MAKING STRIDES IN HIV: OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

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OVERVIEW

Infectious disease specialists **David Hardy, MD, AAHIVS** and **David Alain Wohl, MD** explore ways to optimize therapy selections and switch strategies in the treatment and management of HIV, including the epidemiology of HIV in a pandemic landscape, comparisons of 2-drug and 3-drug regimens, the emergence of long-acting injectable antiretroviral therapies (ART), how to select an ART best suited for the individual and improve your patient's outcome. They will provide a discussion of four common scenarios complete with laboratory findings, as well as treatment and follow-up options. Topics will include current and ongoing disparities in HIV treatment and strategies to overcome them, an introduction to the rapid initiation of ART, data from the STAT, DIAMOND, GEMINI, TANGO, ATLAS, FLAIR and SWORD-1 and -2 trials, an exploration of the uses of cabotegravir/rilpivirine versus dolutegravir/abacavir/lamivudine, the uses of shared decision-making to engage a PLWH in treatment decisions and suggestions on how to optimize treatment outcomes for PLWH who may be treatment-naïve, experiencing weight gain, overwhelmed by pill fatigue or who need to simplify their treatment regimen.

CONTENT AREAS

Epidemiology | Rapid Start ART | 2-Drug Regimens | 3-Drug Regimens| Long-acting Injectable ART | Optimizing Outcomes

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Examine the results from recent trials on 2-drug regimens vs 3-drug regimens for HIV, including efficacy, tolerability, and safety
- Compare and contrast the latest evidence regarding new and emerging antiretroviral therapy options for treatment-naïve and treatment-experienced patients
- Identify those patients who would benefit from new and emerging 2-drug regimens, including long-acting injectable antiretroviral therapy
- Develop personalized treatment strategies for patients with HIV based on patient-specific factors and in alignment with the latest evidence

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TARGET AUDIENCE

A national audience of HIV specialists and infectious disease specialists, plus other physicians with an interest in HIV care, including primary care physicians and emergency medicine physicians.

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The estimated time to complete the activity is 2.00 hours.

This activity was released on November 19, 2021 and is eligible for credit through November 19, 2022

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MAKING STRIDES IN HIV:
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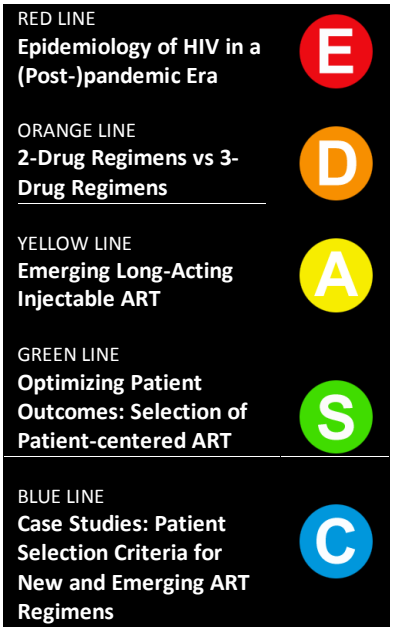
Introduction

In the following article, styled like a subway system with lines and stops so users can choose the path they take through the course, infectious disease specialists **David Hardy, MD, AAHIVS** *(Adjunct Professor of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine)* and **David Alain Wohl, MD** *(Professor of Medicine, Division of Infectious Diseases, Site Leader, HIV Prevention and Treatment Clinical Trials Unit at Chapel Hill, University of North Carolina School of Medicine)* will explore ways to optimize therapy selections and switch strategies in the treatment and management of HIV.



This monograph is from a transcript of a recorded presentation and has been edited for clarity and readability.

Written for an audience of HIV specialists and infectious disease specialists, plus other physicians with an interest in HIV care, including primary care physicians and emergency medicine physicians, the monograph, taken from a series of recordings and edited for clarity, will cover the following topic areas.

In the section **Red Line: Epidemiology of HIV in a (Post-)pandemic Era**, the presenters address *HIV Epidemiologic Trends in the Setting of the COVID-19 Pandemic*, including pre-pandemic declines in morbidity and the decline in treatment during the outbreak. They discuss *COVID-19 and Ongoing HIV Disparities* which explores the reasons why the pandemic has exacerbated health inequality for people living with HIV (PLWH). They highlight the *COVID-19 Common Comorbidities in HIV* that can make treatment more complex and difficult.

In **Orange Line: 2-Drug Regimens vs 3-Drug Regimens**, the specialists discuss *Current Guideline Recommendations for Newly Diagnosed PLWH*, highlighting the rapid initiation of antiretroviral therapy (ART) and the findings from the STAT and DIAMOND trials. In *Clinical Trials of Oral 2DR in Treatment-naïve PLWH*, they outline the outcome of the GEMINI trial with treatment-naïve PLWH. In *Current Guideline Recommendations for ART Switching in PLWH with Virologic Suppression*, they explain the situations that suggest certain switching treatment strategies and offer some recommended switching regimen guidelines. In *Clinical Trials of Switching to 2DR in the Context of Virologic Suppression*, they highlight the findings from the TANGO and SWORD-1 and SWORD-2 trials. Finally, in *Real-World Evidence Supporting Use of 2DR*, the specialists provide an evidence-based rationale for and against 2-drug versus 3-drug treatment regimens.

In **Yellow Line: Emerging Long-Acting Injectable ART**, the presenters provide an *Introduction to Long-acting Injectable ART*, focusing on cabotegravir+rilpivirine (CAB+RPV). In *Clinical Trial Evidence for Long-acting Injectable ART*, they compare injections versus oral ART in the ATLAS trial and dolutegravir+abacavir+lamivudine (DTG/ABC/3TC) versus CAB+RPV in the FLAIR trial. In *Promises and Challenges of Long-acting Injectable ART*, they explain the opportunities and challenges that long-acting injectables can offer. In *Pearls and Pitfalls: Addressing Practical Challenges to Long-acting Injectable ART*, they outline the logistical barriers that need to be addressed to support the use of long-acting injectables in HIV treatment.

In **Green Line: Optimizing Patient Outcomes: Selection of Patient-centered ART**, they explain *ART Selection: Engaging in Shared Decision Making*, how to engage the PLWH in the decision-making process for their treatment. In *Barriers to Adherence and Ways to Overcome Them*, they outline the strategies and techniques to improve patient adherence to newly switched treatment regimens. In *Optimizing Access and Addressing Disparities*, they indicate how support services can be engaged to optimize access to HIV treatments.

Finally, in **Blue Line: Case Studies: Patient Selection Criteria for New and Emerging ART Regimens**, the specialists provide outlines of individual cases, including a general scenario, laboratory evaluations, and treatment and follow-up options for PLWH who are:

1. Treatment naïve
2. Switching after weight gain
3. Overcoming pill fatigue
4. Simplifying their treatment regimen

At the conclusion of this monograph, participants should be better able to:

- Examine the results from recent trials on 2-drug regimens versus 3-drug regimens for HIV, including efficacy, tolerability, and safety
- Compare and contrast the latest evidence regarding new and emerging antiretroviral therapy options for treatment-naïve and treatment-experienced patients
- Identify those patients who would benefit from new and emerging 2-drug regimens, including long-acting injectable antiretroviral therapy
- Develop personalized treatment strategies for patients with HIV based on patient-specific factors and in alignment with the latest evidence

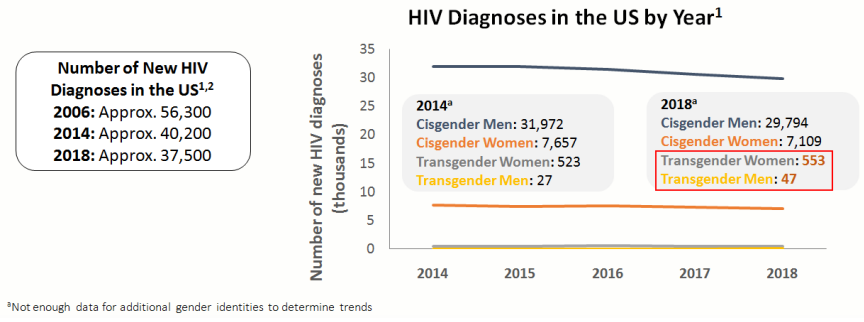
Red Line: Epidemiology of HIV in a (Post-)pandemic Era

HIV Epidemiologic Trends in the Setting of the COVID-19 Pandemic

Hello, my name is Dr. David Hardy and I am long-time HIV researcher and clinician. I've been seeing HIV-positive patients since 1982 and doing research in the field of HIV, both clinical, translational and basic science bench top research, since 1984. Today, I'm going to talk about some very interesting new parts of advancements in the HIV epidemic and also what impact the concurrent COVID-19 pandemic has had on the HIV pandemic as well.

First thing I'm going to talk about then is the epidemiology of HIV in a post-pandemic era. Some of the HIV epidemiologic trends in the setting of the COVID-19 pandemic have been very interesting.

Before the COVID-19 pandemic began, the CDC had clearly demonstrated that for most persons in the United States at risk for HIV, the number of new diagnoses of HIV infection was going down. Between 2014 and 2018, cases were dropping among cisgender men and cisgender women. However, among transgender women and transgender men, the number of cases had actually increased between 2014 and 2018. Overall, the number of cases, however, had dropped from a high in 2006 of around 56,300 down, in 2018, to 37,500.



So overall, the trend was going down over those years, but select groups, primarily persons of transgender, experienced cases that were still going up.

This was also true in most cases among persons of different race and ethnicity. Certainly among persons who are African American, White and Hispanic or Latino, as well as multiple races, the number of new cases of HIV were going down or staying stable. However, among Native Americans, Native Alaskans and Native Hawaiian or Pacific Islanders, the number of cases was actually increasing during this period of time.

SLIDE 5

The Number of HIV Diagnoses in the US Was Decreasing Pre-Pandemic for Most Persons at Risk: By Gender Identity

[1]Centers for Disease Control and Prevention (CDC). May 2020. Accessed June 1, 2021. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-31/content/diagnoses.html
[2]Centers for Disease Control and Prevention (CDC). August 2008. Accessed June 1, 2021. https://www.cdc.gov/nchhstp/newsroom/docs/fact-sheet-on-hiv-estimates.pdf

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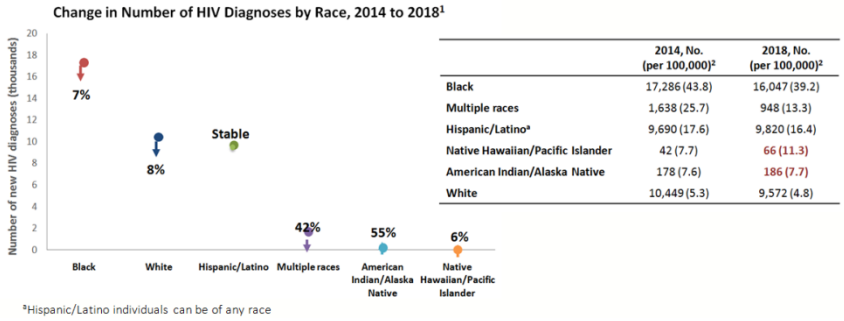
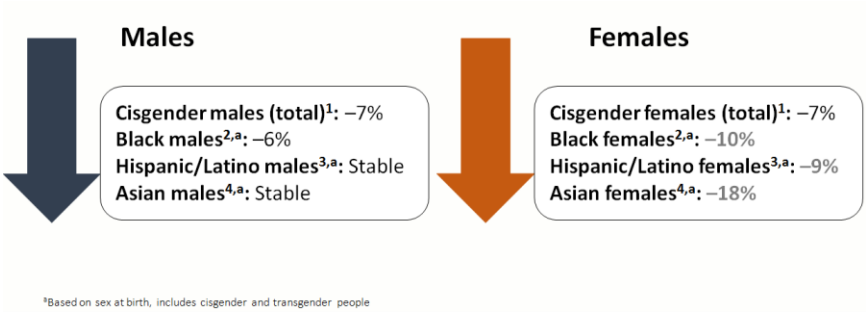


	2014, No. (per 100,000)[2]	2018, No. (per 100,000)[2]
Black	17,286 (43.8)	16,047 (39.2)
Multiple races	1,638 (25.7)	948 (13.3)
Hispanic/Latino[a]	9,690 (17.6)	9,820 (16.4)
Native Hawaiian/Pacific Islander	42 (7.7)	66 (11.3)
American Indian/Alaska Native	178 (7.6)	186 (7.7)
White	10,449 (5.3)	9,572 (4.8)

So again, good news for most persons in the United States, but not for all in terms of the number of cases that were being diagnosed in many different ethnic communities.

One thing that's important to really point out—which is actually of great import—is that women of color have experienced the greatest declines in new HIV diagnoses between 2014 and 2018. This has actually decreased among African American women by 10% between these 5 years of CDC data. But it's also true among cisgender men, Black males. Hispanic/Latino males, however, have been pretty stable and also Asian males. Also, among all cisgender females, Hispanic and Latino females and also Asian females.



So, this is, I think, an important fact to look at, that in most cases, between those 5 years of 2014 to 2018, drops in cases based upon gender and gender identity and race/ethnicity had actually looked promising.

So, what about the impact of the COVID-19 pandemic on HIV? It has been calculated that, according to the National Syndromic Surveillance Program, that between March 13 and September 30 of 2020, when COVID-19 was really impacting most of the United States, there were almost 670,000 fewer HIV screening tests performed. So, big impact on the availability and testing for HIV. During this time there were also almost 5,000 fewer new HIV diagnoses, as one might expect, because of

SLIDE 6

The Number of HIV Diagnoses in the US Was Decreasing Pre-Pandemic for Most Persons at Risk: By Race/Ethnicity

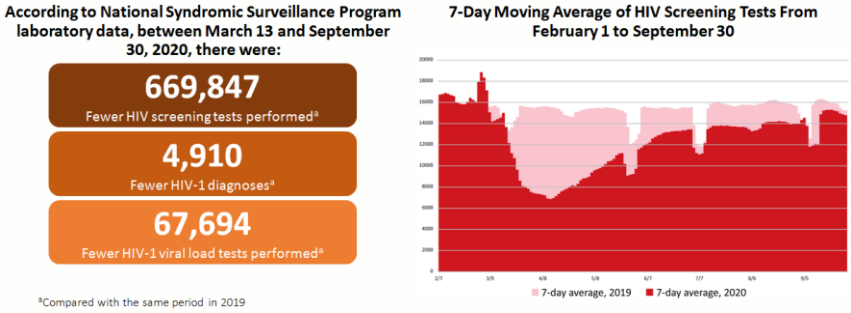
[1]Centers for Disease Control and Prevention (CDC). November 2020. Accessed June 1, 2021. https://www.cdc.gov/hiv/statistics/overview/ataglance.html
[2]Centers for Disease Control and Prevention (CDC). May 2020. Accessed June 1, 2021. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-31/content/diagnoses.html

SLIDE 7

Women of Color Have Experienced the Greatest Declines in HIV Diagnoses From 2014 to 2018

[1]Centers for Disease Control and Prevention (CDC). May 2020. Accessed June 1, 2021. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-31/content/diagnoses.html
[2]Centers for Disease Control and Prevention (CDC). January 2021. Accessed June 1, 2021. https://www.cdc.gov/hiv/group/racialethnic/africanamericans/index.html
[3]Centers for Disease Control and Prevention (CDC). March 2021. Accessed June 1, 2021. https://www.cdc.gov/hiv/group/racialethnic/hispanicdatinos/index.html
[4]Centers for Disease Control and Prevention (CDC). May 2020. Accessed June 1, 2021. https://www.cdc.gov/hiv/group/racialethnic/asians/index.html

the lack of testing, and there were also almost 68,000 fewer HIV viral load tests done during this period of time as well.



We see a large decrease, particularly during the early days of the epidemic in 2020 compared to 2019 when the screening tests dropped dramatically during the months of March and April, but then in May started rebounding up, but never reached the level, even through the end of September of 2020, as high as they were in the previous year, 2019.

SLIDE 8

Screening for HIV Declined During the COVID-19 Pandemic…

Delaney KP et al. Conference on Retroviruses and Opportunistic Infections (CROI). 2021. Abstract 739. https://www.croiconference.org/abstract/impact-of-covid-19-on-commercial-laboratory-testing-for-hiv-in-the-united-states/

But the number of positive HIV and STI tests may have remained stable or maybe possibly increased. It's hard to really know for sure because there was a big decrease in the number of tests that were being done, both for HIV and for other STIs, including gonorrhea, chlamydia and syphilis. But it looks like that, during the height of the pandemic of physical distancing, there were decreases in everything across the board except for new cases of primary and secondary syphilis. As the pandemic progressed and there were some changes during the physical distancing, it looked like that there was an increase in new HIV cases and gonorrhea cases and also, again, in primary and secondary syphilis.

HIV and STI testing per month before and during the COVID-19 pandemic in Oregon, January-September (2019 and 2020)

	% change during height of physical distancing	% change during ongoing physical distancing
HIV tests	**↓50%***	**↓28%***
HIV cases	↓46%	↑12%
Gonorrhea/chlamydia NAAT	**↓58%***	**↓44%***
Gonorrhea cases	↓23%	↑8%
Chlamydia cases	**↓34%***	**↓15%***
Syphilis tests	**↓59%***	**↓38%***
Primary and secondary syphilis cases	↑8%	**↑45%***

*$P < .01$
STI, sexually transmitted infection; CI, confidence interval; IRR, incidence rate ratio; NAAT, nucleic acid amplification test; RPR, rapid plasma regain

SLIDE 9

…But the Number of Positive HIV and STI Tests May Have Remained Stable or Possibly Increased

Menza TW et al. Conference on Retroviruses and Opportunistic Infections (CROI). 2021. Abstract 144. https://ww2.aievolution.com/cro2101/index.cfm?do=abs.viewAbs&abs=1168

So, even though social distancing was still being recommended, the number of new cases of HIV and of some STIs, particularly syphilis, was still going up.

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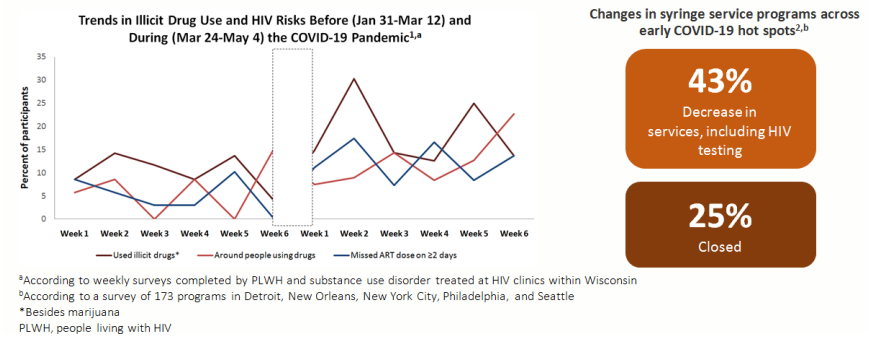
It's also interesting to note that substance use and the availability of syringe exchange programs may have been impacted by the COVID-19 pandemic as well. In those days and weeks before the pandemic really hit hard in March of 2020, we see that the use of illicit drugs, being around people who use drugs, or missed ART doses because of drug use for greater than 2 days, actually increased in those days after the pandemic really hit, after March through May of 2020. It's been also estimated that there was a 43% decrease in syringe services, including HIV testing, and that 25% of syringe exchange programs were closed because of the pandemic. So again, the outcome of this sort of effect has yet to be seen later on.



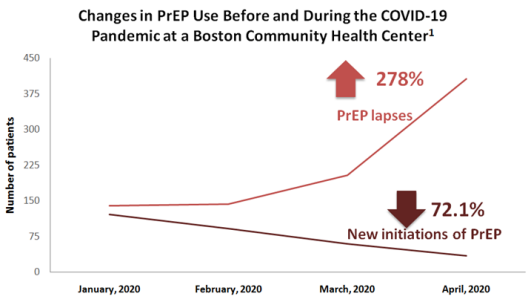
[a]According to weekly surveys completed by PLWH and substance use disorder treated at HIV clinics within Wisconsin
[b]According to a survey of 173 programs in Detroit, New Orleans, New York City, Philadelphia, and Seattle
*Besides marijuana
PLWH, people living with HIV

SLIDE 10

Substance Use and Availability of Syringe Exchange Programs May Have Been Affected by the Pandemic

[1]Hochstatter KR et al. AIDS Behav. 2021;25(2):354-359.
[2]Glick SN et al. AIDS Behav. 2020;24(9):2466-2468.

