phase 1 soon
10-1074: Phase 1-2

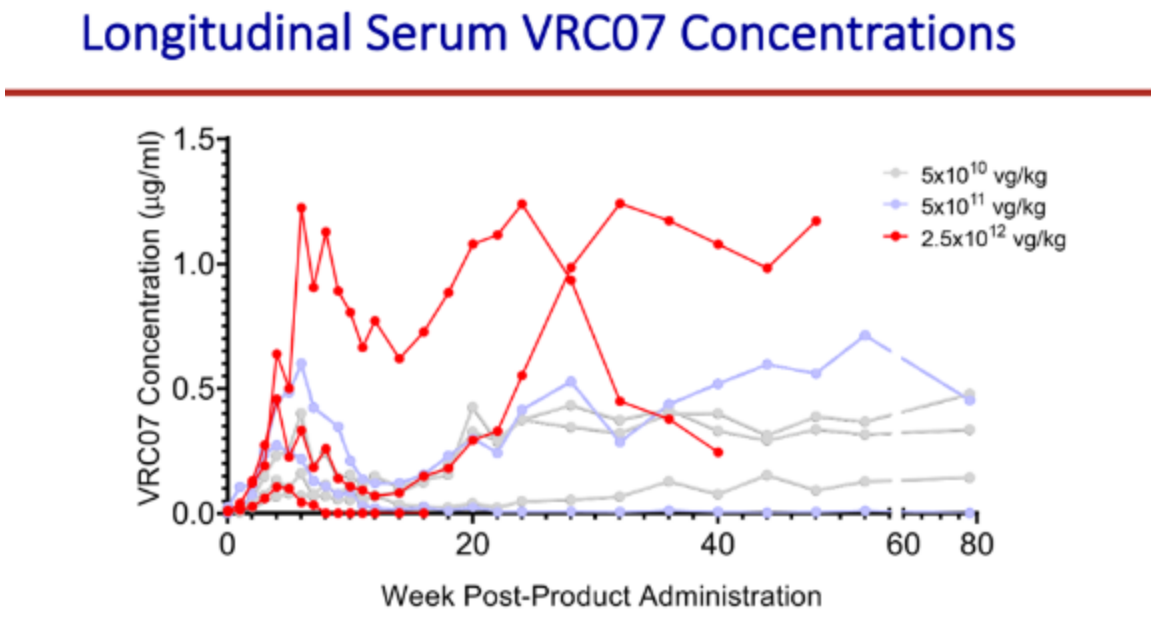
Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups

Promise: may be engineered to be very long-lasting; may be amenable to vectored delivery; may be combined with long-acting small molecules, eg study of LA cabotegravir + VRC07-523 LS (ACTG)

Slide courtesy of Lucio Gama, Ph.D.

New Data on bNAbs in Humans at CROI 2020

- Durable HIV antibody production in humans after AAV-mediated gene transfer
  - > 1 year after single administration of vector
  - Prospect of vectored delivery of bNAbs
- Phase 1 dose escalation trial of N6LS (CD4 binding site Ab) in healthy adults.
  - Licensed by Viiv Healthcare for treatment and prevention of HIV
- Safety and PK of GS-9722 in HIV-negative participants and people with HIV
  - Being developed for cure research



Casazza JP et al, CROI 2020, #41LB

Casazza JP et al, CROI 2020, #41LB; Widge AT et al, CROI 2020, #508; Ruane P et al, CROI 2020, #39

How we will use the new drugs

Long-acting Therapies: Lessons from Other Fields

Therapy	Route/Dosing Interval	Findings	Lessons/Questions for ART
Long-acting reversible contraceptives (LARC)	• IUDs/implants: yrs ("get it & forget it") • Medroxyprogesterone acetate inj: q 3 mo.	• IUDs/implants: lower failure rate than shorter acting contraceptives	• Choice matters! • Could inj. contraceptive & LA ART be combined/delivered together?
Bisphosphonates for osteoporosis	• Yearly injectable; monthly, weekly or daily oral medication	• Adherence and persistence: yearly injectable > weekly oral > daily oral.	• When it comes to dosing interval: the longer, the better
Long-acting injectable psychiatric medications	• Every 3 months	• Decreased discontinuation rate, lower hospitalization • Under-utilized (cost; given in clinic)	• Pay attention to facilitating delivery!
PCSK-9 inhibitors for cardiovascular disease prevention	• Every 2 or 4 weeks • Self administered	• Limited uptake, in part because of cost	• Self-administration desirable • Price competitively so cost not a barrier!

Winner B et al, NEJM, 2012; McClung et al, Bone, 2007; Ziller et al, International Journal of Clinical Pharmacology and Therapeutics, 2012; Cramer et al, Clinical Therapuetics, 2006; Karatasakis A et al, Journal of the American Heart Association, 2017; Kaplan G et al, Patient Preference and Adherence, 2013

Who Will We Treat with Long-Acting ART?

- For most people, oral daily ART will remain effective and convenient option
- LA ART may be good option for people who struggle with daily oral regimen (e.g., swallowing difficulties; not taking oral medications after surgery; stigma – external or internal) or who don't want to take medicine every day
- Combining visits for injections with other appointments may be helpful, e.g. picking up methadone refills, psychiatrist/psychologist/support groups, health centers
- Considerations: long PK tail, need for oral bridging if missed injection, reminders, logistics of administration, managing toxicities if they develop; what to do if recipient becomes pregnant

How Will We Use the New Drugs in People With MDR HIV?

- 55 yo M with HIV since 1990s.
- Has been on multiple regimens.
- Now has virus resistant to all available classes.

