

A blurred background image showing two hands, one from a darker-skinned person and one from a lighter-skinned person, holding a red HIV awareness ribbon. The ribbon is a looped shape with a vertical bar in the center. The hands are positioned as if presenting the ribbon. The overall image is soft-focused and serves as a backdrop for the text.

Antiretroviral Therapy for the Treatment of HIV

Infectious Disease Conference

The Miriam Hospital

Wednesday, August 5, 2020

Speakers

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Disclosures

- None

Objectives

- Identify the recommended combination regimens for use in antiretroviral therapy (ART)-naïve patients, including disadvantages and advantages for each regimen
- Recognize class-specific and drug-specific pharmacokinetic factors that affect the efficacy and safety of ART
- Review recent updates to the DHHS Adult and Adolescent, Perinatal, and Opportunistic Infection Guidelines
- Summarize future treatment options that are currently in development

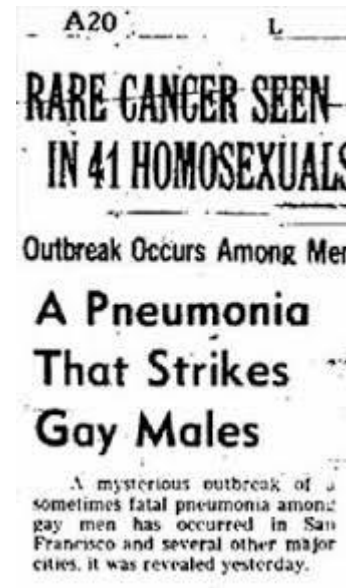
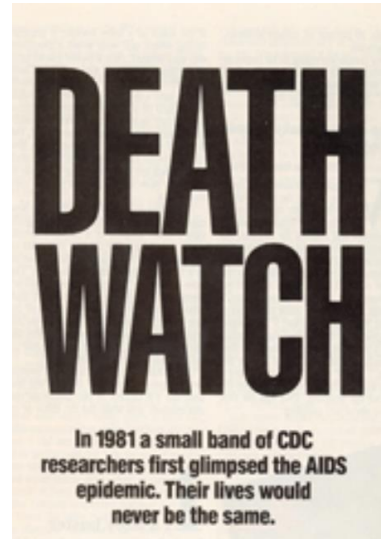
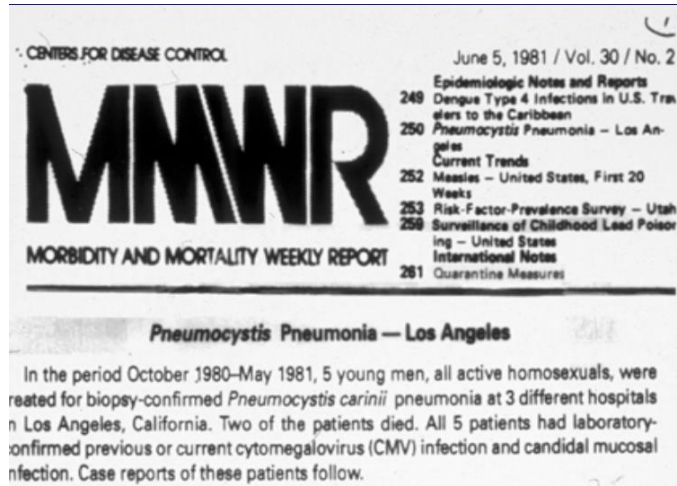
Outline

- Brief History
- When to Treat
- ARV Classes
- First-Line and Second-Line ART Regimens (DHHS & IAS-USA)
- Patient-Specific ART and Clinical Scenarios
- Additional Guideline Updates
- Novel Agents

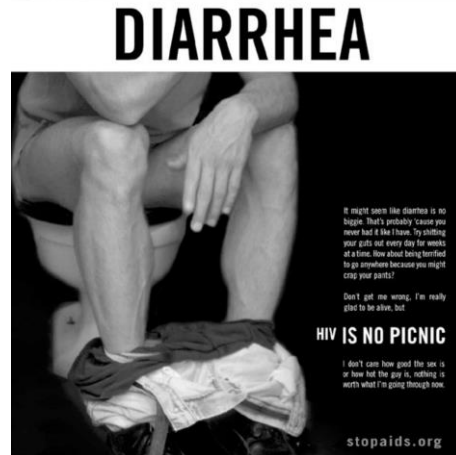
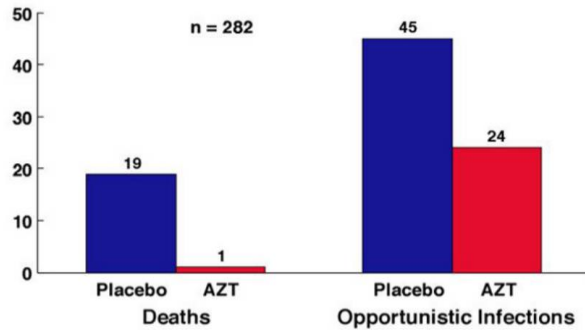