The other area impacted, of course, was PrEP use. A report from Boston showed that changes in PrEP use before and during the COVID-19 pandemic at this Boston community health center actually showed that there was almost a 300% increase in PrEP lapses and a 72% decrease in new initiation of PrEP in persons at risk for HIV infection. These PrEP lapses were most common if someone was young, less than 26, if they were non-White, if they were Latinx and if they were publicly insured.



PrEP, preexposure prophylaxis

- Refill lapses were associated with being:[1]
  - **≤26 years old** (*P* =.001)
  - **Non-White** (*P* =.001)
  - **Latinx** (*P* =.049)
  - **Publicly insured** (*P* =.002)

- Across the US, models estimate that there was a **31.3% reduction** in expected new PrEP users from March to June 2020[2]

SLIDE 11

PrEP Use Decreased During the Early Days of the Pandemic

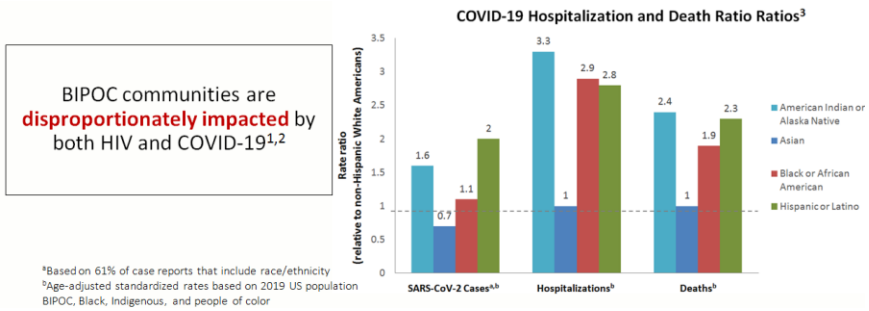
[1]Krakower D et al. AIDS 2020: 23rd International AIDS Conference Virtual. 2020. Abstract OACLB0104. https://programme.aids2020.org/Abstract/Abstract/11755
[2]Huang YLA et al. Conference on Retroviruses and Opportunistic Infections (CROI). 2021. Abstract 731. https://www.croiconference.org/abstract/impact-of-covid-19-on-prep-prescriptions-in-the-united-states-a-time-series-analysis/

I think this really points out the fact that COVID-19 impacted many of our HIV prevention and also treatments programs.

Red Line: Epidemiology of HIV in a (Post-)pandemic Era

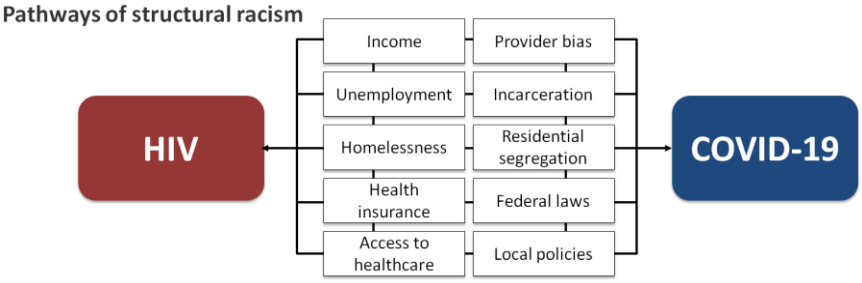
COVID-19 and Ongoing HIV Disparities

Now let's go on and a look at a little more closely about how the overlap between COVID-19 and the ongoing HIV disparities have really impacted our country. We know the COVID-19 pandemic has exacerbated the existing health equities among persons living with HIV. The BIPOC, or Black, indigenous and people of color communities have been disproportionately impacted not only by HIV but also COVID-19. When we look at data that has really looked at COVID-19 hospitalization and death rates, as broken down by race or ethnicity, we see that among persons of color or indigenous, Native Americans, Native Alaskans, Black or African American and Hispanic origin, that all of these were increased somewhere between 1½to as high as 3-fold over persons who are White. The only group that was impacted similarly, or actually in fact less, were Asians, where the number was actually equal to those persons who are White or actually a bit decreased in terms of new COVID diagnoses.



So, it looks like, looking at racial ethnic categories, that more persons of color have been impacted by new SARS-CoV-2 cases, hospitalizations and also death.

We know that these health inequities oftentimes stem from structural racism and that social determinants of health, including socioeconomic status and physical environment, are the more significant drivers of health outcomes than healthcare alone.



SLIDE 13

The COVID-19 Pandemic Has Exacerbated Existing Health Inequities Among PLWH

[1]Millett GA. J Int AIDS Soc. 2020;23(11):e25639.
[2]Fields EL et al. Lancet. 2021;397(10279):1040-1042.
[3]Centers for Disease Control and Prevention (CDC). May 2021. Accessed June 7, 2021. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html

SLIDE 14

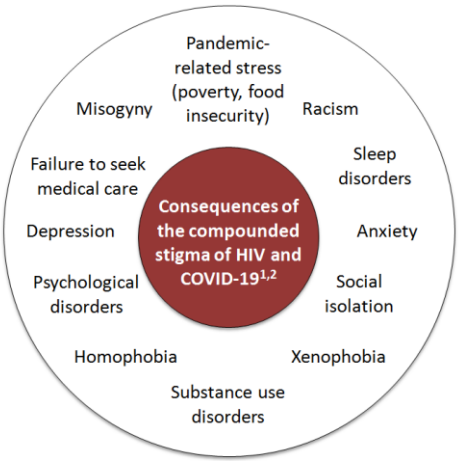
Health Inequities Stem From Structural Racism

Social determinants of health, including socioeconomic status and physical environment, are **more significant drivers of health outcomes** than health care alone

Millett GA. J Int AIDS Soc. 2020;23(11):e25639.

So that what we have seen going on with the HIV pandemic for many years in terms of more disproportionately affecting persons of color, especially those who are Black or Hispanic or Native American or Pacific Islander, these have continued to be major drivers for the increased number of persons of color being affected by COVID-19 as well.

What has really happened here, I think, to really look at some of this also has been sort of the double whammy of both COVID-19 and HIV stigma in that the compounded stigma has been associated with increased mental health stress and failure to seek care. That stigma is oftentimes additive for disenfranchised individuals and may really exacerbate existing health disparities. And that these stigmas may cause some patients to hesitate to disclose their positive status and therefore not seek healthcare.



So, there are many consequences of the compounded stigma of both HIV and COVID-19, and those are some things that do revolve around many of the health inequities that are being seen in the US among HIV-positive persons for many years.

Also one of the things that's happened to a large degree, in many clinics, has been the transition to telehealth and these may actually exacerbate, not improve, some health disparities. It's been noted that Black Americans are significantly less likely to access telemedicine compared to White Americans and that Black patients are often offered the option of telemedicine at lower rates than White and Hispanic patients and are less likely to have the necessary technology to actually be engaged in telemedicine. We also know that the use of telemedicine is reduced among older adults, some patients in urban environments, those who are self-paying patients, who are on publicly-funded insurance and those who have limited or decreased [resources] and those who have limited English proficiency.

SLIDE 15

COVID-19 and HIV Stigma: Double Jeopardy

The compounded stigma associated with HIV and COVID-19 diagnoses may lead to **mental health distress** and **failure to seek care**[1] … Stigma is additive for disenfranchised individuals and **may exacerbate health disparities**[1,3] … These stigmas may cause patients to be hesitant to disclose their positivity status[1]

[1]Waterfield KC et al. BMC Public Health. 2021;21(1):299.
[2]Shiau S et al. AIDS Behav. 2020;24(8):2244-2249.
[3]Okonkwo NE et al. BMJ Evid Based Med. 2020;bmjebm-2020-111426.

Black Americans are significantly less likely to access telemedicine compared with White Americans.[1,2] Black patients are **offered the option** of telemedicine at lower rates than White and Hispanic patients and are less likely to have **access to the necessary technology**.[3]

The use of telemedicine is also reduced for:[2]

- Older adults
- Patients from urban areas
- Self-paying patients
- Patients on publicly-funded insurance
- Patients with limited English proficiency[4]

Young females are driving increased use of telemedicine among Black patients.[1]

The thing that's really been driving some of the increased use of telemedicine among Black patients has been among young females, not among all persons of color who are African American. So, this is something that, again, has been an inequity in the way that telemedicine has been delivering care during the COVID-19 pandemic.

SLIDE 16

The Transition to Telehealth May Exacerbate Health Disparities

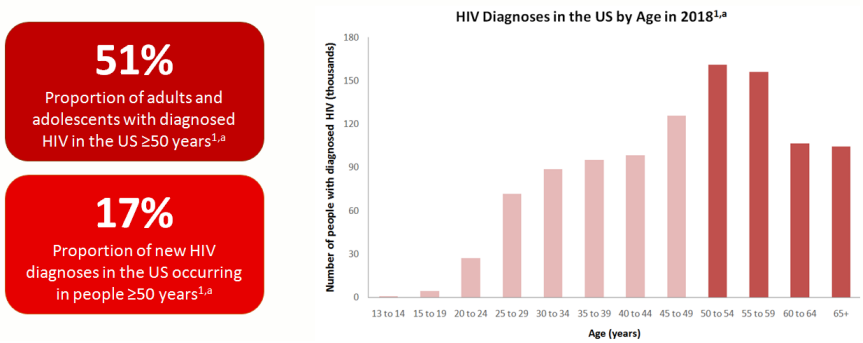
[1]Chunara R et al. J Am Med Inform Assoc. 2021 ;28(1):33-41.
[2]Pierce RP et al. J Telemed Telecare. 2020;1357633X20963893.
[3]Jacobs M et al. J Am Geriatr Soc. 2021.
[4]Rodriguez JA et al. Health Aff (Millwood). 2021;40(3):487-495.

Red Line: Epidemiology of HIV in a (Post-)pandemic Era

Common Comorbidities in HIV

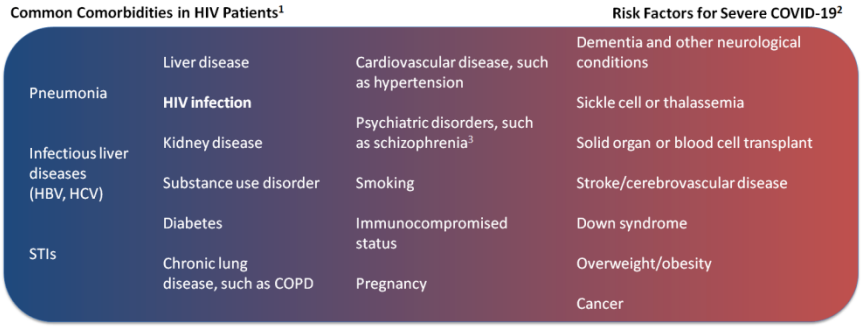
What we know now is some of the common comorbidities that we know occur among HIV-positive persons and can actually be factors for increased COVID-19 infection and also negative clinical outcomes.

For many years, we have known that persons living with HIV are increasing in age. And of course this is really, overall, a good thing, that with the use of combination antiretroviral therapy controlling the virus infection much better, so that persons can now live longer and more fruitful and more full lives. And, of course, aging occurs with that. So we know that, through 2018, over 50% of all persons living with HIV are over 50 years old.



Additionally, around 17% of persons who are newly diagnosed with HIV in that year were persons over 50, so that this is an aging epidemic in the United States.

When we look at some of the risk factors for severe COVID-19 and common HIV comorbidities, we see that they really overlap. Things such as liver disease, smoking, immunocompromised status, diabetes, kidney



disease, liver disease, chronic lung disease are all things that in fact are more common in persons with HIV and also serve as risk factors for being

SLIDE 18

PLWH Are Increasing in Age

[1]Centers for Disease Control and Prevention (CDC). September 2020. Accessed June 1, 2021. https://www.cdc.gov/hiv/group/age/olderamericans/index.html
[2]Back D and Marzolini C. J Int AIDS Soc. 2020;23(2):e25449.

SLIDE 19

Risk Factors for Severe COVID-19 Overlap With Common HIV Comorbidities

[1]Lorenc A et al. London J Prim Care (Abingdon). 2014;6(4):84–90.
[2]Centers for Disease Control and Prevention (CDC). May 2021. Accessed June 1, 2021. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
[3]Nemani K et al. JAMA Psychiatry. 2021;78(4):380-386.

more commonly infected with and doing more poorly, clinically, with COVID-19.

We've noted that the overlapping comorbidities we just discussed can increase the risk for hospitalization and death with COVID-19, but this is something that seems to be occurring primarily because of the comorbidities, not because of HIV infection. We do know that, in some surveys, persons living with HIV have been at increased risk for hospitalization and death due to COVID-19, however when adjusted for comorbidities, the risk for COVID-19 hospitalization is similar to that observed in an HIV-negative person.

COVID-19 Diagnosis, Hospitalization, and Death Rates in New York (March 1-June 7, 2020)[1]

	PLWH, per 1000	Non-PLWH, per 1000	Rate ratio (95% CI)	Standardized rate ratio (95% CI)[a]
Diagnosed with COVID-19	27.7	19.4	1.43 (1.38, 1.48)	**0.94 (0.91, 0.97)**
Hospitalized with COVID-19	8.3	3.2	2.61 (2.45, 2.79)	**1.38 (1.29, 1.47)**
Hospitalized with COVID-19, per diagnosis	299.9	163.5	1.83 (1.72, 1.96)	**1.47 (1.37, 1.56)**
In-hospital death with COVID-19	1.9	0.8	2.55 (2.22, 2.93)	**1.23 (1.07, 1.40)**
In-hospital death with COVID-19, per diagnosis	69.3	38.7	1.79 (1.56, 2.05)	**1.30 (1.13, 1.48)**

- PLWH are at increased risk for hospitalization and death due to COVID-19.[1,2]
- **After adjusting for comorbidities**, the risk for COVID-19 hospitalization is similar to that observed in HIV-negative individuals.[2,a]
  - **Comorbidities**: Severe liver disease, diabetes, cancer, renal disease, and total number of comorbidities

[a]According to a review of data from 292,226 patients across 34 sites in the US National COVID Cohort Collaborative[2]

So, this is really not driven by HIV itself, but by the higher prevalence of many comorbidities among HIV-positive persons. Good news really, I think, but it also points out the fact that there's still a lot of work to be done in terms of diagnosing and following persons with HIV and these comorbidities.

SLIDE 20

Overlapping Comorbidities Increase the Risk for Hospitalization and Death With COVID-19 But Not COVID-19 Itself

[1]Tesoriero JM et al. JAMA Netw Open. 2021;4(2):e2037069.
[2]Sun J et al. Conference on Retroviruses and Opportunistic Infections (CROI). 2021. Abstract 103. https://www.croiconference.org/abstract/covid-19-hospitalization-among-people-with-hiv-or-solid-organ-transplant-in-the-us

Orange Line: 2-Drug Regimens vs 3-Drug Regimens

Current Guideline Recommendations for Newly Diagnosed PLWH (DHHS, IAS-USA)

D

I'm David Wohl. I'm a professor of medicine in the Division of Infectious Diseases at the University of North Carolina at Chapel Hill. Thank you for being here today and for this presentation.

So, next we'll talk about 2- vs. 3-drug regimens and current guidelines weigh in quite nicely about the appropriate person that could be treated with 2-drug vs. 3-drug regimens, and also about the use of antiretrovirals early, as soon as possible, after the diagnosis of HIV.

So, what do the guidelines say about rapid initiation of ART? Well, both the IAS and the Department of Health and Human Service guidelines weigh in on this and both recommend HIV therapy be initiated as soon as possible after the diagnosis of HIV. And there's some semantics here. We talk about rapid ART initiation, but what is rapid? In most people's book, rapid means as soon as possible, ideally within a week. There's also this concept of super-rapid or immediate, same day ART, and that's the initiation of treatment basically at the handshake, at the day of diagnosis. And we'll talk about this and there's been some studies that have looked at this, especially internationally.

Clinical guidelines from the Department of Health and Human Services (DHHS) and International Antiviral Society (IAS)-USA recommend initiating ART as soon as possible after diagnosis, including immediate initiation if possible.[1,2]

Rapid ART: Initiation of ART as soon as possible, within 7 days of HIV diagnosis[1]
Immediate/same-day ART: Initiation of treatment on the day of diagnosis[1]
Rapid ART is recommended in order to:[2]

- Increase the uptake of ART and engagement in care
- Decrease the time to virologic suppression within individuals
- Reduce the time during which newly diagnosed PLWH can transmit HIV
- Improve the rate of virologic suppression among PLWH

SLIDE 23

Rapid Initiation of ART is Recommended by Guidelines

[1]Saag MS et al. JAMA. 2020;324(16):1651-1669.
[2]Department of Health and Human Services (DHHS). December 2019. Accessed May 28, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/initiation-antiretroviral-therapy?view=full

So, rapid or as immediate or as soon as possible ART is recommended because the data show us that there's increased engagement and uptake of HIV therapy in people who get started as soon as possible. Not like the olden days where we would delay therapy, maybe for as long as a month or so to show that the person has the wherewithal or can jump over the obstacles we place before them to indicate that they can do the long haul of taking HIV therapy, possibly lifelong. It also, we know, decreases and

just makes sense [to reduce] the viral load more rapidly. If you start therapy earlier, your viral load's going to drop down quicker. There's also less time then for that person to transmit their virus to others. So, if they have less virus in their body, they have less potential to transmit it to others. And as we'll see, there's just better longer-term data, including virologic suppression, that occurs when people are engaged very early and get signals that this is important, this is something we shouldn't wait on, and we should start this right away. And that sets a pace, and maybe a mindset, that seems to perpetuate in many people over time.

What kind of data do we have? Well, the data that supports this most strongly come from outside the US, including in randomized, clinical trials. In the US, we have less data, but there is data like this that signal that there's a benefit and some of this kind of goes in the duh category. Like, if you start therapy earlier, probably a lot of good things can happen and it turns out really nothing bad happens. And some of the first data we got was from, you know, the San Francisco General Hospital Ward 86 RAPID ART Program. They have pretty much an ideal circumstance where they're able to provide rapid, the day of, immediate HIV therapy to people because they have a closet in the back of their clinic basically that has HIV medicines that they can administer and deliver to people right away.

Virologic Outcomes from the San Francisco General Hospital Ward 86 RAPID Art Program

	Early referral[a] (n=190)	Late referral[b] (n=26)	*P* value
Baseline CD4+ cell count (cells/µL), median (range)	431 (3–1905)	448 (52–1226)	.89
Baseline VL (copies/mL), median (range)	47,995 (0–>10 million)	11,210 (0–224,816)	**.022**
Time from HIV diagnosis to ART start, median (range)	6 days (0–27)	71 days (31–249)	**<.0001**
Follow-up time, median (range)	1.07 years (0–3.92)	1.56 years (0.01–3.53)	.33
Percent with VL <200 copies/mL at any time by 1 year follow-up	96.3%	100%	.40
Percent with VL <200 copies/mL at last VL measurement	93.7%	80.8%	**.022**
Time from ART start to VL <200 copies/mL (median)	43 days	41 days	.84

Considerations and caveats

- Large, well-funded clinic in an urban setting; clinic had supply of medications on hand, which were covered by local government
- High rates of substance use (51.4%), mental illness (48.1%), and housing instability (30.6%) in cohort

RAPID, Rapid ART Program for Individuals with an HIV Diagnosis; VL, viral load
[a]Referred <30 days after HIV diagnosis
[b]Referred 30 days to 6 months after HIV diagnosis

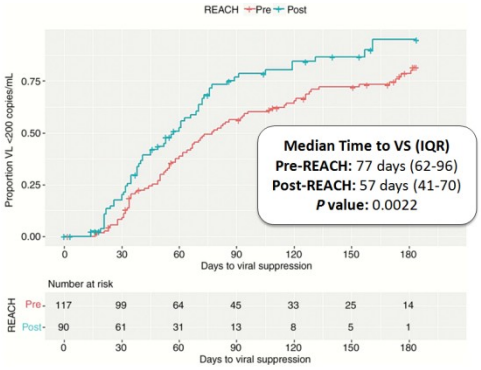
SLIDE 24

RAPID: Rapid Initiation of ART Can Help Maintain Virologic Control in an Urban Environment

Coffey S et al. AIDS. 2019;33(5):825-832.