NRTI	Abacavir	Ziagen	Resistant	(4.5 - 6.5)	9.39
	Didanosine	Videx	Resistant	(1.3 - 2.2)	2.67
	Emtricitabine	Emtriva	Resistant	(3.5)	>MAX
	Lamivudine	Epivir	Resistant	(3.5)	>MAX
	Stavudine	Zerit	Resistant	(1.7)	2.57
	Zidovudine	Retrovir	Resistant	(1.9)	4.80
	Tenofovir	Viread	Partially Sensitive	(1.4 - 4)	1.62
	NRTI Mutations		M41L, D67N, K70S, L74I, V75T, M184V, T215F, K219Q, N348I		
NNRTI	Delavirdine	Rescriptor	Resistant	(6.2)	>MAX
	Efavirenz	Sustiva	Resistant	(3)	>MAX
	Etravirine	Intelence	Resistant	(2.9 - 10)	18
	Nevirapine	Viramune	Resistant	(4.5)	>MAX
	Rilpivirine	Edurant	Resistant	(2)	>MAX
	NNRTI Mutations		L100I, K103S, V179V/I, Y181Y/C, N348I		
	Atazanavir	Reyataz	Resistant	(2.2)	84
	Atazanavir	Reyataz / r‡	Resistant	(5.2)	84
	Darunavir	Prezista / r‡	Resistant	(10 - 90)	35
	Fosamprenavir	Lexiva / r‡	Resistant	(4 - 11)	28
	Indinavir	Crixivan / r‡	Resistant	(10)	64
	Lopinavir	Kaletra‡	Resistant	(9 - 55)	84
	Nelfinavir	Viracept	Resistant	(3.6)	19
	Ritonavir	Norvir	Resistant	(2.5)	>MAX
	Saquinavir	Invirase / r‡	Resistant	(2.3 - 12)	31
	Tipranavir	Aptivus / r‡	Resistant	(2 - 8)	>MAX
	PI Mutations		L10V, I13V, K20R, V32I, L33F, E35D, M36I, K43T, M46L, D60E, I62V, A71V, V82T, L90M		

Potential Drugs for Multi-drug Resistant HIV

Drug	Potential role for MDR HIV
Ibalizumab	✓✓
Fostemsavir	✓✓*
Islatravir (NRTTI)	Possibly
GS-6207 (Capsid inhibitor)	Possibly
Albuvirtide (fusion inh) + 3BNC117 (bNAb)	Possibly
UB-421	Possibly
Leronlimab	Possibly
Broadly neutralizing Ab	Possibly

***Under FDA and EMA review**

What about cost?

Not my honorarium!

Cost and Access: US and Around the World

- Novel agents may not be cost-effective if price is high
  - Example of ibalizumab
  - Because small number of people in US need this drug, effect on overall care costs is limited: $1.8 billion (1.5%) over 5 yrs
  - “Role of rescue”: justifiably spending more on individuals whose life is in peril

- **New drugs, especially those designed for initial therapy, need to be priced lower to ensure access to largest number of people in US and around the world**
  - By 2030, up to 4.6 million people may need 2nd line therapy in Africa; and some will need novel drugs for MDR HIV

Millham et al, JAIDS, 2020; Jonsen, J Law, Medicine and Ethics, 1986; McKie and Richardson, Social Science and Medicine, 2003; Orr and Wolf, Theory Dec, 2015; Estill J, Lancet HIV, 2016

How we will use new drugs

People doing Well on ART	25 yo F wants to take fewer medicines → New regimens will have role if they have fewer drugs, are less toxic, more convenient, offer greater flexibility
People Struggling with Daily Oral ART	45 yo M intermittent viral suppression → long-acting formulations may improve adherence; need systems to facilitate delivery and ensure follow-up.
People with Multi-drug Resistant HIV	55 yo M with virus resistant to all available classes → novel drugs in new classes promise hope

What Is the Future of ART?

But we're going to try!

Why we need new ART: overcome limitations of current therapies with less toxicity, fewer drugs, less frequent dosing, activity against resistant HIV

New drugs in development: targeting novel mechanisms (eg, translocation; capsid; entry); long-acting agents; innovative delivery systems

How we will use new drugs: depends on person and their needs; but for all people with HIV, must redouble efforts to provide more options (including during pregnancy), reduce costs, and ensure access in the US and around the world

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- Melanie Thompson
- Ken Freedberg
- Diana Brainard
- Martin Rhee
- Kim Smith
- Max Lataillade
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HIV and COVID-19

Is HIV a risk factor for severe COVID-19?

Do HIV medications have activity against SARS-CoV-2?

How should we counsel people with HIV regarding COVID-19?

COVID-19: Risk Factors for Severe Disease

Table 1. Established and Potential Risk Factors for Severe Covid-19.*
Older age (e.g., >65 years)
Chronic lung disease
Cardiovascular disease
Diabetes mellitus
Obesity
Immunocompromise†
End-stage renal disease
Liver disease

- Immunosuppression, including advanced HIV (CD4 <200), is risk factor for complications of other respiratory viruses.
- Not known if people with HIV are at risk for severe COVID-19.

Gandhi RT, Lynch JB, del Rio C, NEJM 2020

What Do We Know About HIV and COVID-19?

- Case series from Barcelona, Spain
  - 543 consecutive patients hospitalized with COVID-19
  - 5 people with HIV (<1%)
  - Age range 29 to 49 years old
  - CD4 count >400 in all patients except 1 who had CD4 count <50, concomitant Pneumocystis pneumonia
  - 4 of the 5 discharged from the hospital; one still hospitalized at time of publication