BRIEF HISTORY

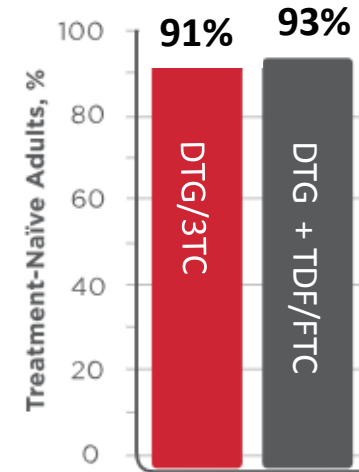
Many Things Have Changed...



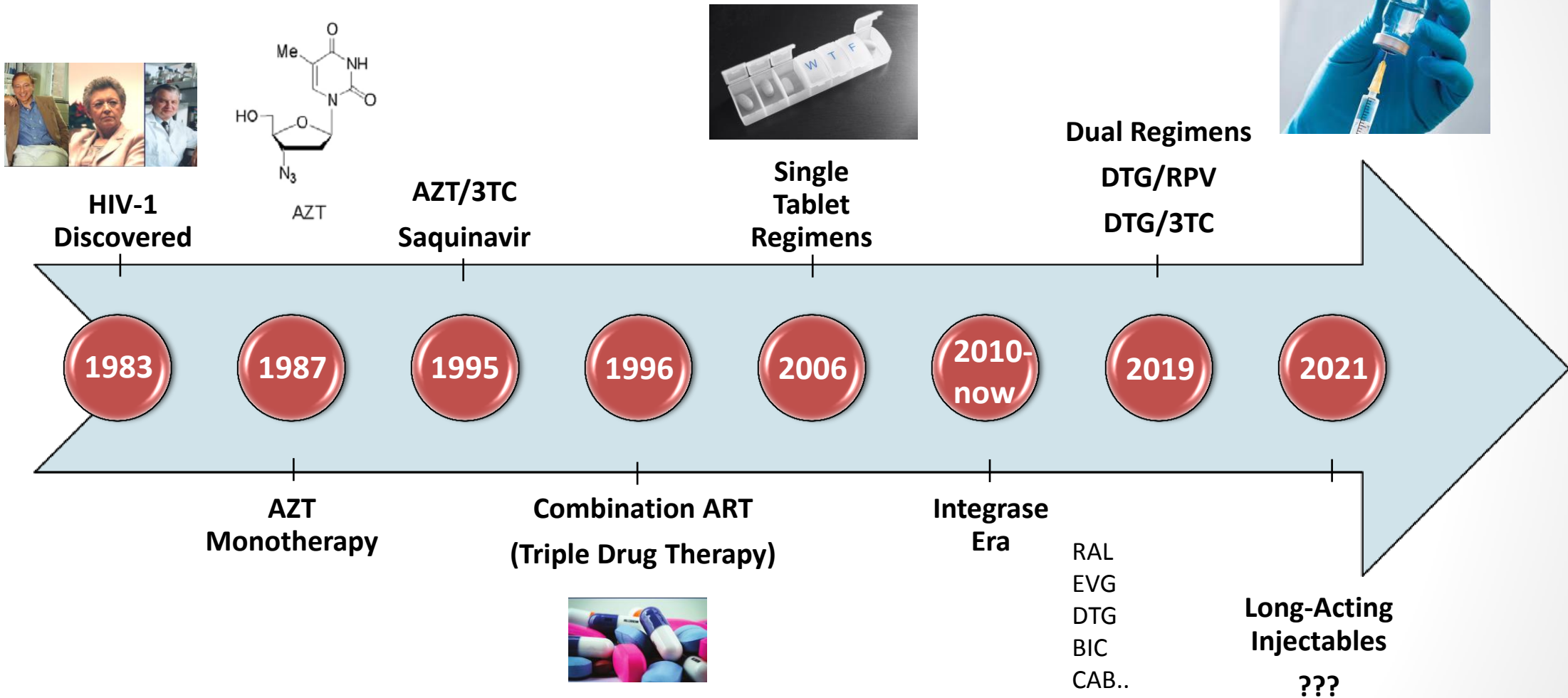
BW 002: 24-Week Study of AZT vs. Placebo in Patients with AIDS or ARC