So, they look at doing this vs. basically what we're looking [at] is historic control. The numbers aren't huge here, but again the signals are pretty strong that, just as we said, the time from diagnosis to ART start is reduced substantially from, you know, from 71 days to 6 days. Makes sense, viral load drops quicker and longer-term data show that these people stay in care better than maybe people who were deferred or didn't take therapy right away.

We see similar data from other parts of the country. Here, it's a program in Atlanta, Georgia, that highlights some of the benefits, but also the challenges of doing a rapid initiation of ART strategy. And this is in a more disenfranchised population maybe than we've seen from other studies in the US, so a lot of folks here that represent where HIV is, especially here in the South.



The REACH program allowed for initiation of ART within 72 hours of HIV diagnosis

Served disenfranchised populations

- 87.9% using publicly-funded insurance
- 75.8% unemployed
- 60.9% with housing instability
- 44% with active substance use

No difference observed in the proportion of patients who achieved VS compared with historical rates

- Significantly reduced time to VS

Funding challenges implementation and sustainability

SLIDE 25

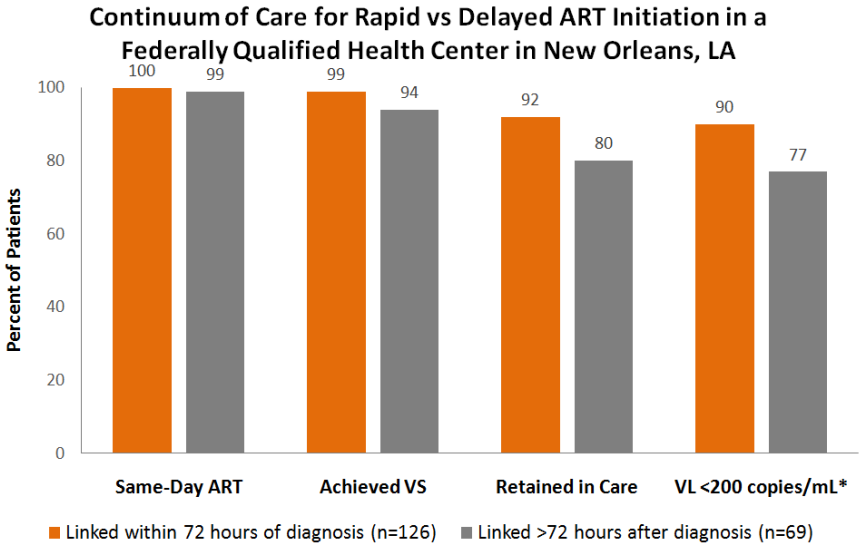
REACH: Rapid Initiation of ART in Atlanta, GA

REACH, Rapid Entry and ART in Clinic for HIV; VS, virologic suppression; IQR, interquartile range
Image courtesy of Colasanti J et al. Open Forum Infect Dis. 2018;5(6):ofy104. CC BY-NC-ND 4.0.

Colasanti J et al. Open Forum Infect Dis. 2018;5(6):ofy104.

What they found was, of course, starting through this program, getting HIV therapy within 72 hours of an HIV diagnosis led to benefits as far as viral load suppression, quicker time to viral load suppression, again which makes a lot of sense. And people actually seemed to do well with this. The problem was implementing this and sustaining it. And this program really had challenges, largely because of the staffing and the intensity that was required to keep this going without the benefits of maybe governmental support, like we saw in San Francisco, where medicines were made available for free. There were many hoops to jump through. But it does show this is a good idea if we can make it happen.

Other data that I think are very encouraging come from New Orleans and there's been a couple of different rapid initiation therapy type programs that have come from this part of Louisiana.



SLIDE 26

Immediate Initiation of ART May Improve Virologic Suppression

Participants (N=195) were started on a 30-day regimen of TAF/FTC + DTG

- The majority of patients were referred from ambulatory care setting
- Over half of patients were enrolled in Medicaid

Differences in **retention** and **virologic suppression** were significant (P <.05)

*Between March 1 and September 1, 2018
TAF, tenofovir alafenamide; FTC, emtricitabine; DTG, dolutegravir

Halperin J et al. Open Forum Infect Dis. 2019;6(4):ofz161.

And we see here, again, smaller data, you know, we're not seeing huge studies like we've seen internationally where there's trials of this. But some demonstration projects, if you will, that giving people therapy very quickly after the diagnosis leads to benefits, especially in virologic suppression, but here we also see a signal for improved retention in care. And that jives really nicely with some of the other data we've seen from across the world that people who start therapy earlier seem to stay in care longer and at higher rates than people who defer therapy.

What do guidelines say about initial HIV therapies and you can see that the guidelines have evolved over time to consolidate, both the IAS and DHHS guidelines to consolidate more towards single-tablet regimens. And the guidelines are pretty, I think, consistent with one another, which causes less confusion when they agree with one another, that basically we're talking about the same select group of medications, heavily integrase inhibitor-based.

Recommended Starting Regimens for Most People with HIV	
DHHS Guidelines[1]	**IAS-USA Guidelines[2]**
Three-drug regimens (3DRs)	
BIC/TAF/FTC	BIC/TAF/FTC
DTG/ABC/3TC[a]	DTG + TAF/FTC
DTG + (TAF or TDF)/(FTC or 3TC)	DTG + TDF/FTC
	DTG + TDF/3TC
Two-drug regimens (2DRs)	
DTG/3TC[b]	DTG/3TC[b]

NOTE: DTG/3TC not recommended as rapid-start regimen.

[a]If HLA-B*5701 negative
[b]Not recommended for rapid ART, requires baseline laboratory evaluation. Not recommended for patients with HIV RNA >500,000 copies/mL, HBV coinfection, baseline M184V mutations, and perhaps CD4+ T cell count <200 cells/µL, although the latter is unclear.
BIC, bictegravir; TAF, tenofovir alafenamide; FTC, emtricitabine; DTG, dolutegravir; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; RAL, raltegravir

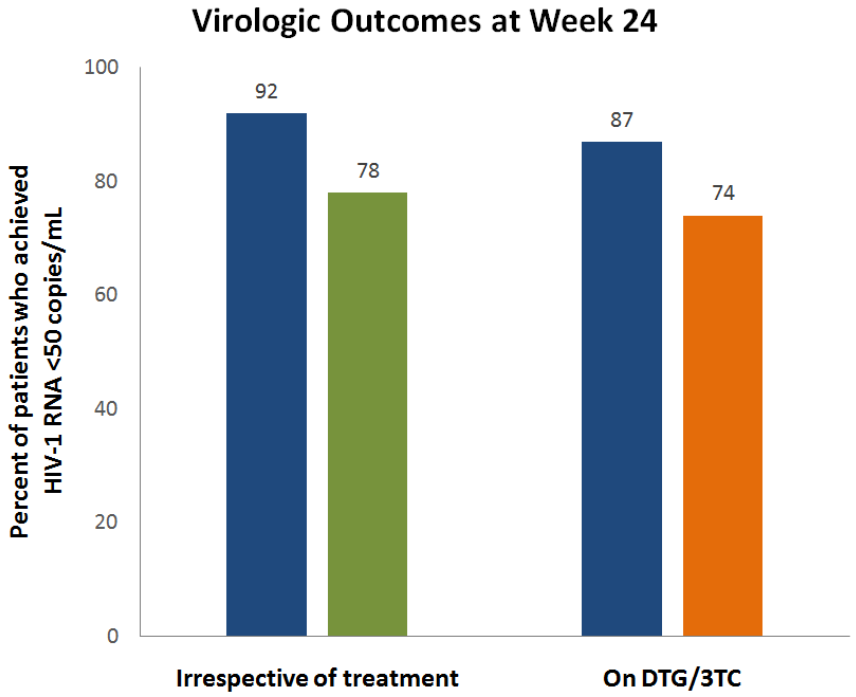
SLIDE 27

Guideline-Recommended Initial ART Regimens

[1]Department of Health and Human Services (DHHS). December 2019. Accessed May 28, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/initiation-antiretroviral-therapy?view=full
[2]Saag MS et al. JAMA. 2020;324(16):1651-1669.

Most are 3-drug regimens, but a 2-drug regimen of dolutegravir plus 3TC is on the list of recommended regimens for most people living with HIV. But when it comes to rapid start, that's where the 2-drug regimen falls out and the guidelines are pretty careful about recommending dolutegravir/3TC because there's an absence of some of the data that we would like, that we'll talk about in a moment, that indicates that this is a good, good combination for the person who's starting HIV therapy. And, of course, we have to think about hepatitis B and also preexisting resistance, transmitted resistance that leads to less confidence in starting dolutegravir/3TC as a 2-drug regimen initially, or rapidly, or quickly, because we don't have those data. Whereas for the other 3-drug regimens, there's more coverage for those types of issues and so it isn't as much of a problem. And we'll go through that quickly.

What data do we have? Again, this is really nascent and we don't have large clinical trials of rapid initiation with 2-drug regimens like dolutegravir/3TC. The STAT trial did look at this. This is a smaller study of 131 people enrolled from a variety of different sites across the US and the way that they analyzed the data we're looking at, observed, intent-to-treat and then the FDA snapshot. And if we break it down with observed being the proportion of people with a viral load less than 50 copies, regardless of a change in their regimen, I mean among those who had data at week 24, which was 111 people, 92% met a viral load of less than 50 copies.



SLIDE 28

STAT Trial: Rapid Initiation of DTG/3TC

DTG/3TC initiated within 14 days of HIV diagnosis (n=131)

Efficacy endpoints

- **Observed:** Proportion with plasma HIV-1 RNA <50 copies/mL, regardless of change in regimen, among those with available data at week 24 (n=111)
- **ITT-E missing = failure:** Participants with no HIV-1 RNA data at week 24 classified as HIV-1 RNA ≥50 copies/mL (n=131)
- **FDA snapshot:** Proportion of participants with plasma HIV-1 RNA <50 copies/mL at week 24 still taking DTG/3TC (n=131[a])

Confirmed virologic failure with no resistance development occurred in 2 participants (remained on DTG/3TC)

[a]11 participants had no virologic data at week 24

Rolle CP et al. HIV Glasgow Virtual Meeting. 2020. Abstract P020.
https://onlinelibrary.wiley.com/doi/10.1002/jia2.25616

But when we start factoring in things that we do often in clinical research, like an intent-to-treat with missing equals failure, the numbers don't look as good and we see only 78% of folks had a viral load that was less than 50 copies and that's all comers, that's the intent-to-treat. So, about 80% of people started on dolutegravir/3TC in an intent-to-treat analysis, miss equals failure, were able to get a viral load that was less than 50 at week 24.

With the FDA snapshot, we're looking at the proportion of patients who had a plasma viral load down to less than 50 copies at week 24 who were still on the dolutegravir/3TC. I would have called that observed, but they call that the FDA snapshot. Here again, you can see it's about 74% who are on therapy. There was confirmed virologic failure, but not resistance. That's what we've seen with dolutegravir-based regimens.

Reason for switch	Visit window	Modified ART	Plasma HIV-1 RNA at week 24
Baseline HBV	Week 1	DTG/3TC + TAF	<40 copies/mL
Baseline HBV	Week 1	BIC/FTC/TAF	NA[a]
Baseline HBV	Week 4	DTG + TDF/FTC	<40 copies/mL
Baseline HBV	Week 4	BIC/FTC/TAF or DTG + TDF/FTC[b]	49 copies/mL
Decision by participant or proxy	Week 4	BIC/FTC/TAF	NA[c]
Baseline HBV	Week 8	DTG/3TC + TAF	<40 copies/mL
Baseline M184V	Week 8	DTG/RPV	NA[d]
Adverse event (rash)	Week 12	DRV/c/FTC/TAF; BIC/FTC/TAF[e]	<40 copies/mL

[a]Participant in study but missing data in window. Week 36 HIV-1 RNA <40 copies/mL; [b]Participant enrolled in another double-blind clinical trial; [c]Participant withdrew after switch from DTG/3TC; [d]Participant had HIV-1 RNA 18,752 copies/mL at baseline, <40 copies/mL at day 47, switched treatment at day 49, had HIV-1 RNA 54 copies/mL on day 57, and withdrew consent due to relocation at week 12; [e]Participant switched ART twice
NA, not available; RPV, rilpivirine; c, cobicistat; DRV, darunavir

SLIDE 29

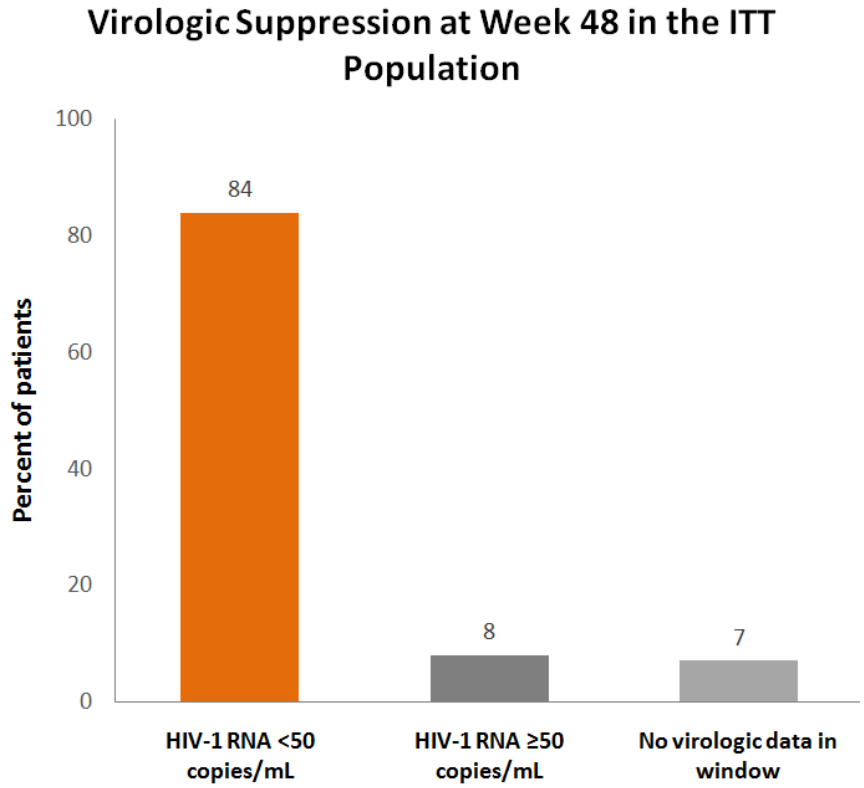
STAT Trial: Reasons for Switching DTG/3TC

Rolle CP et al. HIV Drug Therapy Glasgow Virtual Meeting. 2020. Abstract P020.

And when we look at the people who fell out, so these are the folks that we worry about with dolutegravir/3TC initiation. We worry about folks not having, you know, sensitive virus. We worry about people having hepatitis B infection. And what we see here is that there were8 people who fell into these categories and that's pretty surprising. I think that's a pretty high percentage, but it shows you that it does happen.

Here's a rapid initiation with a very different regimen. Instead of a 2-drug regimen, ostensibly this is a 4-drug regimen. It's darunavir, cobicistat, FTC, TAF. So, this is a pretty loaded regimen. This should do really well, whether or not you have a 184 transmitter resistance, whether or not you have hepatitis B. This is initiated within 14 days of HIV diagnosis. Again, not a huge study but I think signals that this is possible, this is a strategy that could be used. There were2 patients who had baseline M184V mutation. One patient discontinued due to the food requirements for this particular regimen and 1maintained an undetectable viral load through week 48.

So, when we look at these people who had, you know, these baseline mutations, it didn't seem to make a difference as we'd expect with this kind of regimen, with this heavy-duty regimen. Eighty-four percent of people in the analysis, intent-to-treat, getting less than 50.



So again, this really works. We know that this can work. We know that this is a decent strategy and there are regimens that are robust enough to support use, even without knowing hepatitis B status or the chance that there's some transmitted drug resistance. And we don't see, of course, transmitted drug resistance to PIs or to integrase inhibitors by and large.

So, the discussion for us is really how realistic is same-day start for many of us and, as we talked about, rapid is a relative term. My rapid may mean that day; your rapid may mean the mail order pharmacy sends it to that person within the week. In the DIAMOND study, it was within 14 days. So, we have to just qualify what that means. I'm not sure that there's a big difference between zero days, 3 days, 7 days or even 14 days. The sooner, probably the better, but there's probably a leveling off where if you get it within the first week after a person comes in and gets their diagnosis or is willing to start therapy, that's probably pretty good.

SLIDE 30

DIAMOND: Initiation of DRV/c/FTC/TAF

D/C/F/TAF initiated within 14 days of HIV diagnosis

Two patients with baseline M184V/I mutations achieved HIV-1 RNA <50 copies/mL by week 4

- One discontinued due to D/C/F/TAF food requirements
- One maintained an undetectable viral load through week 48

ITT, intention to treat

Huhn GD et al. Clin Infect Dis. 2020;71(12):3110-3117.

SLIDE 31

Discussion: How Realistic is Same-Day Start?

Rapid is a relative term: Is there a difference between same day, <7 days, and <14 days?

What logistical changes do clinics/practices need to make to offer same-day initiation of ART?

There is a lack of high-quality evidence to compare

- Ethical implications of a control arm in rapid-start studies
- B-HASTE (NCT04249037): rapid vs standard start in HIV therapy (ongoing)

How do the populations in these studies compare with most real-world settings?

There are logistical challenges to all of that, especially in this day and age where we're emerging back from COVID, we're starting to see people again in person. There may be staffing issues. So, is the juice worth the squeeze? And that's something that I think every clinic has to evaluate for themselves, given the benefits. At our clinic, writing a prescription, sending it to the pharmacy, that being mailed to the patient, that seems to work really well and I think that qualifies as rapid without any more work than I would do normally or any of our staff. There are lack of really high-quality, well-powered studies, but this kind of goes again into the pragmatic category that it probably works and the signals we see from the US and the data, the evidence we see from outside the US, really do support this. There are other studies that are going to come across again, B-HASTE, which is a smaller study, not again a large study, that will help us understand that BF/TAF, for instance, vs. standard of care has some benefits in rapid initiation.

And the populations that are studied, you know, in these studies, in these little analyses, how do they reflect real-world data? And some of the ones that we've chosen today, I think do represent many of the people who are starting HIV therapy today, but there was an under-representation of women and I think that's another important need that we have for understanding how to make rapid or immediate ART initiation available and beneficial to everyone.

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

Orange Line: 2-Drug Regimens vs 3-Drug Regimens

Introduction to 2-Drug ART Regimens

In this animation, explore two-drug ART regimens that are available for both treatment-naïve and treatment-experienced people living with HIV.

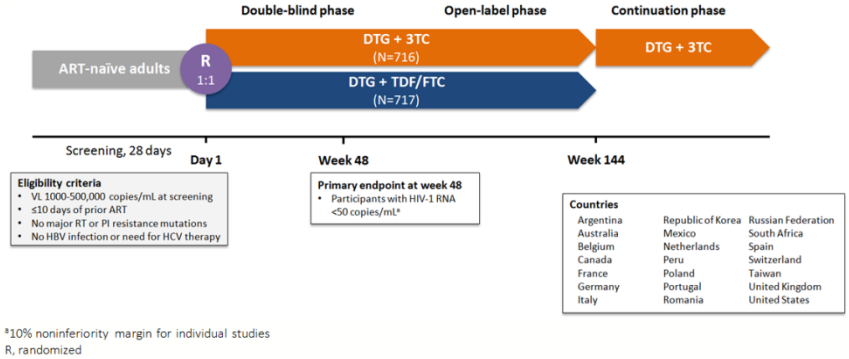
Please view this module in the online course.

Orange Line: 2-Drug Regimens vs 3-Drug Regimens

Clinical Trials of Oral 2DR in Treatment-naïve PLWH

Let's move on to talk some more about 2-drug therapy, specifically in treatment-naïve people, and look at some of the data that underpin recommendations by the guideline committees that we just talked about.

GEMINI put dolutegravir/3TC on the map and it's such an important study. This is a study that, before the results were announced, many of us were betting against dolutegravir/3TC performing very well. And there were some calculations even on the side of how many failures it would take to knock this combination out of the running, how many we would tolerate in this kind of study. Because the perception was that this wasn't going to be potent enough or durable enough. And GEMINI proved that wrong. It showed that not only was this effective, but it had durability.