COVID-19 in patients with HIV: clinical case series

Blanco JL et al, Lancet HIV, 2020

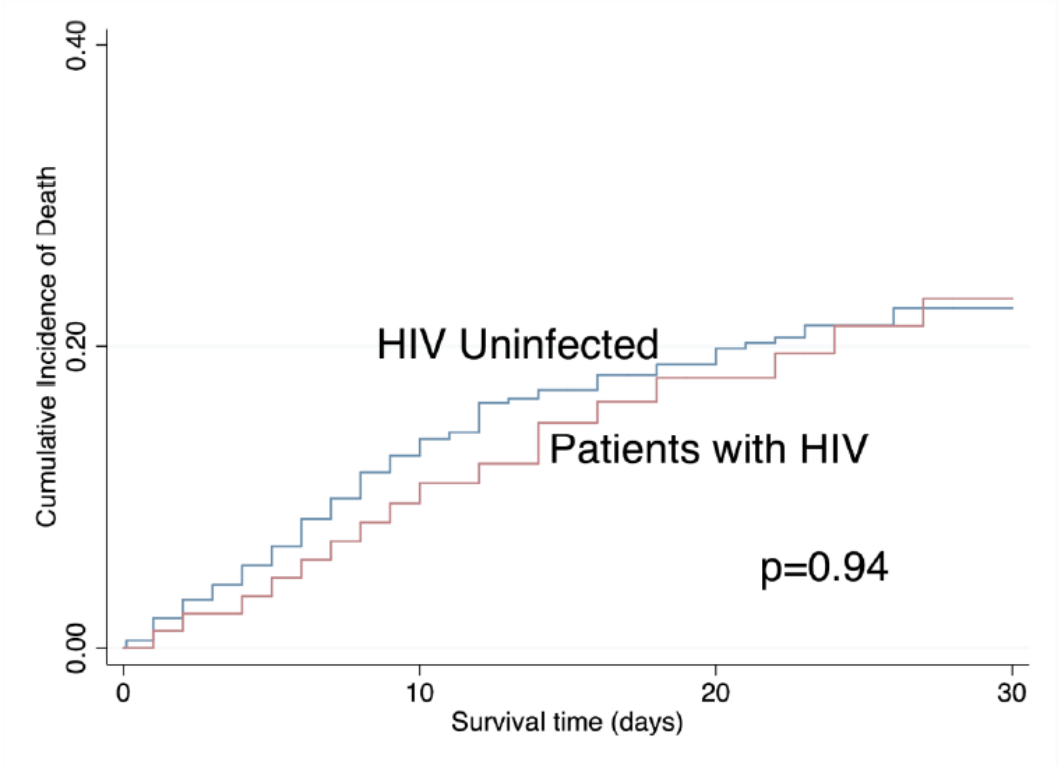
What Do We Know About HIV and COVID-19?

- Case series from Milan, Italy
  - 47 people with HIV with proven (n=28) or probable (n=19) COVID-19
  - 64% had at least one comorbidity
  - 44 (94%) with VL <20; CD4 cell count 636 (+/- 290)
  - 45 recovered, 2 died (mortality 4.2%)
  - Risk of death or admission to an ICU lower in those with HIV than among non-HIV patients (crude mortality 17%, but older patients)

Gervasoni C et al, CID, 2020

What Do We Know About HIV and COVID-19?

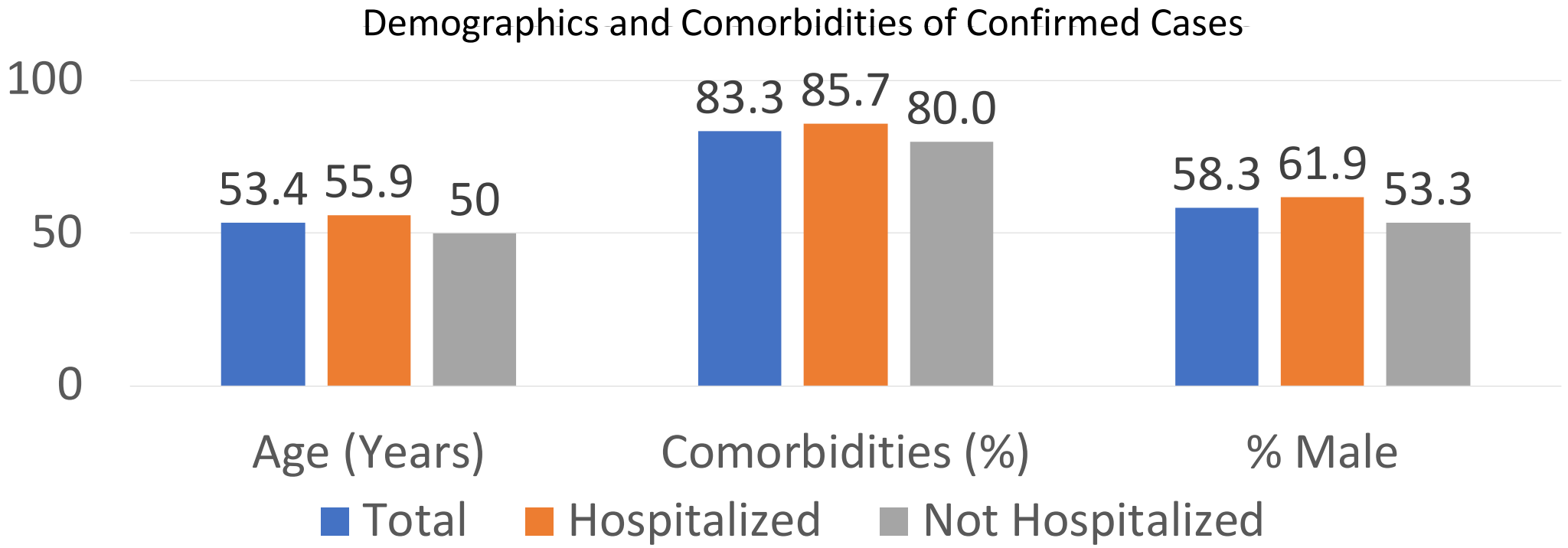
- Mt Sinai, NYC (March 12 to April 23, 2020)
  - 88 PWH compared to 405 patients without HIV matched by age, sex, race/ethnicity, calendar week)
  - PWH had higher rates of smoking (55% vs. 23%) and comorbid illness than comparators
  - Proportion with HIV VL <50: 81%
  - No difference in COVID-19 severity or mortality by HIV status
  - Previous organ transplantation associated with death among those with HIV