Virologic Response (HIV-1 RNA <50 copies) DTG/3TC vs. DTG + TDF/FTC



Tales of ART Past, Present, and Future





WHEN TO START ART

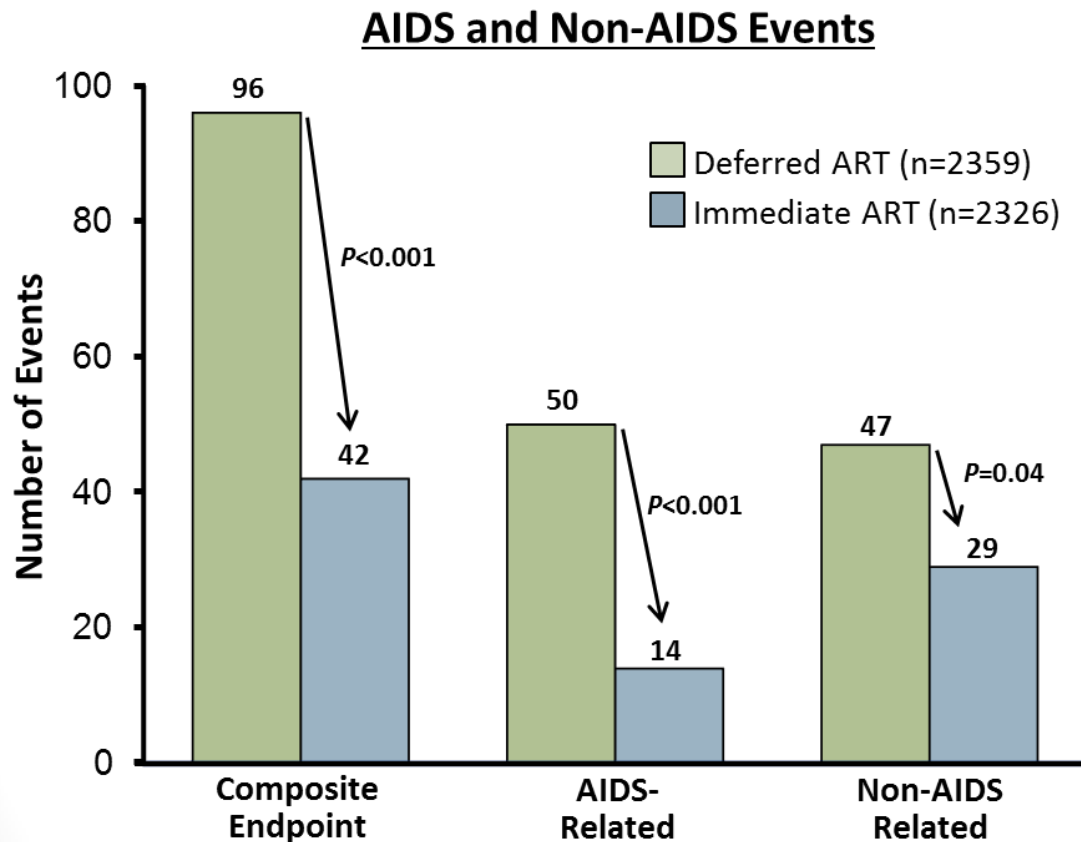
When to Initiate ART

The Swinging Pendulum

CD4 Count (cells/mm ³)	1998	2001	2006	2009	2012	
> 500	Treat if VL >20,000	Treat if VL >55,000	Consider if VL >100,000	Consider in certain patients	Consider in certain patients	Present Treat
350-500	Treat if VL >20,000	Consider if VL >55,000	Consider if VL >100,000	Consider in certain patients	Treat	Treat
200-350	Treat if VL >20,000	Treat	Treat	Treat	Treat	Treat
<200 or symptomatic	Treat	Treat	Treat	Treat	Treat	Treat

Early ART Reduces AIDS and Non-AIDS Events

START



- ART-naïve adults (n=4685)
 - CD4 cell counts >500
 - Randomized to initiate ART immediately or after CD4 count decline to <350
 - Primary endpoint: composite of serious AIDS and non-AIDS events
- Immediate ART reduced risk of serious events or death by 57%
- Most events (59%) occurred in the deferred arm

ART Reduces HIV Transmission Treatment as Prevention (TasP)

- Supported by data from numerous studies from 2008-2016 demonstrating **zero** linked transmissions after >100,000 **condomless** sex acts among serodifferent couples when the partner living with HIV had a viral load **<200 copies/mL**

HPTN 052

PARTNER

PARTNER-2

Opposites
Attract

Advocacy

Undetectable = Untransmittable (U = U)

UNDETECTABLE = UNTRANSMITTABLE



People who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner.