This is a randomized, clinical trial in ART-naïve people, well-powered, over 700 people in each of the arms, randomized to dolutegravir/3TC vs. the standard of the day which was TDF/FTC plus an integrase, dolutegravir here. There was a continuation phase for people who got dolutegravir/3TC initially and for those who were in the control arm to switch over to dolutegravir/3TC for longer-term data collection. This was done all across the world. People came in. This is important because understanding the use of dolutegravir/3TC, it's important to understand what the eligibility criteria were for the study. This enrolled people with a viral load of 1,000 to half a million. Over half a million were not included although there were some at screening who did have a very high viral load of that and we've seen other data since then that indicate that probably over half a million, it will work. But for this particular study, first of its kind with dolutegravir/3TC in treatment-naive folks in a large clinical trial, there was a restriction based on viral load.

No prior ART basically, and also no resistance mutations known to the components and no hepatitis B infection, key because dolutegravir/3TC

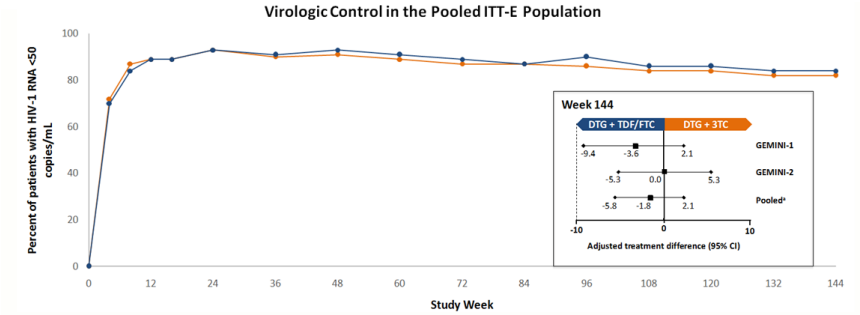
SLIDE 35

GEMINI: Durable Efficacy of DTG + 3TC in Treatment-Naïve PLWH

Cahn P, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection – 3-year results from the GEMINI studies. HIV Glasgow 2020: Abstract P18.

doesn't have drugs that are sufficiently active against hepatitis B. So, we have to think about that when we're thinking about who's the right person for dolutegravir/3TC and this reflects back to our conversation about rapid initiation and do you do it, especially in a place where there may be some hepatitis B chronic infection. That would be where you have to think about is this worth it or not.

What was seen in this trial, again seminal trial, even out to 144 weeks was noninferiority of the 2-drug regimen vs. the 3-drug regimen. Now, the 3-drug regimen, of course, that was pretty standard at the time. TAF wasn't available when this study was being designed and initiated, but I think the data speak for themselves. High levels of virologic suppression, no difference between the dolutegravir/3TC and the dolutegravir/TDF/FTC.



[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline plasma HIV-1 RNA (≤100,000 vs >100,000 copies/mL), baseline CD4+ cell count (≤200 or 200 cells/mm3), and study (GEMINI-1 vs GEMINI-2)
ITT-E, intention to treat-exposed

SLIDE 36

DTG + 3TC Was Noninferior to DTG + TDF/FTC at Week 144

Cahn P, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection – 3-year results from the GEMINI studies. HIV Glasgow 2020: Abstract P18

When we look at the specific outcomes, including the virologic outcomes, when we pool the GEMINI-1 and GEMINI-2 trials which were pretty much identical, we get a lot more information and we can see, again, that in these trials, with dolutegravir or bictegravir, failure is pretty unusual and failure with resistance to integrase just doesn't happen. So, confirmed virologic withdrawal through week 144, 12 people, remember this is a huge study, 12 participants, only 1subsequent to 96 weeks in the dolutegravir/3TC arm. In the triple-drug arm, 9 participants and 2 since week 96. Durability really seen here very nicely. No treatment-emergent integrase or NRTI resistance mutations. There was 1 participant with reported nonadherence in the 2-drug arm who developed a 184 very late in the trial. Nice, nice data. I think anyone who was concerned about the potency and durability of dolutegravir/3TC no longer has that concern.

Summary of Study Outcomes at Week 144 (ITT-E Population)

Snapshot outcome, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA <50 copies/mL	**584 (82)**	**599 (84)**
HIV-1 RNA ≥50 copies/mL	**23 (3)**	**21 (3)**
Data in window and HIV-1 RNA ≥50 copies/mL	4 (<1)	5 (<1)
Discontinued for lack of efficacy	10 (1)	4 (<1)
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	7 (1)	11 (2)
Change in ART	2 (<1)	1 (<1)
No virologic data	**109 (15)**	**97 (14)**
Discontinued study due to AE or death	29 (4)	32 (4)
Discontinued study for other reasons[a]	78 (11)	64 (9)
On study but missing data in window	2 (<1)	1 (<1)

SLIDE 37

Virologic Outcomes in the Pooled GEMINI Trials at Week 144

Confirmed virologic withdrawal through week 144

- DTG + 3TC: 12 participants (1 since week 96)
- DTG + TDF/FTC: 9 participants (2 since week 96)
- None with treatment-emergent INSTI or NRTI resistance mutations

One participant with reported nonadherence in the DTG + 3TC group developed M184V at week 132 and R263R/K at week 144

- Week 132 HIV-1 RNA: 61,927 copies/mL
- Week 144 HIV-1 RNA: 135 copies/mL
- Conferred 1.8-fold change in resistance to DTG

Cahn P, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection – 3-year results from the GEMINI studies. HIV Glasgow 2020: Abstract P18

Orange Line: 2-Drug Regimens vs 3-Drug Regimens

Current Guideline Recommendations for ART Switching in PLWH with Virologic Suppression

What about recommendations for switching ART? We were talking about treatment-naive patients, what about those with suppressed viremia who are switching? Well, why would we do that? Guidelines do a really good job of explaining some of the rationale that we should have when we're thinking about simplification or switching our regimens. Largely it comes down to trying to maintain viral suppression, but make things easier or better for the patient.

So, this might be to reduce pill burden or dietary type issues, food requirements. Mitigate drug-drug interactions, especially as people get older, they're on more and more medications to treat different ailments. There's potential for drug-drug interactions, especially with our older regimens. Maybe there's concerns about pregnancy or risk if a woman does get pregnant. To reduce cost, although that's not as operative here, I think, to many of us in the United States. It is a big issue in many parts of the world, including here. As we talked about, hepatitis B coinfection is something we have to keep in our minds as is resistance. We don't want to switch someone to a new regimen in the hopes of making things better, but you make things worse because you've given them a handicapped regimen. So, do no harm, right? We want to make sure that someone doesn't have resistance to the components that we're treating them with now or switching to that would really hobble the ability of that regimen to work. And we don't, certainly, want to place any of the medications in the new regimen at risk for further development of resistance.

Guideline-recommended reasons for treatment switching:[1]

- Simplification of treatment and pill burden/dosing reduction
- Reduce toxicity and/or enhance tolerability
- Prevent or mitigate drug-drug interactions
- Eliminate food requirements
- In the case of pregnancy
- To reduce costs

HBV Coinfection

In the case of HBV coinfection, continuation or switch to another first-line HBV antiviral (TDF or TAF) is recommended.[1]

Integrase Resistance Mutations

- EVG and RAL have relatively low barriers to resistance, and resistance mutations to one typically confer resistance to the other[1,2]
- Other INSTI (BIC and DTG) have higher barriers to resistance[1]

SLIDE 39

Treatment Switching is Recommended for Simplification or Enhanced Tolerability

"The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options."[1]

[1]Department of Health and Human Services (DHHS). December 2019. Accessed May 28, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/initiation-antiretroviral-therapy?view=full
[2]Anstett K et al. Retrovirology. 2017;14:36.

Orange Line: 2-Drug Regimens vs 3-Drug Regimens

Clinical Trials of Switching to 2DR in the Context of Virologic Suppression

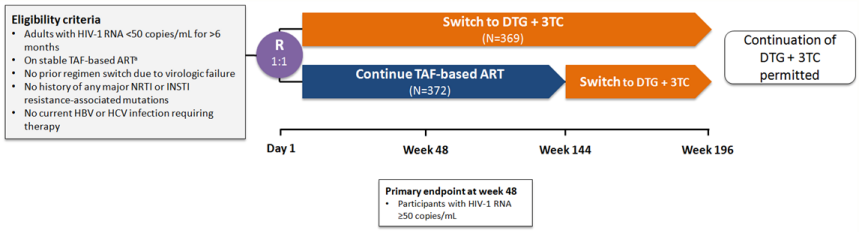
So, what are the clinical trials looking at 2-drug therapy and switching, not starting for initial therapy, but switching? A companion, if you will, to the GEMINI studies which looked at naive patients, people who had not been on HIV therapy, to dolutegravir/3TC is the TANGO trial.

SLIDE 41

TANGO: Switching to DTG + 3TC in Virologically Suppressed PLWH Receiving Stable TAF-Based ART

van Wyk J et al. Clinical Infectious Diseases. 2020;71(8):1920-1929.

- Multicenter, randomized, open-label phase 3 noninferiority study



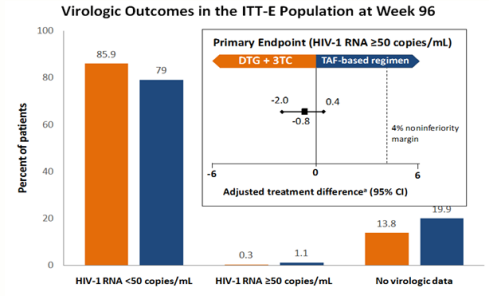
[a]Patients eligible if initial regimen was TAF/FTC with PI, NNRTI, or INSTI, or TDF switched to TAF ≥3 months prior to screening with no other regimen change

TANGO looked at switching people who were virologically suppressed on a TAF-based regimen to dolutegravir/3TC vs. continuing on that TAF-based regimen. Smaller study here, about half the size of what we saw with the combined GEMINI trials. Again, eligibility were pretty clear, had to be on a TAF-based regimen, no prior switch due to virologic failure or resistance known and, of course, no hepatitis B coinfection.

SLIDE 42

DTG + 3TC Was Noninferior in Maintaining Virologic Suppression Compared With a TAF-Based Regimen

van Wyk J et al. HIV Glasgow Virtual Meeting. 2020. Abstract 0441. https://onlinelibrary.wiley.com/doi/10.1002/jia2.25616



Summary of Virologic Outcomes at Week 96 in ITT-E Population

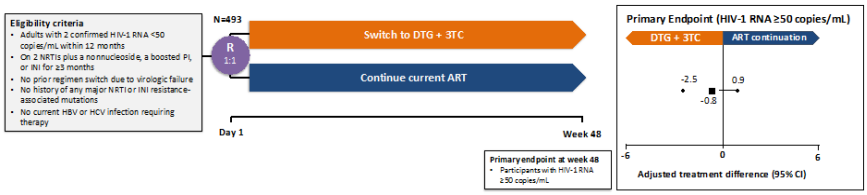
Snapshot outcome, n (%)	DTG + 3TC (N=369)	TAF-based regimen (N=372)
HIV-1 RNA <50 copies/mL	**317 (85.9)**	**294 (790)**
Virologic nonresponse	**1 (0.3)**	**4 (1.1)**
HIV-1 RNA ≥50 copies/mL	0 (0)	1 (0.3)
Discontinued for lack of efficacy	0 (0)	3 (0.8)
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	1 (0.3)	0 (0)
No virologic data	**51 (13.8)**	**74 (19.9)**
Discontinued study due to AE or death	17 (4.6)	4 (1.1)
Discontinued study for other reasons[b]	18 (4.9)	40 (10.8)
Missing data during window (non-COVID-related)	0 (0)	2 (5.4)
Missing data during window (COVID-related)	16 (4.3)	28 (7.5)

[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline third agent class
[b]Protocol deviation, loss to follow-up, physician discretion, participant withdrawal, lack of efficacy (n=1 in TAF-based regimen arm)

Randomized 1:1, switch over to dolutegravir/3TC for those on the control arm and once again, really impressive data out to pretty long periods of time, out to week 96. Viral load less than 50, over 85% pushing out all the way over, you know, down towards 96 weeks is just incredible. Virologic failure rare and no virologic failure with resistance.

SALSA is a very similar study. This is looking at switching to dolutegravir/3TC in virologically-suppressed patients, just like TANGO, but

they could be receiving pretty much any stable ART regimen, didn't have to be TAF-based. And many people in the study were on TDF, almost half.



SLIDE 43

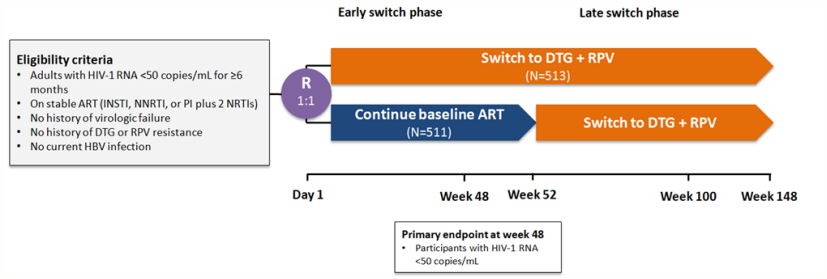
SALSA: Switching to DTG + 3TC in Virologically Suppressed PLWH Receiving Any Stable ART

Llibre JM et al. IAS 2021, 11th IAS Conference on HIV Science. 2021. Abstract OALB0303.

So, this broadened the scope of TANGO, from TANGO, to something a little bit more real-world for many of us who are switching some of our patients, especially those who were on TDF. Again, 1:1 randomization and once again, really no difference between continuing on your ART vs. switching over to dolutegravir and 3TC. So, nice demonstration of the same sort of thing that we were talking about before.

These weren't the first 2-drug therapy studies. We've had SWORD-1 and SWORD-2 if you remember back. This is years ago. And SWORD-1 and SWORD-2 looked at switching from a stable suppressive regimen to dolutegravir plus rilpivirine, not 3TC but rilpivirine.

- Multicenter, randomized, open-label, parallel phase 3 noninferiority studies[1,2]



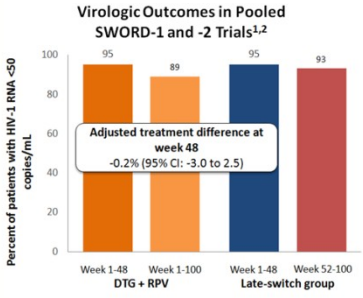
SLIDE 44

SWORD-1 and -2: Switching to DTG + RPV in Virologically Suppressed PLWH

[1]Llibre JM et al. Lancet. 2018;391(10123):839-849.
[2]Aboud M et al. Lancet HIV. 2019;6(9):e576-e587.

This now comes coformulated in 1 pill. This was a 1:1 randomization, very similar eligibility criteria as we've talked about for all these 2-drug therapies that don't include a hepatitis B active drug. Continued baseline ART vs. the switch to dolutegravir plus rilpivirine and all that's involved with that, including the food requirements for rilpivirine and not taking a PPI or an H2 blocker. There was a later switch after a year in the control group to dolutegravir plus rilpivirine and, as we recall, it worked really well. This was well-tolerated, people preferred it in their patient-reported outcome type data.

And we saw high levels of virologic suppression, whether people stayed on their therapy or switched over to the dolutegravir/rilpivirine. And then, in the people who switched over after they were on the control for a year and switched over to dolutegravir/rilpivirine, similar data, underscoring what we saw with the primary analysis and primary analyzation.



Summary of Virologic Outcomes[1,2]

	DTG + RPV		Late-switch group	
Virologic outcome, n (%)	Week 1-48 (N=513)	Week 1-100 (N=513)	Week 1-48 (N=511)	Week 52-100 (N=477)
HIV-1 RNA <50 copies/mL	**486 (95)**	**456 (89)**	**485 (95)**	**444 (93)**
Virologic non-response	**3 (<1)**	**13 (3)**	**6 (1)**	**10 (2)**
HIV-1 RNA ≥50 copies/mL	0 (0)	5 (1)	2 (<1)	3 (1)
Discontinued for lack of efficacy	2 (<1)	7 (1)	2 (<1)	3 (1)
Discontinued, HIV-1 RNA ≥50 copies/mL	1 (<1)	1 (<1)	1 (<1)	0 (0)
Change in ART	0 (0)	0 (0)	1 (<1)	4 (1)
No virologic data	**24 (5)**	**44 (9)**	**20 (4)**	**23 (5)**
Discontinued due to AE or death	17 (3)	27 (5)	3 (<1)	11 (2)
Discontinued for other reasons	7 (1)	17 (3)[a]	16 (3)	9 (2)[a]
Missing data during window	0 (0)	0 (0)	1 (<1)	3 (1)

[a]10 out of 990 (1%) confirmed virologic withdrawals through week 100 (treatment-emergent NNRTI resistance mutations documented in 3 cases, all from early switch arm)

SLIDE 45

Switching to DTG + RPV Maintains HIV Suppression Over 100 Weeks and Is Noninferior to Standard ART

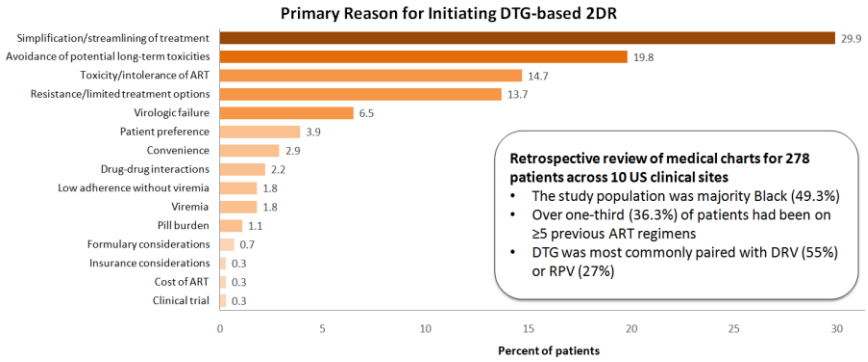
[1]Llibre JM et al. Lancet. 2018;391(10123):839-849.
[2]Aboud M et al. Lancet HIV. 2019;6(9):e576-e587.

In this case of lower barrier to resistance maybe and some other issues that may have led to this, but—and especially with rilpivirine—we did see, again, no integrase resistance, but there was some treatment-emergent NNRTI resistance that was seen. So, this is really important because we don't really see resistance very much in the 3-drug regimens and all the 2-drug regimens I've talked about, no integrase resistance and that's because the integrase is just doing so well here. But a little smattering of companion drug resistance, that can occur.

Orange Line: 2-Drug Regimens vs 3-Drug Regimens

Real-World Evidence Supporting Use of 2DR

What's the real-world evidence supporting use of 2-drug therapy? It's a little bit harder to get at because real-world data can be confounded by why someone switched to a 2-drug therapy and things like that. When we even just look at the primary reason for initiating dolutegravir-based,2-drug therapy in this analysis from several clinics across the US, we see that simplification or streamlining the treatment was the reason.



So, going from more cumbersome, more difficult-to-take regimens to something that was streamlined, like a dolutegravir-based regimen, was the number 1 reason, far and away. There were also the concerns of long-term toxicities which I think is coded for getting off of a tenofovir-containing regimen. Then, toxicities or intolerance and then it starts to get sundry, you know, little issues. Pill burden wasn't as much. The simplification may include pill burden, but it may be include being on fewer medicines and, for some providers, that's really important.

There's some evidence, maybe in real-world data, that those who are switched to 2-drug regimens vs3-drug regimens may experience more virologic failure.

SLIDE 47

Real-World Reasons for Switching to DTG-based 2DR

Ward D et al. AIDS Res Treat. 2020:5923256.

End of observation period status, n (%)	3DR	2DR	*P* value
Remained on treatment	**4919 (66.7)**	**1110 (59.3)**	**-**
Change of treatment	**1779 (24.2)**	**587 (31.4)**	**-**
Due to virologic failure	**119 (6.7)**	**82 (14.0)**	**<0.0001**
Due to adverse event	372 (20.9)	104 (17.7)	0.094
Due to intolerance	11 (0.6)	4 (0.7)	0.773
To avoid long-term toxicities	**80 (4.5)**	**7 (1.2)**	**0.0002**
Due to simplification	320 (18.0)	98 (16.7)	0.477
Due to drug interactions	79 (4.4)	21 (3.6)	0.368
Loss to follow-up	18 (1.0)	3 (0.5)	0.320
Other	764 (43.0)	264 (45.0)	0.389
Missing value	*16*	*4*	-
Lost to follow-up	**637 (8.6)**	**161 (8.6)**	**-**
Death	**36 (0.5)**	**14 (0.8)**	**-**

This is an analysis from Spain, but in this analysis there's again this confounding issue that happens in real-world data that's hard to mitigate unless you use some sophisticated strategies. In this study, the people who were assigned to a 2-drug regimen or people who switched to 2-drug, they've had a history of more virologic failures compared to the people who were staying on 3-drug regimens.