Sigel K et al, CID, 2020

HIV and COVID-19: MGH Series

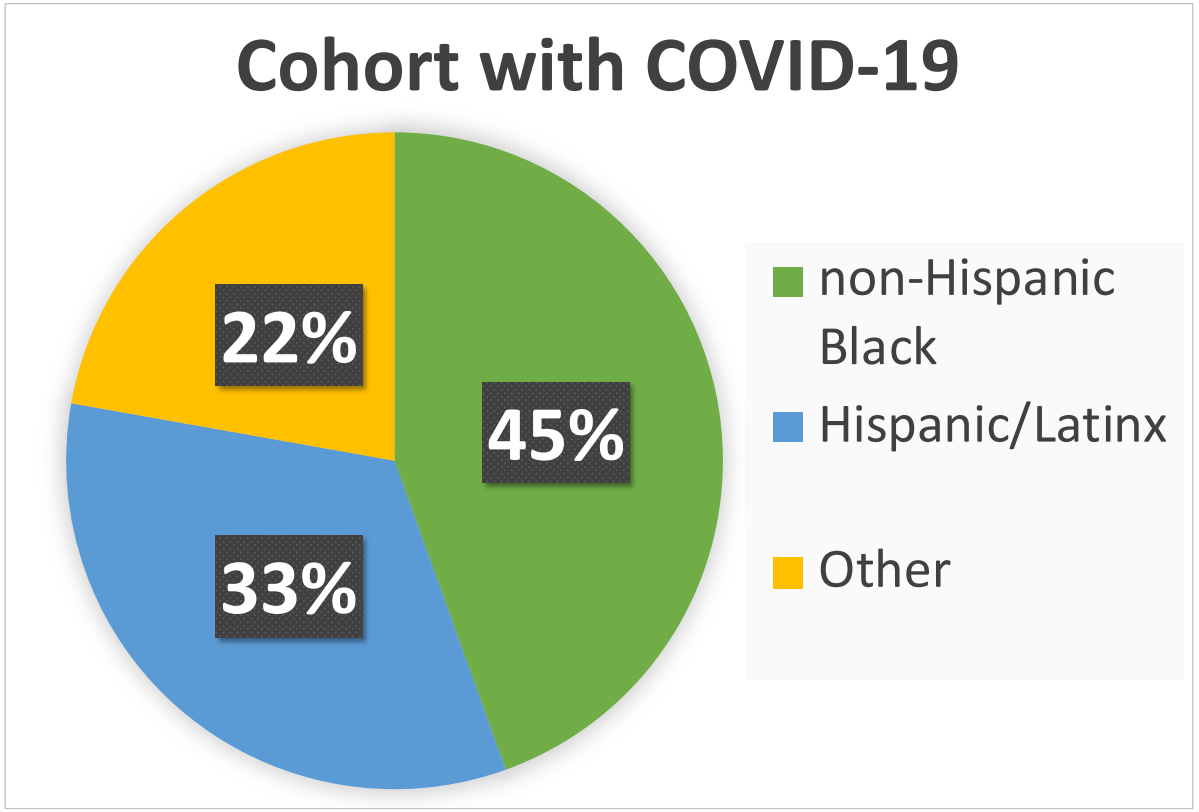
- Between March 3 and April 26, 2020, systematically identified 36 people with HIV with confirmed COVID-19; another 11 with probable infection
- Almost 85% had a co-morbidity: obesity, cardiovascular disease, etc.



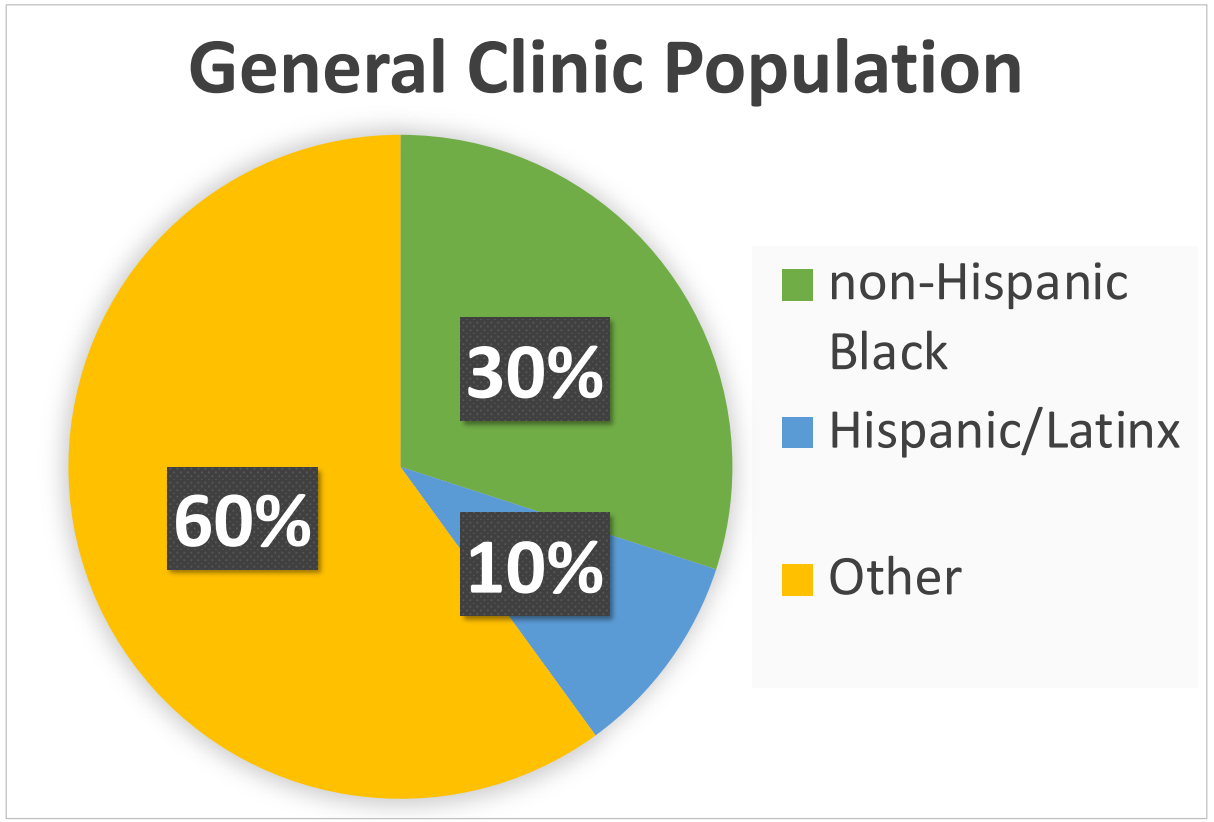
Meyerowitz E et al, AIDS 2020

HIV and COVID-19:
Disproportionate Burden Among Racial/Ethnic Minorities

77% of people with HIV and COVID-19 were non-Hispanic Blacks or Latinx



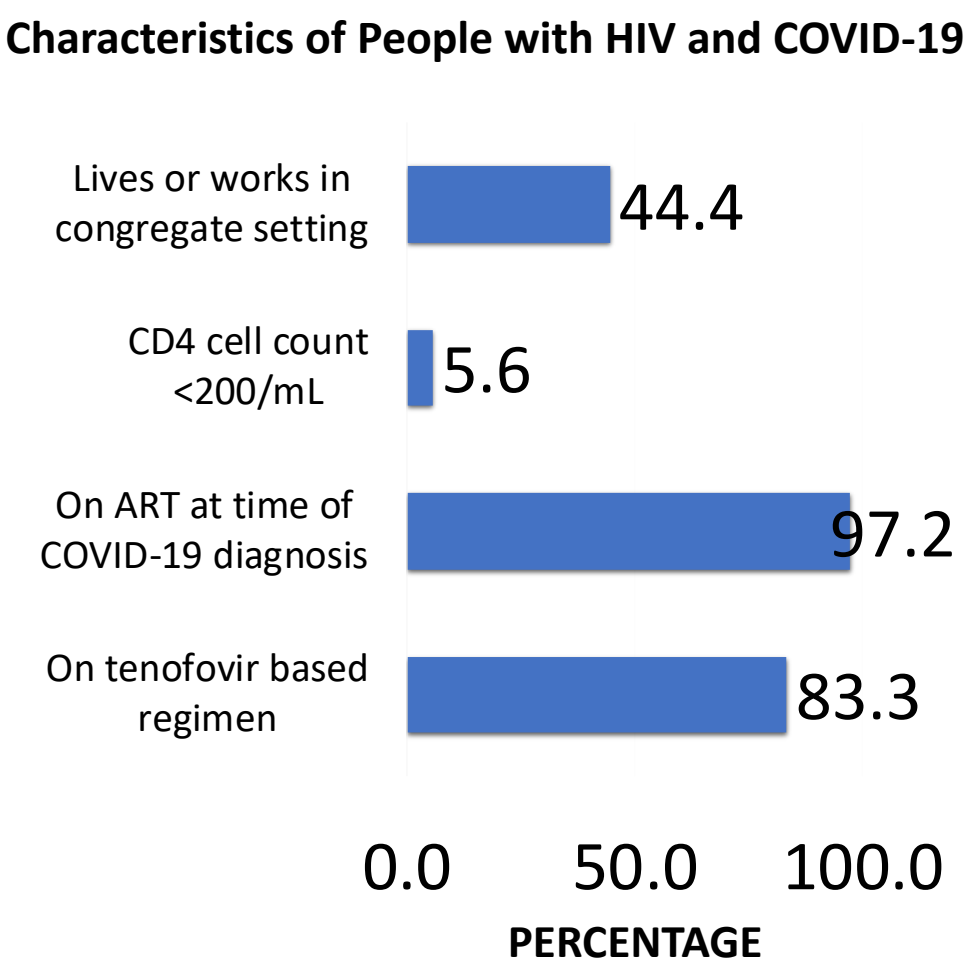
40% of people with HIV in MGH Clinic are Blacks or Latinx



Meyerowitz E et al, AIDS 2020

HIV and COVID-19: Frequent Link to Congregate Settings

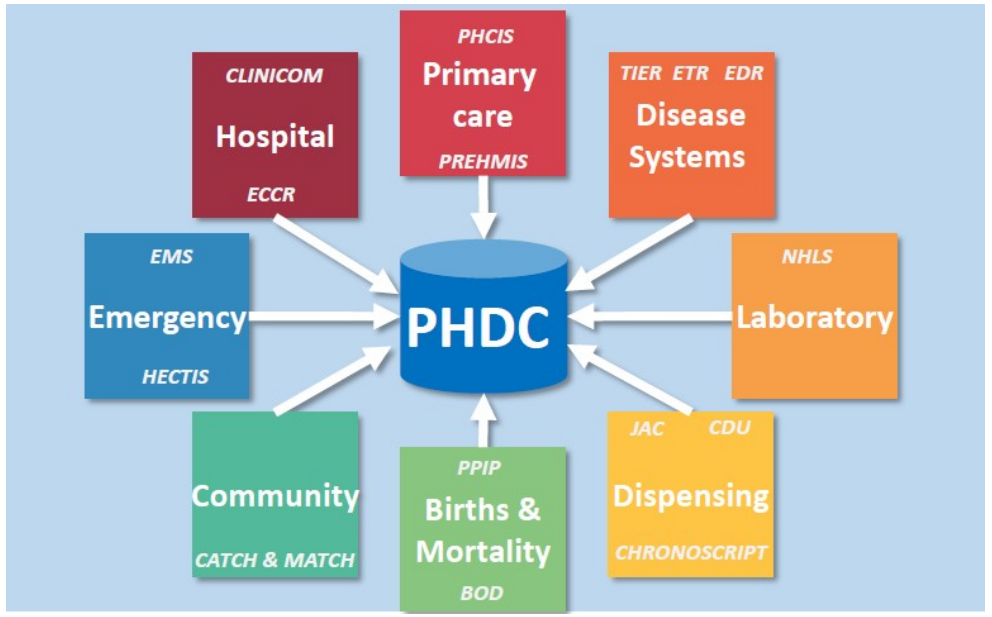
- Nearly half (16/36) lived or worked in a congregate setting
- Only 2 had CD4 cell count <200
- All except one were on ART
- One person had newly diagnosed AIDS and cryptococccal meningitis