So, it's really hard to compare in some of the studies, you know, the outcomes that we might in a clinical trial. But certainly, it really does indicate that when we switch people to 2-drug regimens, we should do so intelligently.

We should use regimens that people can take and many of the 2-drug regimens that are indicated here, it's not dolutegravir/3TC but it's a boosted PI plus something else. And people on boosted PIs, even if they're on just 1 other drug in addition to their boosted PI, may not do as well as someone who might on dolutegravir/3TC, for instance, or dolutegravir/rilpivirine, which I think would have fewer side effects.

SLIDE 48

Virologic Failure May Be More Common in 2DRs Than in 3DRs

- Retrospective analysis of data for 7,481 patients in a multicenter Spanish cohort
- **3DR**: INSTI-containing triple therapy
- **2DR**: DTG- and/or boosted PI-based two-drug combination

Adjusted hazard ratios (95% CI) for 2DR vs 3DR

- **Discontinuation**: **1.29** (1.15-1.44)
- **Virologic failure**: **2.06** (1.54-2.77)
- **Toxicity**: 1.18 (0.94-1.48)

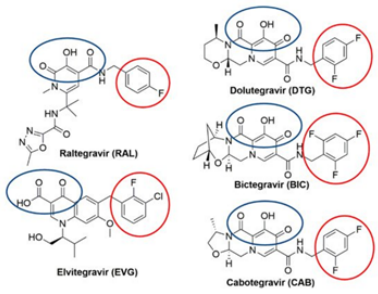
Teira R et al. PLoS One. 2021;16(4):e0249515.

Yellow Line: Emerging Long-Acting Injectable ART

Introduction to Long-acting Injectable ART

Dr. David Hardy: Now, let me tell you a little bit about some of the emerging, exciting, long-acting injectable ART regimens.

In January of 2021, the Food and Drug Administration approved the first long-acting injectable antiretroviral regimen, including cabotegravir plus rilpivirine, for adults living with HIV infection.



Cabotegravir (CAB): Integrase inhibitor: Structural analog of DTG[2]
Rilpivirine (RPV): NNRTI

Long-acting injectable CAB + RPV can be given once monthly following a 1-month lead in with oral CAB + RPV to ensure tolerability.[1]

HIV-1, human immunodeficiency virus type 1; NNRTI, nonnucleoside reverse transcriptase inhibitor.
Image courtesy of Smith SJ et al. Viruses. 2021;13(2):205. CC BY 4.0

This is the first extended-release medication regimen that's been approved by the FDA for persons with HIV infection. Cabotegravir is a newly-approved integrase inhibitor and a structural analog of a drug we already have available, called dolutegravir. The other component of the injectable medication is called rilpivirine, an NNRTI which was previously approved as an oral medication many years ago.

Under the current approval, the long-acting injectable medications, cabotegravir and rilpivirine, are given once a month, 1 injection in each buttock after a 1-month oral lead-in of oral cabotegravir and oral rilpivirine. And this is given in order to enhance the safety, to make sure the patient tolerates these medications prior to receiving a long-acting, intermuscular injection.

SLIDE 51

Cabotegravir + Rilpivirine: the First Extended-Release Injectable Drug Regimen for Adults With HIV

In January 2021, the Food and Drug Administration approved long-acting injectable cabotegravir plus rilpivirine for adults living with HIV-1.[1]

[1]Food and Drug Administration (FDA). News Release. January 2021. Accessed June 8, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-extended-release-injectable-drug-regimen-adults-living-hiv
[2]Smith SJ et al. Viruses. 2021;13(2):205.

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

In February 2021, the DHHS released a statement outlining the use of CAB + RPV injections as a **treatment optimization strategy** for PLWH currently on oral ART

CAB + RPB can be considered in those who have been virally suppressed for ≥3 months, and who:[2]

- Have no baseline resistance to CAB or RPV
- Have no history of virologic failure
- Do not have active HBV infection, unless also treated with an oral anti-HBV regimen
- Are not pregnant or planning to become pregnant
- Are not receiving contraindicated medications with potential drug interactions

DHHS, Department of Health and Human Services

The medications were approved for virologically suppressed adults with HIV infection. Following the approval by the FDA in January of 2021, the Department of Health and Human Services ART Advisory Panel released a statement outlining the use of these 2 medications as a treatment optimization strategy for persons living with HIV currently on oral medications. They actually pointed out that this regimen—this option—could, in fact, be considered for those who are virally suppressed for at least 3 months and who have the following characteristics: no baseline resistance to either cabotegravir or rilpivirine; no previous history of virologic failure; do not have chronic active hepatitis B infection unless they're treated with an additional oral anti-hepatitis B regimen; they're not pregnant or planning to become pregnant; and are not receiving any contraindicated medications that may interact with either cabotegravir or rilpivirine.

SLIDE 52

Long-Acting CAB + RPV is Approved for Virologically Suppressed Adults with HIV-1

[1]Food and Drug Administration (FDA). News Release. January 2021. Accessed June 8, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-extended-release-injectable-drug-regimen-adults-living-hiv
[2]Dept. of Health and Human Services (DHHS). February 2021. Accessed June 8, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/hhs-adults-and-adolescents-antiretroviral-guidelines-panel?view=full

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

Yellow Line: Emerging Long-Acting Injectable ART

Introduction to Dosing and Scheduling for Long-Acting Injectable ART (LAIs)

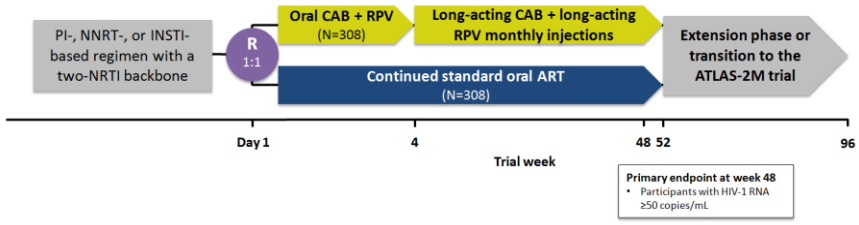
In this animation, explore dosing and scheduling for cabotegravir plus rilpivirine (CAB plus RPV), the first once-monthly, injectable fully anti-retroviral regimen.

Please view this module in the online course.

Yellow Line: Emerging Long-Acting Injectable ART

Clinical Trial Evidence for Long-acting Injectable ART

Let's look at some of the clinical trial evidence that supports this approval by the FDA. There've been 3 trials which are really important to review to kind of see where this data's coming from. The first trial is called the ATLAS study and it looked at the use of the switch to injectable medications compared to continuing oral medications in adult patients who were already well-suppressed on a protease inhibitor and NNRTI, or in a gray space regimen with 2 new backbones.



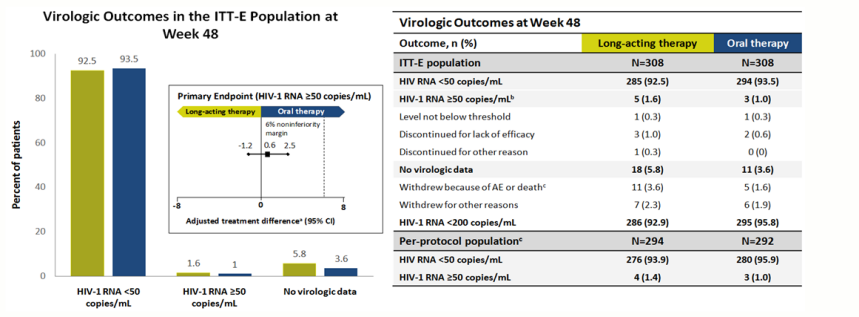
SLIDE 56

ATLAS Trial: Efficacy of Long-acting CAB + RPV Injections vs Oral ART

Swindells S et al. NEJM. 2020;382:1112-1123.

The patients were randomized 1:1 to either continue that oral regimen or, first of all, go onto an oral lead-in regimen of about 4 weeks of oral cabotegravir and oral rilpivirine. Those patients, as they maintained their undetectability, were then continued on injectable long-acting cabotegravir and long-acting rilpivirine monthly injections, 1 injection in each buttock, and this has been continued now to as long as over 96 weeks.

The primary endpoint in this study was, in fact, at 48 weeks. And at that point, it demonstrated that the patients who reached an endpoint which meant, in these already well-suppressed patients, that the patient became virologically unsuppressed or detectable.



Virologic Outcomes at Week 48		
Outcome, n (%)	Long-acting therapy	Oral therapy
ITT-E population	N=308	N=308
HIV RNA <50 copies/mL	285 (92.5)	294 (93.5)
HIV-1 RNA ≥50 copies/mL[b]	5 (1.6)	3 (1.0)
Level not below threshold	1 (0.3)	1 (0.3)
Discontinued for lack of efficacy	3 (1.0)	2 (0.6)
Discontinued for other reason	1 (0.3)	0 (0)
No virologic data	18 (5.8)	11 (3.6)
Withdrew because of AE or death[c]	11 (3.6)	5 (1.6)
Withdrew for other reasons	7 (2.3)	6 (1.9)
HIV-1 RNA <200 copies/mL	286 (92.9)	295 (95.8)
Per-protocol population[c]	N=294	N=292
HIV RNA <50 copies/mL	276 (93.9)	280 (95.9)
HIV-1 RNA ≥50 copies/mL	4 (1.4)	3 (1.0)

[a]Based on Cochran-Mantel-Haenszel stratified analysis with adjustment for sex at birth and class of third agent as baseline [b]A level of ≥50 copies/mL was observed at week 48 or at the time of discontinuation before week 48 [c]There was 1 death in the oral therapy group due to methamphetamine overdose [d]Excluded participants with protocol deviations that were likely to affect efficacy assessments or lead to discontinuation of treatment

SLIDE 57

Long-acting Therapy Is Noninferior to Continuation of Oral Therapy in Virologically-Suppressed Adults with HIV

Swindells S et al. NEJM. 2020;382:1112-1123.

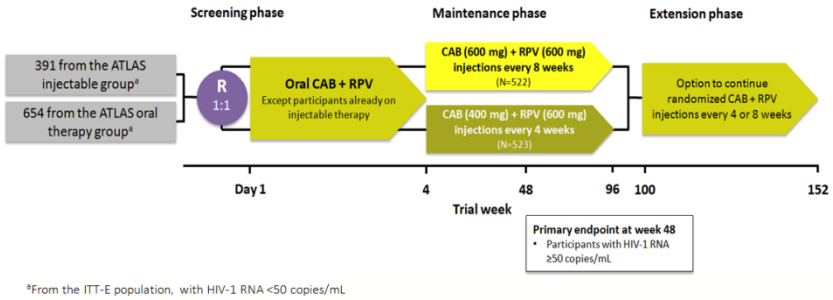
This occurred in 1.6% of patients who were on the injections and 1% in the patients who maintained their oral medication. Or, looking at it in a

different way, 92.5% of the patients receiving injections maintained their undetectable viral load and 93.5% in the oral arm, when compared, continued their undetectable levels as well.

So, this study actually reached its primary endpoint, demonstrating that the once-monthly dual injection therapy was, in fact, noninferior or similar to continuing oral therapy in those patients that were already virologically suppressed. It was good to see that this option was in fact working virologically just as well as continuing an oral regimen. It is important also to point out the fact that there were side effects which we'll talk about in just a minute.

The ATLAS-2M study is the next important study in the development of injectable medications. The data from this study is currently being reviewed by the FDA and its results have not yet been acted upon based upon the frequency of injections. In ATLAS-2M, patients were randomized to receive injections either once every 4 weeks, or once a month, or once every 8 weeks, or once every 2 months, with an increased amount of medication injected.

- Multicenter, randomized, open-label, phase 3b noninferiority trial



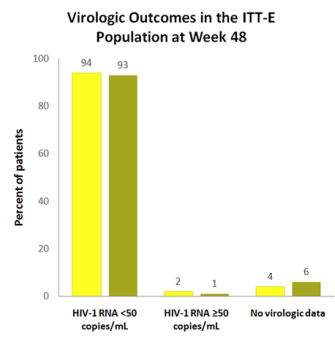
[a]From the ITT-E population, with HIV-1 RNA <50 copies/mL

SLIDE 58

ATLAS-2M: Long-acting CAB + RPV Dosed Every 4 or 8 Week in Virologically Suppressed PLWH

Overton ET et al. Lancet. 2021;396(10267):1994-2005.

The patients who came into this trial, about 390 were from the ATLAS injectable group and those patients were already on Q4 week or monthly injections. They were randomized to continue to receive every 4 weeks, or every eight weeks as a new regimen. And then there was an additional 650 patients that come in from the ATLAS oral arms or about 500 patients who were, in fact, added to this study from outside the ATLAS study that were already well-suppressed on oral ART regimens. In those patients that were on oral regimens to begin with, those persons did undergo a lead-in regimen of oral cabotegravir and oral rilpivirine and then the randomization to every-8-week injections or every-4-week injections continued.



Virologic Outcomes at Week 48

Outcome, n (%)	8 weeks (N=522)	4 weeks (N=523)	Difference (95% CI)	Adjusted difference (95% CI)[a]
HIV RNA <50 copies/mL[b]	492 (94)	489 (93)	0.8 (-2.2, 3.7)	0.8 (-2.1, 3.7)
HIV-1 RNA ≥50 copies/mL[c]	9 (2)	5 (1)	0.8 (-0.6, 2.2)	0.8 (-0.6, 2.2)
Level not below threshold	3 (1)	2 (<1)	-	-
Discontinued for lack of efficacy	6 (1)	2 (<1)	-	-
Discontinued for other reason	0 (0)	1 (<1)	-	-
Change in background therapy	0 (0)	0 (0)		
No virologic data	21 (4)[d]	29 (6)	-	-
Withdrew because of AE or death	9 (2)	13 (2)	-	-
Withdrew for other reasons	12 (2)	16 (3)	-	-

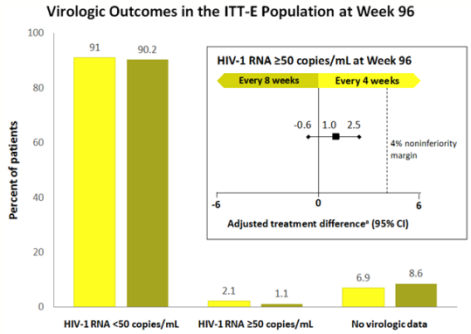
[a]Cochran-Mantel-Haenszel stratified analysis adjusting for previous CAB + RPV long-acting exposure; [b]Noninferiority determined if lower bound of adjusted difference was above -10%; [c]Noninferiority determined if upper bound of adjusted difference was below 4%; [d]Lost to follow-up (2), withdrawal by participant (4), protocol deviation (1), investigator decision (4), lack of efficacy (1)

SLIDE 59

The Efficacy of 8- and 4-Week Dosing of Long-acting Injectable CAB + RPV Is Similar

Overton ET et al. Lancet. 2021;396(10267):1994-2005.

The primary endpoint of this study was at 48 weeks and, at that 40-week evaluation point, virologic outcomes actually demonstrated that a very small number of patients had breakthrough viremia, only 2% in the every-8-week arm and only 1% in the every-4-week injectable arm. Looking at that in the converse way, 94% of patients in the every-8-week arm maintained nondetectability and in the every-4-week arm, 93% of patients maintained their undetectability. Although the number of patients numerically in the every-8-week arm was a little greater at 9 vs. 5 in the every-4-week arm, this difference did not reach statistical significance and thereby showed that the every-4- or every-8-week form of injections were in fact similar in terms of their efficacy at keeping viral load suppressed.



Virologic Suppression and Resistance Outcomes[b]

Outcome, n (%)	8 weeks (N=522)	4 weeks (N=523)
Confirmed virologic failure	9 (1.7)	2 (0.4)
RPV resistance-associated mutations	7 (1.3)	1 (0.2)
INSTI resistance-associated mutations	5 (1)	2 (0.4)

[a]Cochran-Mantel-Haenszel stratified analysis adjusting for previous CAB + RPV long-acting exposure
[b]At week 96

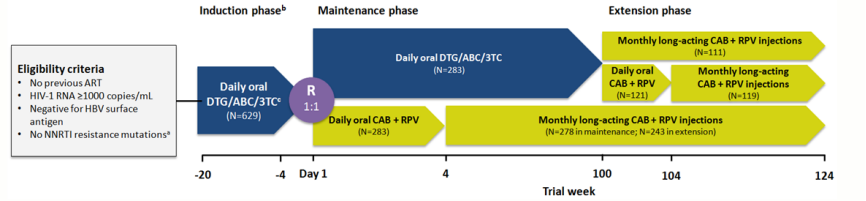
SLIDE 60

Virologic Suppression Is Maintained at 96 Weeks

Jaeger H et al. Conference on Retroviruses and Opportunistic Infections (CROI). Abstract 401. https://www.croiconference.org/abstract/week-96-efficacy-and-safety-of-cabotegravir-rilpivirine-every-2-months-atlas-2m/

Even out through week 96, what we're seeing here in the ATLAS-2M study is that there's still very high levels of undetectability, 91% in the every-8-week, 90.2% in the every-4-week. So that a small number of people have actually broken through, not statistically different between the 8-week arm and the 4-week arm and really continues to demonstrate noninferiority between these 2 injection regimens of using the medication now every 2 months. We hope that, in the future, the FDA will act on this information and be able to offer persons a different regimen of frequency of injections very soon.

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES



- All patients in extension phase switched from oral DTG/ABC/3TC to injectable, but some elected no oral CAB + RPV lead-in
- **Oral dosage:** CAB 30 mg + RPV 25 mg
- **Injectable dosage:** Loading dose, CAB 600 mg + RPV 900 mg, then 400 mg + 600 mg

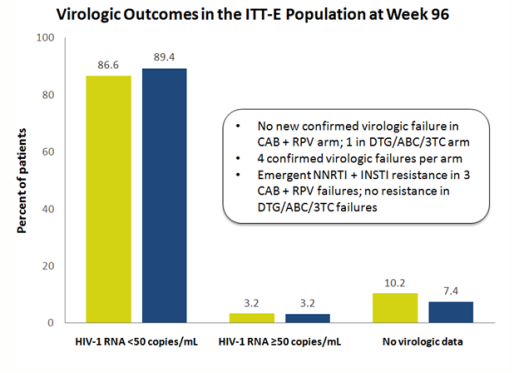
[a]K103N permitted; [b]Patients with HIV-1 RNA <50 copies/mL from week 16 to week 20 continued to maintenance; [c]Alternative non-ANC NRTIs permitted for intolerance of HLA-B*5701 positivity

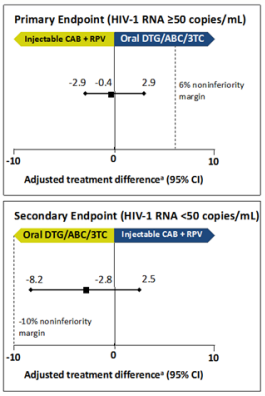
SLIDE 61

FLAIR: Long-acting Injectable CAB + RPV Every 4 Weeks vs Daily Oral DTG/ABC/3TC in Treatment-Naïve PLWH

[1]Orkin C et al. NEJM. 2020;382:1124-1135.
[2]D'Amico R et al. HIV Glasgow Virtual Meeting. 2020. Abstract O414. https://onlinelibrary.wiley.com/doi/10.1002/jia2.25616

Now, another study that was important in the development of injectable medications is called the FLAIR study. This was a study that actually took persons who were naive to antiretroviral medication, who had no previous medication, had a viral load of at least 1,000, did not have hepatitis B virus coinfection and no NNRTI resistance mutations on screening. They were, in fact, first of all given oral dolutegravir, abacavir 3TC for a period of about 4 weeks. Once undetectability was reached and maintained, they were then randomized to either continue on that oral 3-drug, single-tablet regimen, or switch over to, first of all, oral lead-in of cabotegravir plus rilpivirine, and then after 4 weeks of maintaining undetectability, switch over to injections of cabotegravir and rilpivirine long-acting on a once-monthly basis.