Meyerowitz E et al, AIDS 2020

HIV and COVID-19: South Africa

Western Cape routine public sector data to look at risk of COVID-19 death



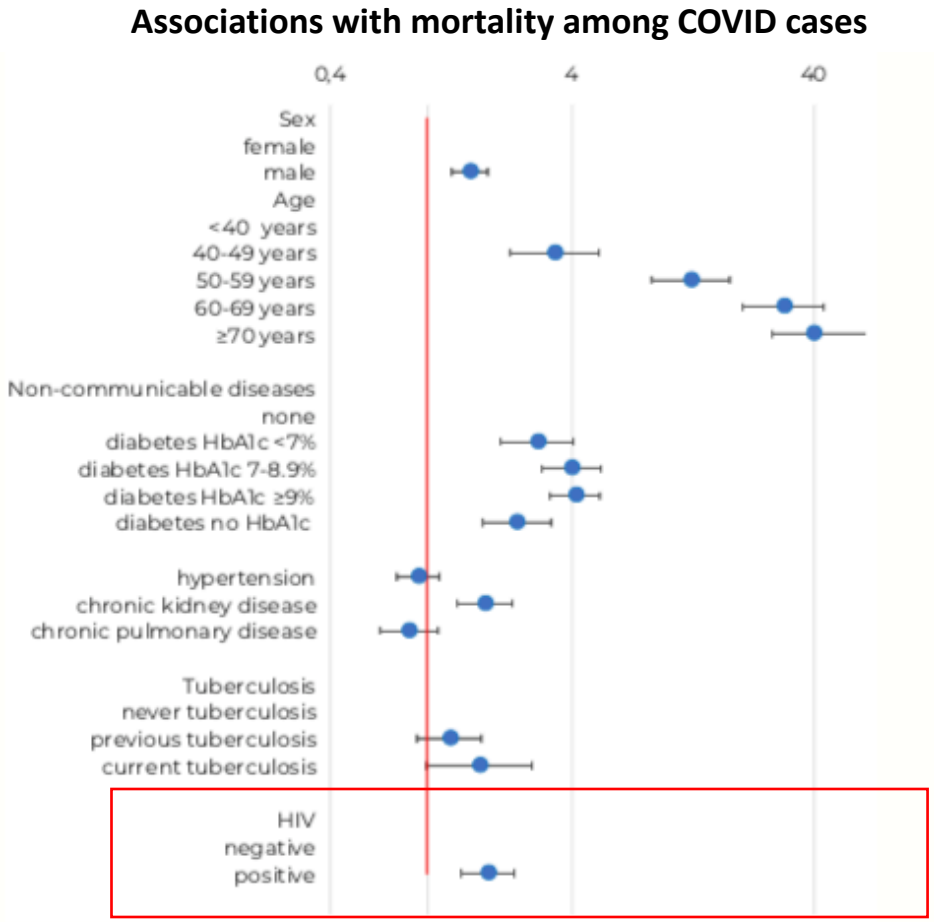
- **Factors associated with COVID-19 death in all adult public sector patients >20 years of age** (3.5 million patients "active" in the public health system)

Western Cape Government

National Institute for Communicable Diseases,
Covid-19 Special Health Surveillance Bulletin, June 22, 2020

HIV and COVID-19: South Africa

- About 3.5 million active public sector adult patients; about 536,000 with HIV
- ~12,500 COVID-19 and not deceased; 435 COVID-19 deaths
- Adjusted hazard ratio for death for HIV: 1.78 (1.38, 2.29); irrespective of viral suppression
- <10% COVID-19 deaths attributable to HIV
- Cannot rule out residual confounding (eg due to socioeconomic status, obesity)



National Institute for Communicable Diseases, Covid-19 Special Health Surveillance Bulletin, June 22, 2020

HIV and COVID-19: “Twin” Pandemics?

- Non-HIV comorbidities common in people with HIV and COVID-19: suggests these risk factors may play a dominant role in COVID-19 outcomes
- High rate of COVID-19 among racial and ethnic minorities: Structural factors and health care disparities may drive “twin” epidemics of HIV and COVID-19
- High rate of COVID-19 among people with HIV who live or work in congregate settings → more must be done to protect vulnerable people in these settings
- Additional data from registries urgently needed

HIV and COVID-19

Is HIV a risk factor for severe COVID-19?

Do HIV medications have activity against SARS-CoV-2?

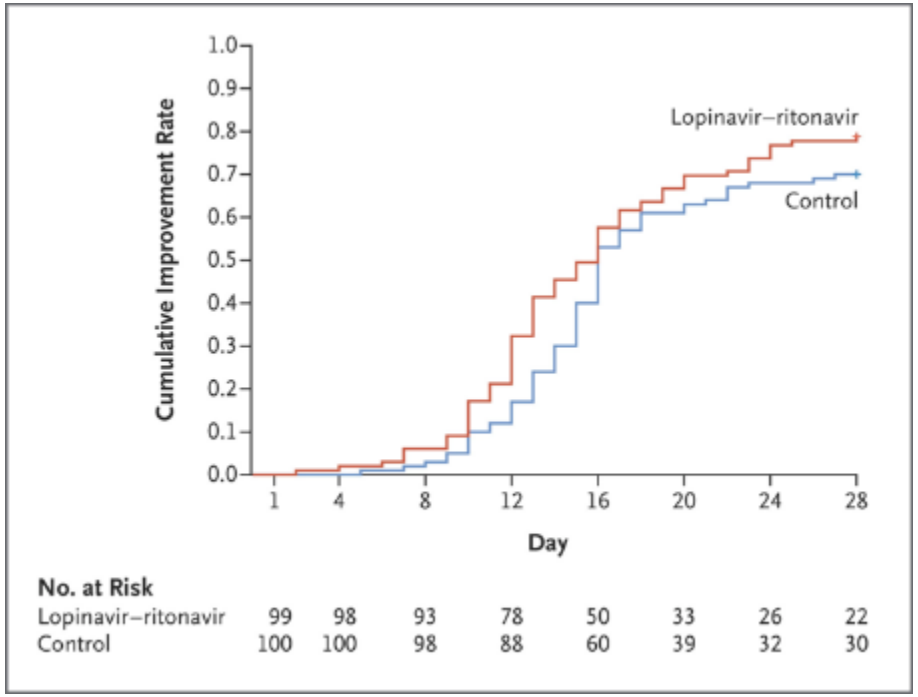
How should we counsel people with HIV regarding COVID-19?