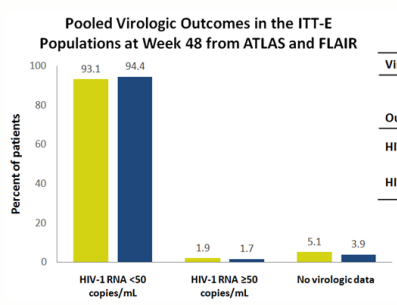
SLIDE 62

Long-acting CAB + RPV Is Noninferior to Oral DTG/ABC/3TC for Maintaining Viral Suppression

[1]Orkin C et al. Conference on Retroviruses and Opportunistic Infections (CROI). 2020. Abstract 482. https://www.croiconference.org/abstract/long-acting-cabotegravir-rilpivirine-for-hiv-treatment-flair-week-96-results/
[2]Orkin C et al. NEJM. 2020;382:1124-1135.

The primary endpoint for the FLAIR study, just like for the ATLAS studies, was at 48 weeks and, at that point, there was undetectability in a similar group of patients in each arm, meaning that a small number of patients in each arm did, in fact, break through, but it was less than 1% as well. At 2 years, even farther out, the number of patients that had breakthrough viremia was exactly the same, 3.2%, with almost 87% of patients in the injectable arm receiving cabotegravir and rilpivirine undetectable and 89% in the continued oral medication. Again, noninferiority was maintained even 2 years out from beginning of this study.

When both studies, the FLAIR and the ATLAS study, are combined, what it showed was that in comparing the injectable arm, given once a month, vs. the oral arm of daily medication, 93% in the injectable arm and 94% in the oral arm had indictable virus at 48 weeks.



Virologic Outcomes at Week 48

Outcome, n (%)	Long-acting therapy (N=591)	Oral therapy (N=591)	Difference (95% CI)	Adjusted difference (95% CI)[a]
HIV RNA <50 copies/mL[b]	550 (93.1)	558 (94.4)	-1.35 (-4.11, 1.41)	-1.37 (-4.12, 1.39)
HIV-1 RNA ≥50 copies/mL[c]	11 (1.9)	10 (1.7)	0.17 (-1.34, 1.68)	0.16 (-1.35, 1.67)

[a]Based on Cochran-Mantel-Haenszel stratified analysis, adjusted for 10 strata
[b]-10% noninferiority margin
[c]4% noninferiority margin

SLIDE 63

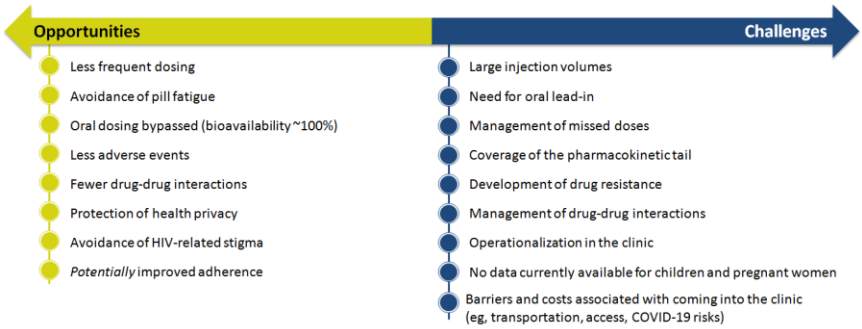
Combined Results from ATLAS and FLAIR Demonstrated That Monthly CAB + RPV Injections Were Noninferior to Oral Therapy

Rizzardini G et al. *J Acquir Immune Defic Syndr.* 2020;85(4):498-506.

Yellow Line: Emerging Long-Acting Injectable ART

Promises and Challenges of Long-acting Injectable ART

So, some of the promises and challenges of long-acting injectable antiretroviral therapy are ones that we really need to think about as we go into this era in which patients have the option for being able to no longer take medications once a day, even a single-tablet regimen, but come in for monthly injections of 2 medications which have been shown to be similar to continuing oral medications for maintaining undetectability. We know that there are many opportunities and also challenges with doing this.



SLIDE 65

Long-acting Injectables Offer Several Opportunities and Challenges in HIV Care

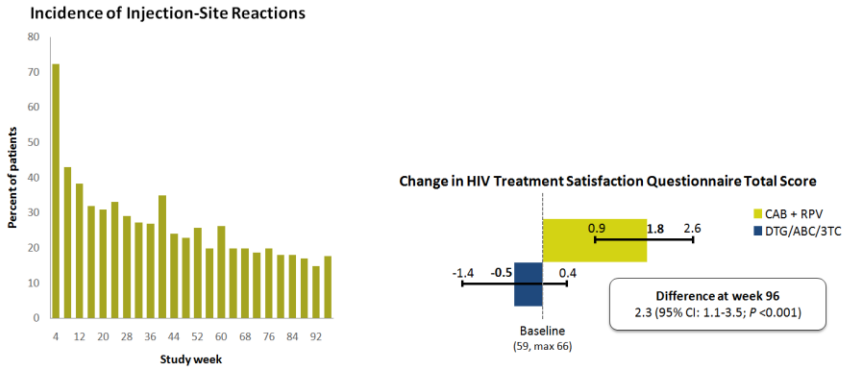
Scarsi KK and Swindells S. J Int Assoc Provid AIDS Care. 2021;20:23259582211009011.

The opportunities really I think can be very patient-attracting and that is less frequent dosing, the avoidance of pill fatigue, 100% bioavailability because there's no oral absorption issues, oftentimes less adverse events, fewer drug-drug interactions, health privacy is also something that many patients seem to like because it really just makes the responsibility for maintaining prescriptions that of the healthcare system. Patients no longer have to pick up or maintain pills on their own. And with this, a really important avoidance is HIV-related stigma for those patients that have a hard time being able to take their medication or house their medication at their own home, that's something that can actually make living with HIV much easier. This is also, I think, a great way to potentially improve adherence, although that's not been proven at this point in time.

Some of the challenges, of course, are the following: the injections require somewhere between 2 to 3 ccs of an injectable fluid, easy to inject. There is currently a need for an oral lead-in in the FDA-approved medications. However that is being tested, and the oral lead-in may not be necessary. The ATLAS-2M study is looking at that. How do you manage missed doses if someone comes in more than a week off schedule? How do you cover the pharmacologic tail after someone stops the medication, because we know the medications—because they are so long-acting—can maintain in the tissues, in the blood, for as long as up to a year? There has

been some development of drug-resistant mutations in small numbers of patients in both FLAIR and ATLAS. This has occurred primarily in a subset of patients that have a particular clade of virus called Clade A, and those who may have underlying mutations prior to starting the therapy, primarily NNRTI mutations which will be a complicated situation with any patient who is starting medication later on. There are some drug-drug interactions that need to be managed, of course.

The biggest thing, I think, is also structural changes that may need to occur in clinics. How do clinics then start seeing patients on a more frequent basis? Instead of every 3–6 months, every month, to give injections. Even though the intensity of the visit is much, much less, the timing is something that some clinics are going to have to change in their way of doing things. And then, of course, also looking at new data for children and pregnant women. And then also about associated cost for giving the injections and the labor costs to actually do that.



And, of course, the most common sort of reactions are injection-site reactions, 99% of which however were grade 1 or grade 2. Almost 90% resolve in less than 7 days, median of 3, but there were also some very important improvements in terms of the way the patients actually responded to therapy in terms of their own perception of what their quality of life was like. This is something that oftentimes clinical trials measure, but don't oftentimes find as a big important situation. But in this study there was a significant difference at week 96 between those patients in the FLAIR trial that received injections vs. those who continued their oral medications. That the majority of patients who were randomized to the injections actually saw a significant increase in their quality of life while those on the oral medication actually saw a small decrease in their overall quality of life. So, the injections actually did show some improvement there from the patients' standpoint.

SLIDE 66

Injection-Site Reactions and Improved Patient-reported Outcomes in the FLAIR Trial

Most injection-site reactions (99%) were grade 1 or 2.

- 89% resolved in ≤7 days (median, 3 days)

Long-acting injectable therapy was associated with significant improvements in HIV-related quality of life compared with oral DTG/ABC/3TC.

Orkin C et al. Conference on Retroviruses and Opportunistic Infections (CROI). 2020. Abstract 482. https://www.croiconference.org/abstract/long-acting-cabotegravir-rilpivirine-for-hiv-treatment-flair-week-96-results/

Now, one of the things that one might think might be the best place to use these long-term injections would be in persons who are having trouble with adherence. So that the responsibility to take a daily pill or pills is replaced by a monthly or, perhaps in the future, every 2 month, injections.

Long-acting injectables may help improve adherence by eliminating the need for daily pills, but it is unclear if they are appropriate in PLWH with nonadherence.[1]

- Poor adherence can potentially cause prolonged periods of subtherapeutic drug levels if a dose is missed, which **may lead to resistance** (as shown in table).[1]

Summary of Confirmed Virologic Failures in ATLAS-2M[2]

	CVFs, n (%)	With RPV RAMs[a]	RPV RAMs observed at failure	With IN RAMs[a]	IN RAMs observed at failure
Every 8 weeks (N=522)	8 (1.5)	6	K101E, E138E/K, E138A, Y188L	5	Q148R,[b] N155H[b]
Every 4 weeks (N=523)	2 (0.4)	1	K101E, M230L	2	E138E/K, Q148R, N155N/H

[a]6/6 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change >2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change >2.5); [b]Or mixture
CVF, confirmed virologic failure; RAM, resistance-associated mutation; Q8W, every 8 weeks; Q4W, every 4 weeks

Recommendations from the IAS-USA guidelines suggest that PLWH with poor adherence to treatment are unlikely to be good candidates for long-acting injectable therapy.[1]

We do not know this yet and there's more data that's needed. We think that improving adherence with injections may actually be good because it eliminates the need for daily pills. This concept is being tested in a currently ongoing ACTG trial called 5359, and at the conclusion of that study, we'll hopefully be able to determine whether this new injectable medication regimen option is something that can improve adherence in those persons that have had a difficult time maintaining virologic suppression with daily oral medications.

Currently, the IAS-USA guidelines suggest that persons living with HIV with poor adherence to treatment are not good candidates for long-acting injectable therapy. So, we'll have to see whether or not this new advance is something that can actually help improve this adherence or not.

It's also important to point out that, like all medications, injectable cabotegravir and rilpivirine is contraindicated because of certain drug-drug interactions, such as some anticonvulsants, phenobarbital, carbamazepine, antimicrobials such as rifabutin, rifampin and rifapentin, some systemic glucocorticoids, such as dexamethasone where more than 1single dose is given and herbal products, such as St. John's wort. We also know that there needs to be some observation for not using medications that may actually change the concentrations of either the 2 components

SLIDE 67

The Use of Long-acting Injectables in PLWH With Nonadherence Is Uncertain—More Data Are Needed

[1]Saag MS et al. JAMA. 2020;324(16):1651-1669.
[2]Overton ET et al. Conference on Retroviruses and Opportunistic Infections (CROI). 2020. Abstract 3334. https://www.natap.org/2020/CROI/croi_03.htm

of cabotegravir or rilpivirine due to liver enzyme induction and this is something that needs to be carefully worked up prior to the medications being given.

Long-acting injectable CAB + RPV is contraindicated with:

- **Anticonvulsants**: Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin
- **Antimycobacterials**: Rifabutin, rifampin, and rifapentine
- **Systemic glucocorticoids**: Dexamethasone (more than a single-dose treatment)
- **Herbal products**: St. John's wort (*Hypericum perforatum*)

Co-administration of these drugs significantly decreases plasma concentrations of CAB and/or RPV due to UGT1A1 and/or cytochrome P450 CYP3A enzyme induction

- May reduce the virologic response

UGT, uridine diphosphate-glucuronosyl transferase

SLIDE 68

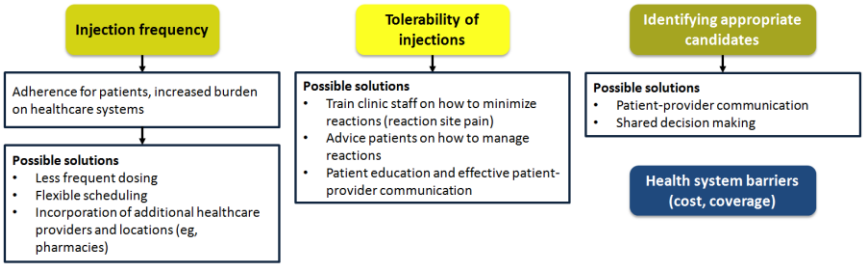
Long-acting CAB + RPV Is Contraindicated With Select Drugs

Food and Drug Administration (FDA). January 2021. Accessed June 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf

Yellow Line: Emerging Long-Acting Injectable ART

Pearls and Pitfalls: Addressing Practical Challenges to Long-acting Injectable ART

So, some of the pearls and pitfalls of addressing practical challenges in using long-acting injectable ART have been some of the following ideas. Providers with long-acting injectable ART clinical experience suggest that the major barriers to real-world implementation really lie around injection frequency.



So that if patients are actually injected once a month, there needs to be a system set up so that person's going to actually understand how to remember to come in for the injection so they don't have lower levels of medication and that there needs to be some sort of reminder systems for that to actually happen. But also flexibility in the clinic schedule to be able to offer this.

Tolerability of injections actually works pretty well. Again, like I mentioned, the biggest problem has been injection-site reactions and what has been found with this is that oftentimes patients can actually find ways to decrease those by using cold or perhaps sometimes heat or by taking an oral anti-inflammatory medication, such as ibuprofen, prior to this, to be able to decrease those injections sometimes.

Probably the most important thing is to really sit with the patient and talk with them about the pros and cons of injectable therapy because this is something that may sound great, but patients really need to hear the reality of what the injectable medication's all about. So, I think that's another way to identify the most appropriate candidates by having a heart-to-heart discussion in which shared decision-making is a part of that process.

SLIDE 70

Logistical Barriers Will Need to be Addressed to Support the Use of Long-acting Injectables in HIV Treatment

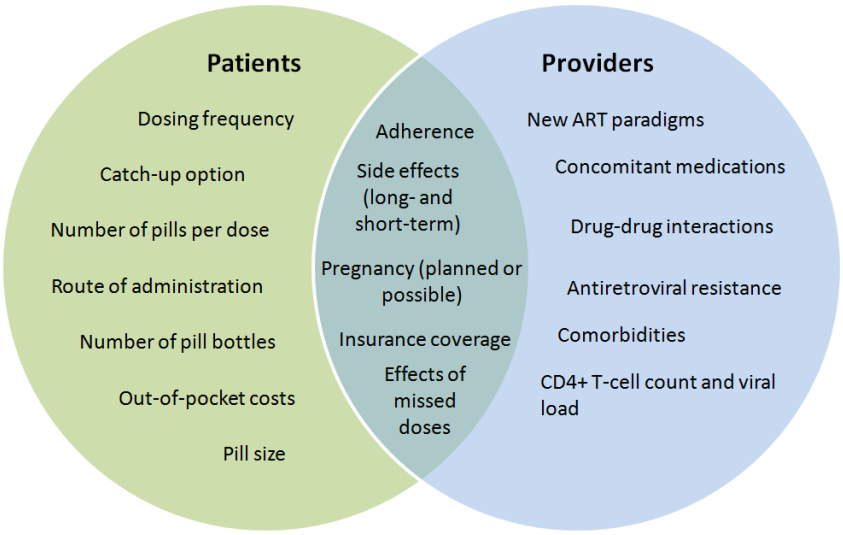
Providers with long-acting injectable ART clinical trial experience suggest that the major barriers to real-world implementation are as shown in the chart.

Mantsios A et al. BMC Health Serv Res. 2021;21(1):255.

Green Line: Optimizing Patient Outcomes: Selection of Patient-centered ART

ART Selection: Engaging in Shared Decision Making

Dr. David Wohl: Let's talk about optimizing patient outcomes and the selection of patient-centered ART. So, how do we choose the right drugs for the right people? And part of this is doing something that many of us already do, but for which there's a science that underpins the benefits of doing this, and this is called shared decision-making.



SLIDE 73

A Shared Decision-Making Approach to Treatment is Needed to Ensure Patient and Provider Concerns are Both Addressed

Yelverton V et al. AIDS Patient Care STDS. 2018;32(9):240-348.

And while it may be intuitive of what shared decision-making is, when we think about it a little bit more scientifically, we can think about it as patients having things that are really important to them, considerations, concerns, problems. Whereas providers have their own list and sometimes these overlap nicely, but in other cases they don't. And there's many studies that show, when we list patient perspectives of what's important to them vs. what's important to providers, again there's overlap but sometimes they're very disparate. And providers may care a lot about things like substance use and adherence, whereas patients may be thinking more about the struggles in their lives, their mental health issues, the cost, the challenges of getting to clinic.

So, there's a bunch of things that we have to consider from the patient perspective, not ignoring the things that really matter to us as well, that are important to us. But shared decision-making allows us to come to this middle space where we can think about things together. There is shared. It's not placing everything in the patient realm but moving things over from what historically had been pretty much a provider decision to making it a dual decision.

Most PLWH are interested in being involved in decision-making related to their care[a]

- Especially **newly diagnosed patients**

However, many patients do not feel comfortable discussing concerns with their providers because:

- They do not feel that anything can be done
- Their provider never mentioned the issue
- They do not want to appear difficult

Among newly diagnosed patients, **73%** reported that they wanted to be more involved in decisions regarding their treatment, but only **62%** felt informed enough to be involved.

- **One-third** reported that their healthcare provider does not regularly ask them about concerns with their medications

[a]According to a 2019 survey of 2389 PLWH in 25 countries

SLIDE 74

Most PLWH Want to be Involved in Their Care but May Not Know How to Engage

Okoli C et al. AIDS Behav. 2021;25(5):1384-1395.

Most people living with HIV do indicate, as we would imagine, that they want their care to be something that they're engaged in and involved in. Oftentimes, they don't know how to have that happen. And partly this is because some of our clinic visits are abbreviated, we don't have as much time as we'd like to spend with patients. New patient evaluations can be longer and are a great way to establish a foundational relationship where you can engage with one another and have a discussion about what's important to that person and what's important in their life and even understanding their life. Do they work different shifts? Do they go to bed at different times, different days of the week? Who's at home that's supportive? Who's at home that they're trying to hide their HIV from? These are all things that can be put into the shared decision-making mix that will allow you to emerge with a decision that's good for both parties, both the provider and for the patient.

So, there's lots of data that showed this, and I think it's really important that providers be encouraging of partnering with their patients so that, you know, not just treatment decisions, but for all sorts of decisions that have to be made. We've had to talk about flu shots for many years. Now we're having to talk about COVID-19 vaccination. Shared decision-making is a strategy and a tool that we can use for making multiple types of decisions along the course of a person's care.

So, what's involved in the nitty gritty of effective shared decision-making? Well, some of the science that's gone behind this have identified these 6 realms or domains. Situational awareness, the patient's problem is clearly described. Choice awareness, acknowledge that there's more than one

way to do this and that's why we've got to put our heads together and figure out how to proceed. Option clarification, what are the options? Many patients do not know what options are in front of them. If I don't do this, what would I do? Harms and benefits, the pros and cons. This is hard because you don't want to get down into the weeds where a person's petrified of doing anything and there's stasis.

Situation diagnosis	Patient's problem is clearly described
Choice awareness	Clear acknowledgement that there is more than one logical way to address or change the situation and that the patient's input matters in deciding how to proceed
Option clarification	Available options are explicitly listed and described
Harms and benefits discussion	Pros and cons of the available options are clearly explained
Patient preferences deliberation	Patient preferences are explicitly elicited, and discussion is intentionally initiated
Making the decision	Patient is invited to make or defer a decision

So, we need to be able to balance this and provide clearly, here's some of the benefits, here's some of the downsides of making that choice. And the patient preferences, deliberation. Patient preferences that are explicitly elicit. Tell me what's important to you. Is it important that you have something that you can take at night? Is it important that you have something that you can take on the road? Is it something that you don't want to have a food restriction with? Those types of things. And then, making the decision, that the decision is made together, in conference with one another.

There are decision-making tools, because this can be complicated, that can be a road map and some of them are visual, but not all of them include all of these. But the good ones do and some have been validated. More and more, as we have tough decisions to make, it may be that we need to use some of those shared decision-making tools to help our patients understand specifically here their ART choices.

SLIDE 75

Effective Shared Decision-Making Requires Patient Education and Engagement

Shared decision-making aids can be employed to support discussions, but most do not include all 6 key elements (shown in table)

Wieringa TH et al. Syst Rev. 2019;8(1):121.