COVID-19 and HIV: The Question of LPV/r

- In vitro, LPV/r inhibits SARS-CoV protease
- Randomized trial of LPV/r with interferon-beta in MERS is ongoing (MIRACLE trial)
- LPV/r has been used as off-label treatment for people with COVID-19 and clinical trials, including one launched by WHO, are underway
- In an open label trial, 199 hospitalized patients with COVID-19 randomized to either 14 days of LPV/r or standard of care alone.
- No statistically significant difference was seen between the 2 groups in time to clinical improvement or mortality

The NEW ENGLAND JOURNAL of MEDICINE

March 18, 2020

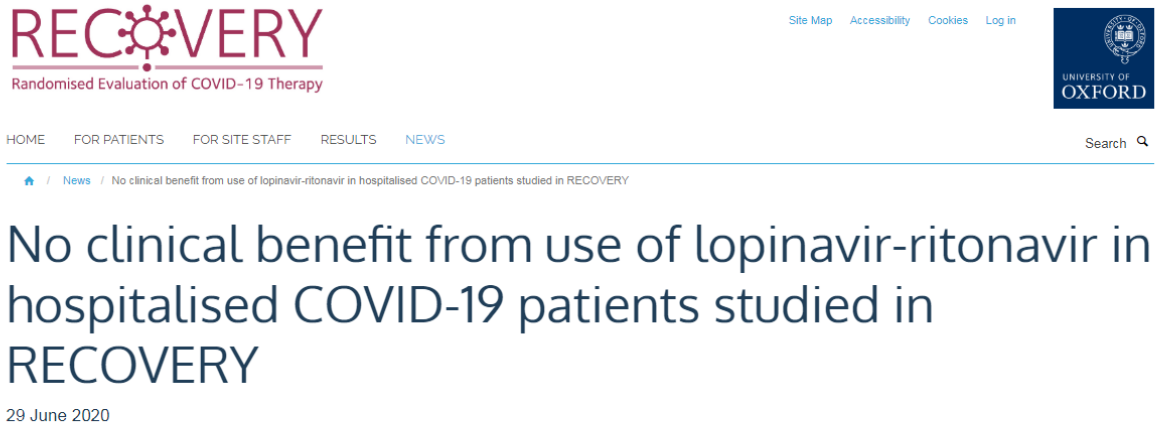


Cao B et al, NEJM, 2020

LPV/r Pharmacokinetics in People with COVID-19

- In vitro, half-maximal effective concentration (EC50) against SARS CoV-2: 16.4 micrograms/mL
- EC50 for HIV: 0.07 micrograms/mL
- Series of 8 patients with COVID-19 in Austria
- Received lopinavir/ritonavir 400/100 twice daily
- Trough levels: median 13.6 micrograms/mL
- Lopinavir highly protein-bound: only 1-2% free drug
- Unbound drug concentrations of lopinavir are much lower than what is anticipated to inhibit the SARS-CoV-2 protease: ~ 60-120 fold higher concentration required to reach EC50 at trough levels

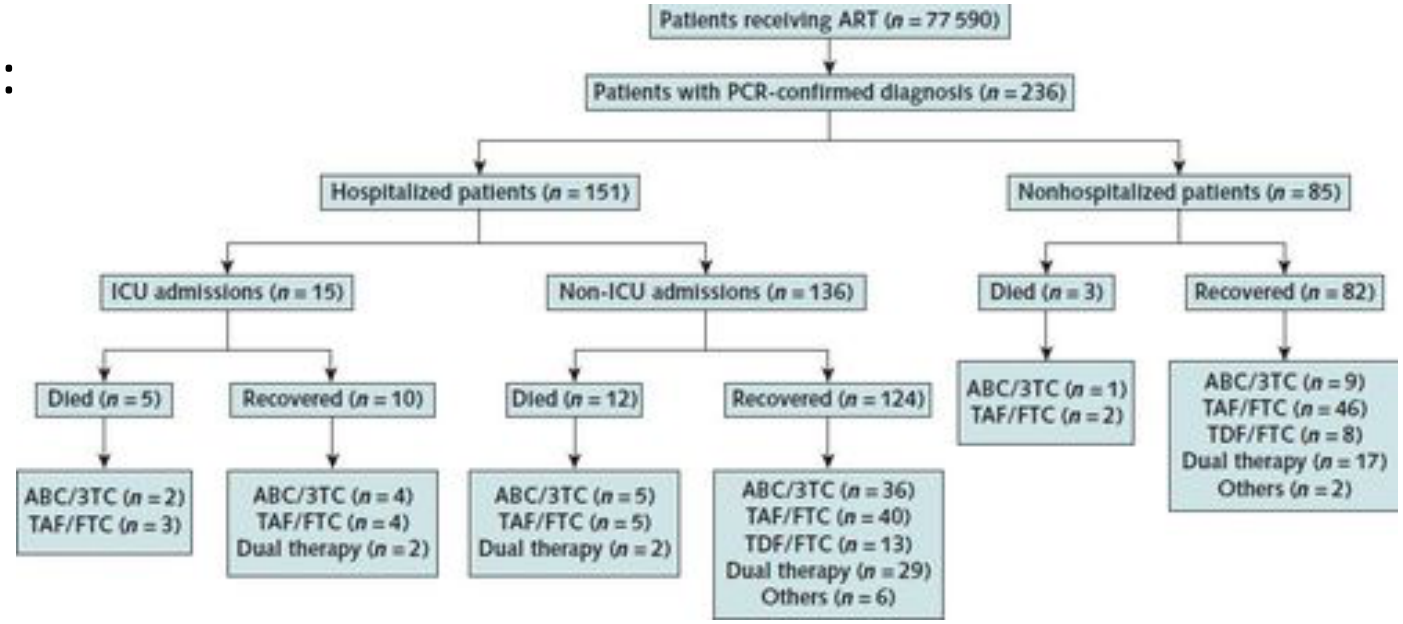
Schoergenhofer, Ann Int Med, 2020



- 1596 patients randomized to LPV/r compared with 3376 randomized to usual care
  - 4% required mechanical ventilation when they entered the trial; 70% required oxygen alone; 26% did not require any respiratory intervention
- 28 day mortality: 22.1% in the LPV/r group, 21.3% in the usual care group; relative risk 1.04 (95% CI 0.91 – 1.18, p=0.58)
- No evidence for beneficial effects on risk of progression to mechanical ventilation or length of hospital stay

COVID-19 Among People with HIV on ART

- 77,590 people with HIV receiving ART in clinics in Spain
- N=236 diagnosed with COVID-19, 151 hospitalized, 20 died
- Risk of COVID-19 diagnosis and hospitalization lowest among those on TDF/FTC. Hospitalization:
  - TDF/FTC: 10.5 (per 10,000 people)
  - TAF/FTC: 20.3
  - ABC/3TC: 23.4
  - Other regimens: 20
- Residual confounding possible