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

Green Line: Optimizing Patient Outcomes: Selection of Patient-centered ART

Introduction to Weight Gain with ART Regimens

In this animation, explore the statistics behind common weight gain in patients with HIV who are started on antiretroviral therapy and how you can help them to mitigate these results.

Please view this module in the online course.

Green Line: Optimizing Patient Outcomes: Selection of Patient-centered ART

Barriers to Adherence and Ways to Overcome Them

So, barriers to adherence and ways to overcome them. There's been decades of research looking at adherence to medication separate from HIV medications, but certainly within HIV. We've spent a lot of time thinking about how to get people to a point where they're able to adhere to their medications. Older regimens required a high level of adherence, over 90%, and so much of the work was done to that. With ART being much more forgiving, if you will, there's been less of a stress on people taking their medicines every day or 90% of the time. Again, most of these medications, even if you take them 75% of the time, do a great job of keeping the viral load suppressed. But we don't want to stress or challenge regimens, especially regimens that have a lower barrier to resistance.

Linkage to care is defined as the *completion of an outpatient appointment with a clinical provider with the expertise to treat HIV and prescribe ART*

- Newly diagnosed PLWH should be linked to care within 30 days of diagnosis

Delays in linkage to care may be caused by:

- Insufficient socioeconomic resources
- Active substance use
- Mental health problems
- Stigma
- Disease severity (asymptomatic)

Active facilitation and **maintaining a relationship with the patient** can help improve linkage to care.

In the US, lower rates of linkage to care are observed among:

- Young people
- Black people
- People with injection drug use

SLIDE 79

Efforts to Promote Linkage to Care Must Be Delivered With Both Sensitivity and Persistence

Department of Health and Human Services (DHHS). October 2017. Accessed June 8, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/adherence-continuum-care

Efforts to promote linkage to care, you know, that's really key, and the foundation for adherence to medicines is adherence to care. And so, linkage to care is really the number 1 thing that we have to think about, especially among newly diagnosed folks. How do we get people into care so that we have opportunities to talk to folks, counsel them, make sure decision-making type decisions with them? And there's been a lot of research that's looked at this and some of the barriers that exist. Certainly, delays in linkage to care can be caused by a long list of things and this may be distrust of the medical care system, the complexity of

medical care, financial/economic issues, active substance use that challenges, you know, smart decision-making or helpful decision-making and, with that, mental health problems. People are sometimes stigmatized, either internally or externally, and also people may not feel that there's a need to engage in care if they feel well.

Active facilitation, maintaining a relationship with a patient can help improve linkage to care and that may be with a clinician or it may be with a social worker, it may be with somebody who's working with someone at a shelter or at a jail. There's all sorts of opportunities for someone to make those kind of connections. Be thoughtful, persistent and sensitive to get folks into the care that they need.

Poor retention in care is associated with a greater risk for death and is associated with a variety of factors, including **poor patient-provider relationships**

Strategies to improve retention in care include:

- Case management and social outreach services
- Data-based approaches to identify patients who can be re-engaged with care
- Clinic-wide marketing to improve appointment attendance
- Flexible appointment scheduling and clinic hours
- Financial assistance programs

All clinic personnel play an important role in supporting the retention in care of PLWH by providing a positive patient experience and working collaboratively with patients to overcome barriers to care.

SLIDE 80

Retention in Care Is Important to Improve Survival Rates Among PLWH

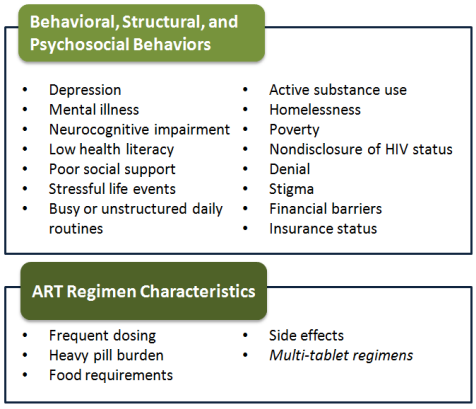
Department of Health and Human Services (DHHS). October 2017. Accessed June 8, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/adherence-continuum-care

Retention in care, as I've already indicated, is really important for people living with HIV. An incredible amount of data shows mostly the same thing. People who miss visits, people who have gaps in their care do not do as well as people who are consistent in retaining in care, coming to their visits. And when we do see that these folks drop out of care, it's often an indication that there may not be a good enough patient-provider relationship or even it may be a poor clinic-patient relationship. It's not just the providers in the back room, the exam rooms, it's everyone from the front desk all the way to the person who takes your vital signs to the person who draws your blood. These things are important for maintaining that relationship and that support that makes someone feel welcome, that pronouns we use, the way that we address people, the acceptance level that people feel when they come into our clinic. Is it a welcoming space? It is some place that cares about me? Loads of messages can be sent within an instant of walking into a clinic. These are hard, but again,

we really want to make sure that we keep people in care because it helps them tremendously over the long haul of what is a lifelong battle for people living with HIV.

Many strategies have been looked at. The Department of Health and Human Services document which is really a wealth of information goes through some of the strategies, some evidence-based, that show how you can retain people in care with the right tools at your disposal.

Adherence is a tough one because it's pretty easy to wag your finger and say you should be taking your medicine and all of us fall into that, that group of you should be doing this, you should be eating less fatty foods, you should be exercising more, you should be, you should be.



Strategies to address nonadherence include:

- **Patient self-reporting**: ask about adherence in a simple, nonjudgmental, routine, and structured format that normalizes suboptimal adherence
  - Ask about the number of missed doses within a given period
- **Reviewing pharmacy records**
- **Electronic measurement devices**
  - Bottle caps, dispensing systems

Pill counts **are not** recommended

SLIDE 81

Adherence to ART Should be Regularly Assessed in a Constructive, Nonjudgmental Manner

Department of Health and Human Services (DHHS). October 2017. Accessed June 8, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/adherence-continuum-care

And with adherence, we can do the same thing but most of the research shows it doesn't work very well to do that and improving adherence has been hard to do. There's lots of interventions that have been tried; not too many that have been shown to really make meaningful differences in people being able to take their medicines. And what I think we're dealing with is folks are swimming up a stream where the current against them is pretty strong. There's stuff that's going on systemically, structurally in our neighborhoods, in our communities and even in our country that really do make it hard for people to prioritize taking a pill every day, believe it or not. And some of those are within the domain of the individual, some are their relationships with other people, some are within their neighborhood or community and some are writ large.

So, with the individual, it could be their depression, their mental health issues, neurocognitive impairment, all sort of things like that. The stress of the individual living in a society where people stigmatize them or discriminate against them or police harassment. There's so much that's going on. Thinking about food insecurity, how can you even think about taking your medications every day when you want to get your viral load

down and your CD4 cell count up when you don't have enough food or you're worrying about feeding others. The list goes on.

It's very hard to deal, short of a revolution, with all those issues. We can only do what we can do and the nexus of control for us in a clinic is the individual in front of us and the people in the other rooms next to us that can help us. The social workers, the counselors, you know, the people in the community that can help support these people. And that's what we have to bring to bear. This is complicated work. This is not easy and it's going to take some time, but we don't want the wag the finger approach. We want to understand where people are coming from and we want to be, as much as possible, nonjudgmental. Many people have trouble taking their HIV medicines. What about you? How is it going? I saw that your viral load was a little bit up last time, is something getting in the way? I know that your mom got sick from COVID-19 and you were taking care of her and it bummed you out. That impact you taking your medicines? It's a much more welcoming, accepting and solution-driven approach rather than the more punitive or you should be doing.

We don't want to be police, we don't want to count people's pills. You know, we can review pharmacy records, we can get an indication of something to talk about, but I do think, you know, if people's viral load starts going up, that's pretty much all you need to know.

Addressing nonadherence requires a multidisciplinary approach, time, and good patient-provider relationships.

Key components of **strategies to improve treatment adherence** may include:

- Patient education
- Social support (eg, transportation assistance, nurse case managers, substance abuse therapy)
- Payment assistance programs
- Counseling
- Development of a treatment plan that the patient can commit to (via shared decision making)
- Establishing a relationship built on trust and compassion
- Maintaining regular communication (eg, text reminders)
- Positive reinforcement
- Regular biologic monitoring (assess viral load at each visit)

SLIDE 82

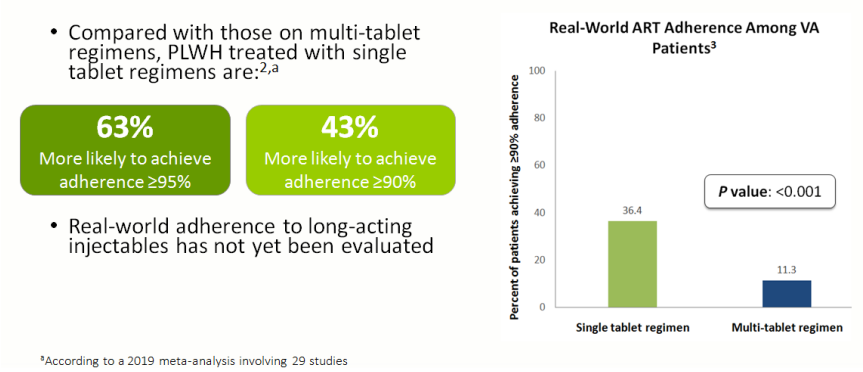
Strategies to Improve ART Adherence Should Be Tailored to the Individual Needs of the Patient

Department of Health and Human Services (DHHS). October 2017. Accessed June 8, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/adherence-continuum-care

Strategies to improve adherence, again, long list of things that have been tried, not too many have stuck. But there are some fundamentals here. I think it doesn't take too much to think that a good relationship with your patient, the welcoming that we've talked about and some of the simple things, whether it be offering up a pill box, whether it be helping someone program their phone to remind them to take their medications.

Strategies like, well, if you brush your teeth twice a day, maybe put your medicines next to your toothbrush or in your shoes or wherever you can remember it. Is it a memory issue or is it something else? Is it something that, you know, you don't like the medication because it makes you have gas or it makes your belly upset? Let's think about those things and let's problem solve together.

One thing we do have at our disposal is making it a lighter lift. If we can have people take medications that are easier to take, then maybe they'll take them more easily and there are, believe it or not, studies that show exactly that.



SLIDE 83

Treatment Simplification to Improve Adherence Is an Indication for Changing Treatment[1]

[1]Department of Health and Human Services (DHHS). December 2019. Accessed May 28, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/initiation-antiretroviral-therapy?view=full
[2]Altice F et al. Patient Prefer Adherence. 2019;13:475-490.
[3]Yager J et al. AIDS Patient Care STDS. 2017;31(9):370-376.

If you simplify the regimen, taking it, it's not earth-shattering to believe that if you take someone on a multi-tablet regimen and switch them to a single tablet, that (a) they like it and (b) they take it better. The field is moving towards not even daily, 1-pill-a-day therapy, 365 pills a year, but can we take a pill every week or can we take a shot every month or every 2 months or an infusion every 6 months or maybe a shot every 6 months? This is where the field is moving because people don't want to take something every day. Not only is it a nuisance for some folks and difficult for many, but it's also a reminder. We don't think about it and it's not something you ask about, but every time someone takes that 1 single tablet, they may be reminded that they have HIV and that may not go over well with them, with their inner voice, with their psyche. There may be internal stigmatization. There may be guilt. There may be something that's rubbed off in the way people are perceived that makes them not feel good when they think that they have HIV. And so this is a reminder and it's hard for us who aren't living with HIV to think about that.

So, I applaud these efforts to go to, you know, less than daily therapy, something that could be given intermittently, something that could be long-lasting. And that again is where the field is definitely moving

Green Line: Optimizing Patient Outcomes: Selection of Patient-centered ART

Optimizing Access and Addressing Disparities

What about optimizing access and addressing disparities? Supportive services are key and none of us can practice HIV medicine in a vacuum. This is not just a clinical entity. This is not just biology and we give antiretrovirals that decrease the replication of virus and then we have people's T-cell counts rebound.

Recognizing and overcoming cost barriers

Connecting patients with resources

Flexible appointment scheduling and transportation

Counseling to overcome stigma, substance use disorder, or mental health issues

Addressing the unique needs of underserved populations

There is so much more that's wrapped around that kernel of the biomedical that has to be thought about and that's part of effective treatment of HIV. Just as effective and just as meaningful as a potent antiviral is the wraparound services that are there to support people in taking their therapy, in achieving those goals.

So, we have to understand about all these different things that we all are grappling with and, unfortunately, HIV medicine today is not so much which is the right antiviral and what, how does it work and resistance, it's how do I find a medication that is covered by my patient's insurance or public health plan. How do they get it? Can it be mailed? Do they have to pick it up at a pharmacy? Those are the types of things. Does it require them to have more monitoring because transportation's tough? Can they hide it pretty easily if they're trying to, you know, not let other people know that they're taking these medications? Does it have a high barrier to resistance because they're challenged in taking their medications? Those are the kind of things that we have to think about and where we need a deep bench of resources to help us deliver that care.

SLIDE 85

Support Services Can Be Engaged to Help Optimize Access to HIV Treatment

Department of Health and Human Services (DHHS). October 2017. Accessed June 8, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/adherence-continuum-care

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

Case Study 1: Treatment Naïve

Dr. David Wohl: Let's talk now about specific cases and talk about patient selection criteria for both new and emerging ART regimens. So, the first case study is a treatment-naive person living with HIV infection and this is Kevin. So, Kevin is a treatment-naive, 28-year-old male who was diagnosed recently with HIV. He is experiencing housing instability due to substance use. He uses alcohol and crack cocaine. He lives in a shelter. He sometimes lives with friends who let him stay for a week or two on their couch. He doesn't have any underlying comorbidities. He's a smoker, he's smoking about a pack per day now. And the goal, when we talk about Kevin, is to get him on a regimen, of course, that could get his viral load down, that he can take and that has durable qualities, right? We want it to be something that he can take that's simple, that's easy, high barrier to resistance. If he doesn't take it exactly the way he should, that it's forgiving, if you will.

SLIDES 88-91

Case 1: Treatment-naïve PWH

Kevin is a treatment-naïve 28-year-old white man who was recently diagnosed with HIV: Case covers initiating simple ART, laboratory evaluation, treatment and follow-up

Laboratory Evaluations

CD4+ cell count: 623 cells/µL
HIV RNA levels: 550,000 copies/mL
Other measures:

- HBV sAg positive; HBV viral load 11 IU/mL
- HCV Ab negative
- Creatinine 0.9 mg/dL
- ALT 43 mg/dL

So, what do know about Kevin's HIV? So, his CD4 cell count is 623, his HIV RNA level is quite high, it's over half a million. The other thing we learn on testing is that Kevin, unfortunately, has been infected with hepatitis B and has chronic active hepatitis B with a detectable hepatitis B viral load. His surface antigen is positive. He is, fortunately, hepatitis C-negative. His renal function's good, his ALT is at upper limit of normal but okay.

Treatment

Viral RNA >500,000 copies/mL and HBV+ status exclude DTG/3TC

- HLA status unknown, avoid DTG/ABC/3TC

Other considerations to facilitate discussion

- Viability of immediate start depends on clinic resources
- STR to improve adherence
- After a shared decision-making discussion, Kevin is started on the STR **BIC/TAF/FTC**

Kevin is also provided resources on substance and alcohol use disorder counseling and connected with local housing resources

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So, here we have a viral load that's over half a million and he's hepatitis B-positive. So those are 2 things that we have to think about right away when we're thinking about HIV therapy. And if precludes dolutegravir/3TC and maybe the dolutegravir/3TC would be fine at a higher viral load; it's just not been studied as much as people who have lower viral loads than that very, very high level. But the hepatitis B is the deal breaker because dolutegravir/3TC, even though 3TC has some activity against hepatitis B, it's insufficient and resistance develops pretty quickly. And so it's a suboptimal regimen for hepatitis B.

So, that's off the list. We don't know his HLA B57-01, so we would avoid abacavir, but most of us would avoid abacavir anyhow, it doesn't seem to add as much and there's alternatives that we think about, basically it can be TDF or TAF. Other considerations to facilitate our discussion is the viability of starting therapy right away and that depends upon what resources are available and, thinking about, can we get him on 1 single tablet. That would decrease the burden for him of maintaining bottles and refills and all that sort of stuff.

So, Kevin and you talk about this. We talk about what's important for him. He wants to be able to have a medication that's compact, easy to take, doesn't cause him side effects. He'd like a single pill. He doesn't want multiple pill bottles. All the types of things that most anyone would want. And so we prescribe him a single tablet regimen, high barrier to resistance on our end, really potent on our end. On his end, it's simple to take, it's a smallish pill, very low risk of side effects, so BF/TAF. He's also provided with resources on substance use and alcohol use, counseling and he's connected with some local housing resources, the best our clinics can do oftentimes.

But he does miss his next follow-up appointment. We start him on the medicine, we wanted to see him back in 2–3 weeks. He doesn't come, so someone was able to connect with him from the clinic. There's all sorts of ways that this can happen. Maybe somebody texted him after hours. He was not in any place—he wasn't in a shelter during the daytime because they kick people out of the shelter—he was on the street, he didn't have a way to be connected. But in the evening, maybe he is more reachable. So, someone thought to text him in the evening and got him on the phone.

Follow-up

Kevin missed his next follow-up appointment

A nurse was able to connect with him to reschedule the appointment

His HIV viral load after 6 weeks on treatment has been reduced to **102 copies/mL**

HBV viral load undetectable

To improve follow-up adherence moving forward:

- Incorporate regular engagement and communication (through EMR portal, text reminders)
- Ensure Kevin has connected with social support services for SUD/AUD and housing support
- Recommend additional counseling, such as support groups for PLWH

His viral load, when he was able to come in after 6 weeks on treatment, was down almost, almost, almost undetectable. Kevin's been missing some doses right before the viral load was done, probably that's what's happening. Fortunately, his hepatitis B viral load was undetectable. And, you know, talking further with Kevin, saying you've done a great job, we want to get you across the finish line. You know, what else can we do? So, you know, more communication. He gets texts. He may not respond to them right away, but reminders are helpful because he doesn't always remember that he had to come to his appointment. That's how he missed his first appointment. He's got other things that he's dealing with or because he was going to try to get a job in a kitchen and wasn't able to come that day.

Make sure he has the social support services that, you know, to treat the things that really need to be treated and to support his needs as much as we can. Our clinics sometimes only can do so much, but connecting with community resources is really important. And, additional counseling, of course, is going to be helpful. Maybe a support group. Maybe others who are in his situation that you've been able to organize. Many of us have these types of things at our disposal and just have to leverage them as much as possible.

Blue Line: Case Studies: Patient Selection Criteria for New and Emerging ART Regimens

Case Study 2: Switching After Weight Gain

Dr. David Wohl: Let's talk about a case of switching after excess weight gain following starting a new regimen. So, this is Rashida and she's a 62-year-old woman who was diagnosed with HIV a dozen years ago and she was initially started on elvitegravir/cobicistat/TDF/FTC. Worked great, single tablet. She liked it, but was recently switched to B/F/TAF because the provider was trying to avoid some of the drug-drug interactions that can occur with cobicistat. It's a pharmacological booster. The provider was also concerned about being on TDF long-term and she didn't want Rashida to have issues with bone demineralization or to be worried every time the creatinine went up a little bit, is this kind of TDF-related renal injury. So, she switched her to this TAF-based regimen.

Following her treatment switchover, Rashida says she's gaining weight, she's gained about 2 kg in the last 6 months and it's only been since she switched and she hasn't done anything really differently. And she's wondering whether or not switching the medicine led to her weight gain. So, the goal for our shared decision-making conversation here would be to discuss the weight effects of her regimen, specifically with the components that she was on before and what she's on now and how much of that might be contributing to her weight gain.