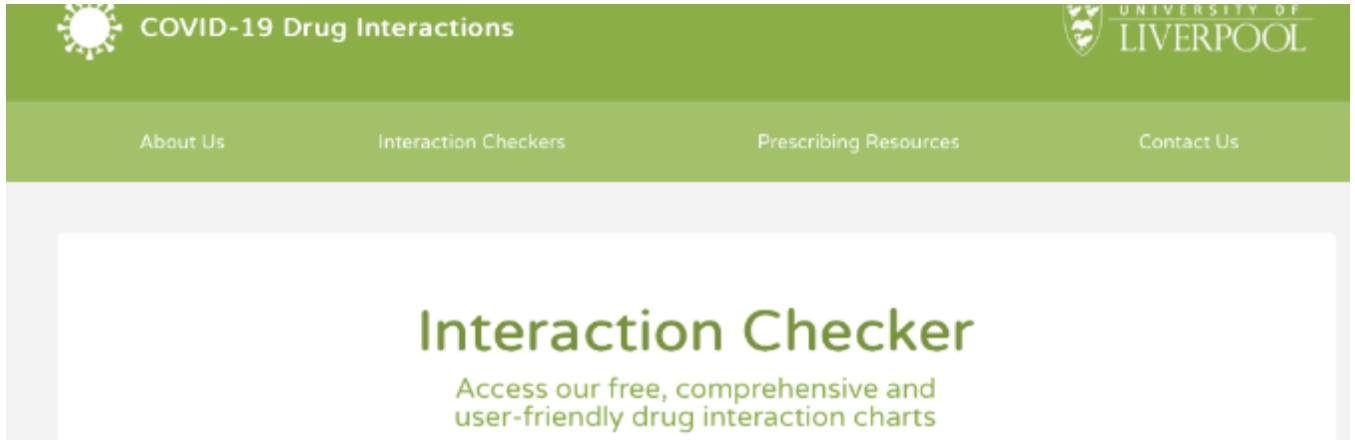
J del Amo et al, Ann Int Med, 2020

ART and COVID-19: Other Drugs

- No evidence that other HIV PIs, like darunavir, have in vivo activity against SARS-CoV-2

- TDF/FTC is being evaluated for prophylaxis but no definitive data that it has effect on preventing or treating SARS-CoV-2 infection

Managing COVID-19 in People with HIV



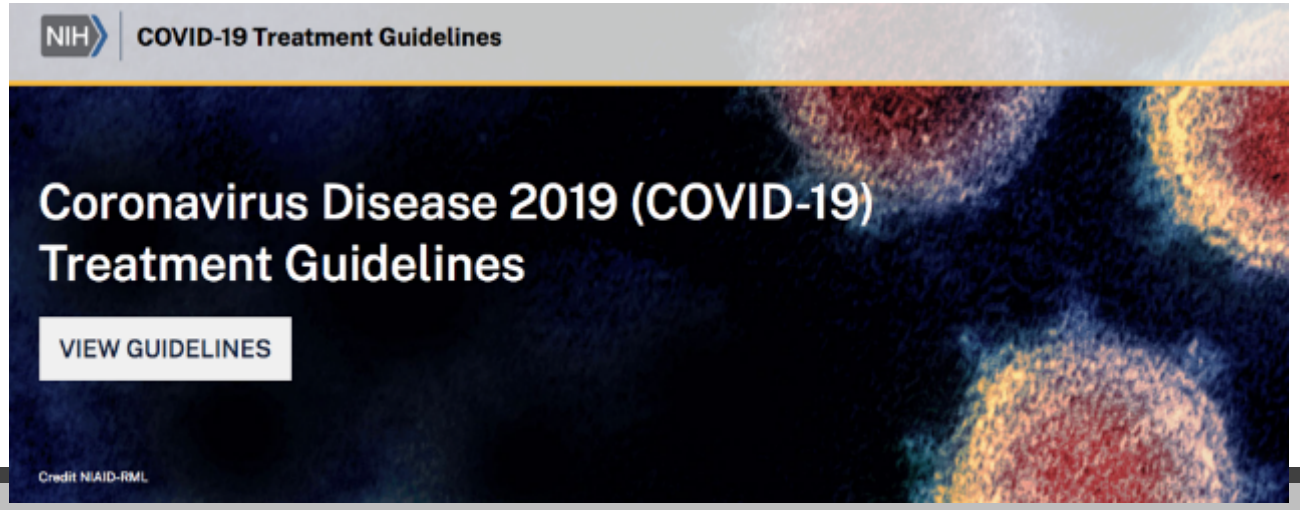
Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA, 4/11/2020

COVID-19 Guideline, Part 2: Infection Prevention

COVID-19 Guideline, Part 3: Diagnostics

Adarsh Bhimraj*, Rebecca L. Morgan**, Amy Hirsch Shumaker, Valery Lavergne**, Lindsey Baden, Vincent Chi-Chung Cheng, Kathryn M. Edwards, Rajesh Gandhi, William J. Muller, John C. O'Horo, Shmuel Shoham, M. Hassan Murad**, Reem A. Mustafa**, Shahnaz Sultan**, Yngve Falck-Ytter**



HIV and COVID-19

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HIV and COVID-19

DHHS: Interim Guidance for COVID-19 and Persons with HIV

COVID-19: Special Considerations for People Living with HIV

Version: April 17, 2020

HIV and COVID-19: Practical Considerations

- If an HIV PI is not part of a person's regimen, the regimen should NOT be changed to include a PI
- In general, ART changes should be avoided unless there is a compelling clinical reason
- Maintain adequate supply of medications (at least 30 d, ideally 90 d)
- Influenza and pneumococcal vaccinations should be kept up to date
- For persons with suppressed VL and stable health, routine medical and lab visits should be postponed to the extent possible

Final Thoughts

- The disproportionate impact on racial and ethnic minorities of both COVID-19 and HIV highlight how social forces drive disparate infectious diseases → we need to address these structural forces to end intolerable disparities in health care access and outcomes for these “twin” epidemics.

- We cannot let the COVID-19 pandemic cause us to lose sight of how far we’ve come in our quest to end the HIV epidemic.

- Despite the overwhelming need to respond to COVID-19, we must continue to move forcefully to end the HIV epidemic here and around the world

Acknowledgements

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- Virginia Triant
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