Laboratory Evaluations and Clinical History
CD4+ cell count: 540 cells/µL
HIV RNA levels: Viral load undetectable
Other measures:

- BMI 28.4 kg/m^2
- Blood pressure 135/80 mmHg
- A1C 6.2%

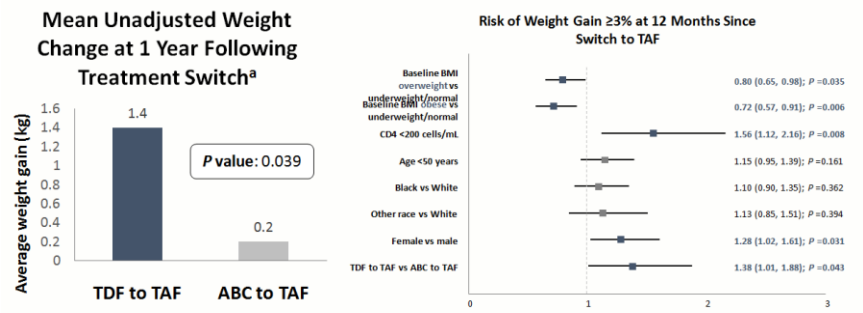
Good news is her CD4 cell count is relatively high, 540. Viral load undetectable. And to give you a sense of what we're talking about, her BMI now is 28.4. Blood pressure is pretty good, A1C's borderline at 6.2%. So, there are some concerns here about Rashida having weight issues. She's overweight by BMI classification strictly, heading, if she continues to gain, towards obesity once we get to a BMI of over 30 in most people and most body shapes, that would be considered obese.

SLIDES 93-97

Case 2: Switching After Weight Gain

Rashida is a 62-year-old Black women who was diagnosed with HIV 12 years ago; following her switch to BIC/FTC/TAF, she is concerned that she has experienced significant weight gain: Case covers laboratory evaluation and clinical history, exploration of a potential cause of weight gain, treatment and follow-up

Well, there are data we can share with Rashida that may help her make a decision and help us make a decision with her. And while we think of TAF being something that may cause weight gain, we're learning that it's a little bit more complicated and it may be that it's the switch from the weight-suppressive TDF to TAF or something else that may be responsible for this bump in weight. That TDF, if you will, has some anorexic effects, that TDF decreases what would normally be a weight increase that occurs with time. And we've seen this even with PrEP.



[a]According to a study of treatment switching in 970 treatment-experienced PLWH (828 TDF to TAF, 142 ABC to TAF)

SLIDE 95

Weight Change Following Switch From TDF to TAF May Be due to Weight-Suppressive Effects of TDF

Sax P et al. *Open Forum Infectious Diseases*. 2020;7(supp 1):S846-S847.

So, in a nice analysis that was done looking at data from different clinical studies, switching from TDF to TAF was associated with weight gain, much like what we've seen with Rashida on the same sort of, you know, magnitude. Whereas switching from abacavir to TAF wasn't associated with nearly the same type of weight gain because abacavir isn't necessarily as suppressive as TDF is as far as weight.

And this was more profound in some people more than others. And we do see some data that indicate that women are more susceptible to gaining weight once they switch from TDF to something else. There may be other considerations. It's hard to say whether or not race and ethnicity plays a role. Having a lower CD4 cell count also, at the initiation or at the switch, can also be a factor. That may mean these are people who are more profoundly ill, if you will, with HIV who, and their switch happens, and then they gain. Not only are we gaining some weight because we're decreasing the suppressive effects of TDF, but maybe we're getting better control of the HIV and the CD4 cell counts.

So, this is complicated stuff, but it's not just because when you switch to a regimen and you gain weight, the new regimen is making you gain weight. We have to also think about that maybe the regimen that someone was switched from was suppressing their weight and TDF may not be the only drug that does this. There's other data that suggest that efavirenz along with TDF, particularly, might also do this and even

boosted PIs which may make sense, given some of the GI issues that we have with boosted PIs.

Treatment

Discuss weight effects of TDF and TAF

- TDF as a **weight suppressant**, rather than TAF as a cause of **weight gain**

Removal of TDF is cause of weight gain rather than initiation of TAF

Consideration of other risk factors for weight gain

- Sex, baseline BMI, age

So, we discuss this. It's a complicated conversation. Rashida understands these are the issues. She's on a good regimen. There are downsides to switching her back to TDF. There are downsides to switching her back to a pharmacological booster and there may be some things that we can do to help Rashida lose some of the weight that she's gained. And she hasn't tried yet. So, you know, again, having her understand some of the issues is going to be key as we make this shared decision-making.

Follow-up

After discussing the causes of weight effects associated with switching from TDF to TAF, Rashida agrees that a treatment switch is not needed

Counseling is provided on managing weight gain with treatment switch

- **Lifestyle considerations**: Diet, exercise, day-to-day activities

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What did we discuss at the end? Well, that maybe trying lifestyle changes. Let's look at your diet. Let's cut out some of those excess calories. Can we do a little bit more exercise than we're doing right now? Can we take the stairs instead of elevators? Things like that. And Rashida, she's all in. We got a nutritionist to talk to Rashida about her diet and we did talk to her about, you know, is there a YMCA nearby that she could join and that's affordable and Rashida says there is. These are things that we can help, little things that can add up in a big way rather than switching her medications or implicating a medication, like TAF, in her weight gain, maybe unnecessarily.

Case Study 3: Overcoming Pill Fatigue

Dr. David Hardy: Now, let me move on to a couple of cases that I hope will be able to illustrate some of the points that I've made in terms of ART, in terms of new antiretroviral therapy advancements. Let me go over a case that really illustrates some of the strategies for overcoming pill fatigue and present to you Lucas. He's a 30-year-old Hispanic man who was diagnosed with HIV 5 years ago. At diagnosis, his viral load was high at 580,000 copies and his CD4+T cells were low at 170. For this reason, his provider started him boosted darunavir and TDF/FTC. He remained adherent on this regimen when started in 2013 and his viral load became undetectable and his T cells increased over 650. In 2019, when the single tablet regimen for his components came out, he was switched to the single tablet regimen of darunavir, cobicistat, TAF and FTC. At his most recent visit, Lucas is now starting to describe difficulty with maintaining adherence to this daily pill regimen. Along with more common loose stools requiring medication to stop the stools, like diphenozylate/atropine, in order to maintain his good adherence with the medication. While he still comes in for his regular check-ups and admits, he does admit, however, at these times, that he's been missing medications more commonly. So, the goal here is really to address his pill fatigue, his gastrointestinal side effects and to find ways to improve his adherence.

SLIDES 99-102

Case 3: Overcoming Pill Fatigue

Lucas is a 30-year-old Hispanic man who was diagnosed with HIV 5 years ago; Lucas reports increasing difficulty with maintaining adherence to his daily regimen along with more common loose stools: Case covers laboratory evaluation and clinical history, treatment and follow-up

Laboratory Evaluations and Clinical History
CD4+ T cell count: 650 cells/µL
HIV RNA: 43 copies/mL
Other measures:

- Blood pressure 150/96 mmHg
- Creatinine 2.0 mg/dL
- Hgb A1c 6.7%
- TSH 4.7 mU/L

Hypertension currently managed with a thiazide diuretic

In discussions, Lucas also suggests that he believes that part of his problems with adherence may be related to symptoms of depression

- Depression developed over the last 6 months or so

Currently, his CD4 cell count is 650, his viral load is showing a small probably blip at 43 copies, his blood pressure's a little high at 150/96, his creatinine is 2.0, hemoglobin A1C is 6.7 and his TSH is normal at 4.7. His hypertension is being now managed with a thiazide diuretic. And in discussion, Lucas also believes that he may have problems with

adherence, maybe related to some symptoms of depression, because he does also admit to some typical symptoms that have been occurring over the past 6 weeks or so.

Treatment

Facilitate shared decision-making to promote treatment adherence

- Providing education on importance of adherence for maintenance of viral suppression
- Connecting Lucas with resources to manage his new onset depression (counseling, psychiatry consult)

Discuss options for ART regimen change to improve adherence and address side effects is an indication for treatment-switching

- BIC/TAF/FTC
- CAB/RPV- LA

So, during this visit and over the next few visits, discussion is made about ways to try to improve his adherence, to provide education on importance of adherence in maintaining viral suppression and also, importantly, because depression can be a big problem for adherence as well, is to connect Lucas with resources to manage his new-onset depression, both counseling and a psychiatry consult.

In terms of his ART adherence, regimens that can improve this are discussed with him in terms of addressing side effects and also in terms of adherence. So, 2 regimens are actually brought forward. One is a single tablet regimen of bictegravir, TAF and FTC, a regimen that actually would eliminate probably his gastrointestinal side effects but would also maintain a daily oral medication. We also talked about with him the use of monthly cabotegravir/rilpivirine long-acting injections as a way to both improve his gastrointestinal side effects but also eliminate his pill fatigue.

Follow-up

After discussing treatment options with Lucas, you decide together to initiate long-acting CAB/RPV injectable therapy after an oral lead-in

- Lucas is educated on the importance of adherence to maintain therapeutic doses

Using the EMR portal to promote adherence

- Sending monthly text reminders

Maintaining regular follow-up

So, after discussing various treatment options with Lucas, including the 2 just mentioned above, we decide together to initiate long-acting

injectable cabotegravir and rilpivirine after a brief oral lead-in to make sure he tolerates the medications well before advancing into the injectable medications. Lucas is also educated on the importance of maintaining adherence which means that now, instead of taking an oral medication every day, he needs to come in for a visit at least once a month to get his injection—and more often if other health issues come up.

We start to utilize our electronic medical record portal to be able to promote his adherence by sending him monthly text reminders from both the clinic and from the pharmacy to make sure that he is continuing to get regular injections and also maintain regular follow-up. Lucas really enjoys the less complex injectable regimen. He has been able to maintain minimal injection-site reactions and is really enjoying his ability to no longer have the same kind of adverse events and the trouble of maintaining oral medication on a daily basis.

Case Study 4: Simplifying Treatment Regimen

Dr. David Hardy: Now, let me also present to you a case about managing virologic resistance. Clara is a 43-year-old African American woman who was diagnosed with HIV 7 years ago. She is currently being treated with a mega-HAART regimen, including raltegrovir BID, atazanavir boosted with ritonavir, etravirine given BID and TAF/FTC. This is because she had some difficulty with previous complex regimens and has developed resistance to several agents.

Recently, she was promoted at her work and says that it keeps her much busier and that the treatment regimen, once again, has become too cumbersome. While she tries to stay adherent, she notes that she has been missing more doses, frequently, and would like a simpler antiretroviral regimen. So, the goal for Clara is to do treatment simplification, if possible, in the midst of managing some pretty significant antiretroviral resistance.

SLIDES 104-112

Case 4: Managing Virologic Resistance

Clara is a 43-year-old Black woman who was diagnosed with HIV 7 years ago and is currently treated with a **"mega-HAART"** regimen which has become too cumbersome: Case covers BRIGHTE trial for multidrug resistant cases, laboratory evaluation, treatment and follow-up

Laboratory Evaluations and Clinical History

CD4+ T cell count: 350 cells/µL

HIV RNA:

- Current: 3000 copies/mL
- 6 months ago: 900 copies/mL
- 1 year ago: 280 copies/mL

Current and historic HIV genotype testing reveals the following resistance-associated mutations (RAMS):

- NRTI/NNRTI - M184V, M41L, K70R, L210W, K103N, Y181C
- PI - D30N, I50L, V82A
- InSTI - Q148H and N155H

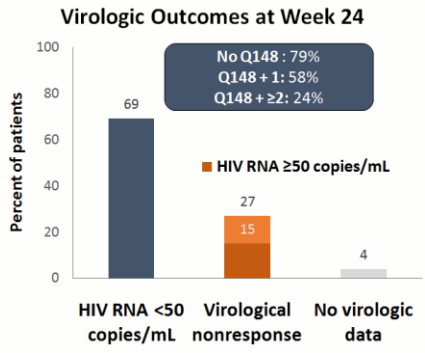
Currently, her CD4 cell count is 350 and her HIV RNAs from the last 3, last month, and her HIV RNA levels over the last year have shown significantly increasing amounts of virus detected in her blood. A year ago, her viral load was 280; 6 months ago it was 900; and currently it's at 3,000 copies/mL. Her current and historic HIV genotype testing reveals several resistance-associated mutations, including NNRTI range, an M184V, an M41L, a K70R, an L210W, a K103N and a Y181C. As far as PIs, she has resistance at the following locations: D30N, I50L and V82A. And most problematic are integrase mutations at Q148H and N155H.

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

- The VIKING-3 trial examined the addition of DTG (50 mg BID) to current ART in adults with HIV RNA ≥500 copies/mL.
  - 20% with Q148[a] +1 secondary mutation[b]
  - 11% with Q148 + ≥2 secondary mutations

Change in HIV RNA Following Addition of DTG to Failing ART Regimen

Outcome	+DTG 50 mg BID (N=183)
Plasma HIV RNA level, log_{10} copies/mL	
Baseline, mean (SD)	4.26 (0.93)
Change from baseline at day 8, mean (SD)	-1.43 (0.61)
P value	<0.001
95% CI	-1.52, -1.34

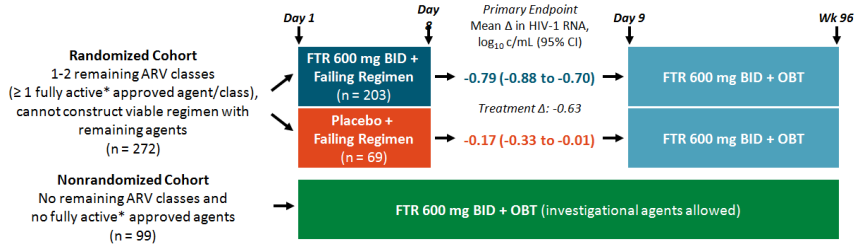


SLIDE 106

DTG-based Therapy Maintains Virologic Suppression in Treatment-experienced PLWH

Castagna A et al. *J Infect Dis*. 2014;210(3):354-362.

So, we know that with these kind of integrase mutations, a Q148 plus one other mutation, that there's still an over 50% response rate in terms of getting viral load undetectable. The VIKING-3 trial demonstrated this, and patients, when they were given dolutegravir on a BID basis, and this is what we think we can actually use to improve part of Clara's regimen.



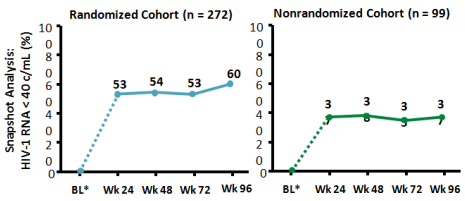
*No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV.

SLIDE 107

BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults With Multidrug-Resistant HIV

Kozal. NEJM. 2020;382:1232. Pialoux. AIDS 2018. Abstr THPEB045.

We also know that fostemsavir has been effective in suppressing viral load in heavily pretreated patients with multi-drug-resistant virus and, at a dose of 600 mg twice a day, that regimen has been actually very effective at attaining undetectability in up to 60% of patients, even out as far as 2 years with increases in CD4 cell counts as well.



- Cumulative safety outcomes through Wk 96 for all treated patients
  - Drug-related AEs: grade 2-4, 21%; serious, 3%
  - AEs leading to d/c: 7%
  - Death: 8%; most due to AIDS-related events or acute infections, 1 deemed treatment-related (IRIS)

Outcome at Wk 96, n (%)	Randomized (n = 272)	Nonrandomized (n = 99)
HIV-1 RNA < 40 c/mL	163 (60)	37 (37)
HIV-1 RNA ≥ 40 c/mL	81 (30)	43 (43)
No virologic data	28 (10)	19 (19)
▪ D/c due to AE or death	15 (6)	14 (14)

*Snapshot analysis excluded BL data; 1 patient had BL HIV-1 RNA < 40 c/mL. AE, adverse event; BL, baseline; d/c, discontinued; IRIS, immune reconstitution inflammatory syndrome.

SLIDE 108

BRIGHTE: Virologic and Safety Outcomes Through 96 Wks

Lataillade. IAS 2019. Abstr MOAB0102.

MAKING STRIDES IN HIV:
OPTIMIZING TREATMENT SELECTIONS AND SWITCH STRATEGIES

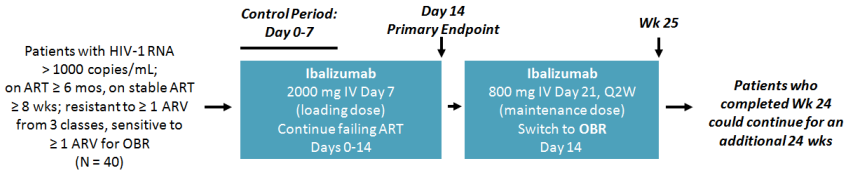
Another potential option would be ibalizumab, an every-2-week infusion of an antibody, monoclonal antibody, which actually blocks the ability for HIV to enter a cell.

SLIDE 109

TMB-301: Ibalizumab in Pretreated Patients Infected With Multidrug-Resistant HIV

Emu. NEJM. 2018;379:645.

- Single-arm, open-label phase III trial in patients with virologic failure
  - Primary endpoint: HIV-1 RNA decrease ≥ 0.5 $\log_{10}$ copies/mL from baseline to Day 14



- 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance
- Mean BL VL 4.5 $\log_{10}$ copies/mL; mean BL CD4+ cell count: 150 cells/mm^3

BL, baseline; OBR, optimized background regimen; VL, viral load.

And this is also a regimen that has been used effectively in many patients. In this situation, however, we do not think this would probably be the best option for Clara because of her busy schedule and the difficulty of coming in for an infusion every 2 weeks.

SLIDE 110

TMB-301/-311: Virologic Outcomes Through 96 Wks

- TMB-311: patients enrolled in US and Puerto Rico who completed 25 wks in TMB-301 continued ibalizumab 800 mg Q2W for up to 96 wks

Virologic Outcome	Day 14[1] (N = 40)	Wk 25[1] (N = 40)	Wk 48[2,3] (N = 27)	Wk 96[4] (N = 27)
≥0.5 $\log_{10}$ HIV-1 RNA decrease, %	83*†	63	NR	NR
≥1.0 $\log_{10}$ HIV-1 RNA decrease, %	60	55	67	NR
Mean $\log_{10}$ HIV-1 RNA decrease	1.1	1.6	2.1	NR
Median $\log_{10}$ HIV-1 RNA decrease	NR	2.5	2.8	2.8
HIV-1 RNA <50 copies/mL, %	NR	43	59	56
HIV-1 RNA <200 copies/mL, %	NR	50	63	NR

*Primary endpoint; $P < .0001$ vs 3% at end of control period. †3 patients without ≥0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14 later reached HIV-1 RNA <50 copies/mL with ibalizumab + OBR.[5]

[1]Emu. NEJM. 2018;379:645. [2]Emu. IDSA 2017. Abstr 1686. [3]Emu. HIV Glasgow 2018. Abstr O345. [4]Emu. CROI 2019. Abstr 485. 5. DeJesus. HIV Glasgow 2018. Abstr P064.

Treatment

Considerations with multi-class virologic resistance mutations

Discussion of treatment options to improve adherence and manage resistance to achieve virologic suppression

- Addition of twice-daily-dosed DTG (VIKING Study)
- Utilize existing ARVs with good activity
- Utilize ARV(s) with novel mechanism(s) of action
- Create dosing symmetry

After discussing options with Clara, she is switched to a **DTG 50mg BID, DRV/c 600mg/100mg BID, FTR 600mg BID** regimen (3 tablets BID)

And so, what we do is consider this, her many multi-class virologic resistance, we discuss treatment options to improve adherence, we add the medication of dolutegravir twice daily as demonstrated by the VIKING study and also fostemsavir twice daily as from the BRIGHTE study that actually have good activity against her virus, we know. And also use medications primarily that have new mechanisms of action from this. We use a regimen that actually will allow dosing symmetry, so that she's taking the same 3 pills in the morning as she's taking in the evening and really simplify her regimen to try to make sure that it's as simple as possible.

So, after discussing options with her, we switch her to a regimen of dolutegravir 50 mg twice a day, DRV/cobi1 tablet 600 mg, 100 mg twice a day and fostemsavir 600 mg twice a day as well. That's 3 tablets, the same 3 tablets, twice a day.

Follow-up

Clara returns for follow-up 3 months after switching treatment

- She reports that she is happy with her new regimen and that it has been easier to remember to take her medication

Her HIV RNA levels have dropped to <50 copies/mL

- She returns at 6 months for continued monitoring; her HIV RNA levels continued to be <50 copies/mL and her CD4+ T cells are now 550/mm^3

Need for continued monitoring and regular follow up

When Clara returns for a 3-month visit, she reports she's happy with her new regimen and she says it's easier for her to take and she's been doing a much better job with it. We note that, at this visit, her viral load is now less than 50 and she returns again 6 months later and finds that her viral load maintains at less than 50 and her CD4 cell count has now increased to 550 cells. We continue to monitor her and follow her regularly and hope that this new regimen will keep her undetectable for a long period of time. Thank you very much.