September, 2017

When to Start ART

ASAP

Panel's Recommendations

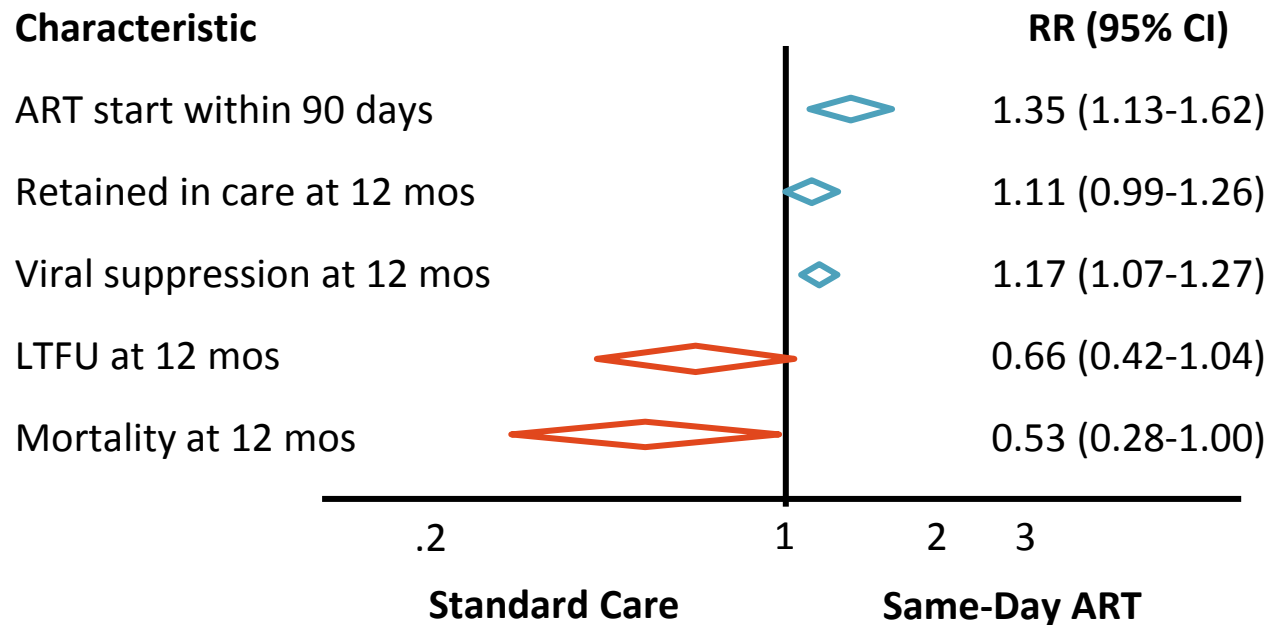
- Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality **(A)** and to prevent the transmission of HIV to others **(A)**
- The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV **(AII)**.
- When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Most urgent patients: Acute HIV infection, pregnancy, AIDS-defining conditions, HBV or HCV co-infection, HIV-associated nephropathy

RAPID Initiation of ART – Systematic Review of RCTs



RAPID ART associated with:

- **Increased** likelihood of ART initiation, retention in care, viral suppression
- **Decreased** likelihood of loss to follow-up and death

RAPID Initiation of ART

- Observational, real-world data in the U.S. is emerging
 - Ward 86 RAPID Start Program in San Francisco
 - CrescentCare Start Initiative in New Orleans
 - Rapid Entry and ART in Clinic for HIV (REACH) program in Atlanta
 - PHARM-D RAPID Program in Providence

PHARMACIST-DRIVEN RAPID ART REDUCES TIME TO VIROLOGIC SUPPRESSION IN RHODE ISLAND

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¹The Miriam Hospital, Division of Infectious Diseases, Providence, Rhode Island, USA
²Alpert Medical School of Brown University, Providence, Rhode Island, USA



CROI 2020
#0498

BACKGROUND

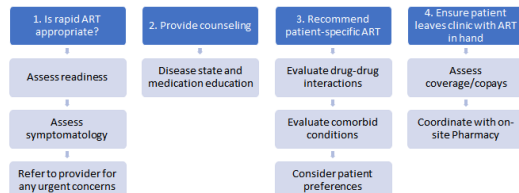
- Rapid start antiretroviral therapy (ART) protocols have emerged as an innovative care model for persons newly diagnosed with HIV (PNDWH). RCT data from Haiti and South Africa and observational data from the US have demonstrated positive clinical outcomes with rapid ART. However, logistical challenges limit widespread implementation and sustainability. Shifting to a model where clinical pharmacists are at the forefront of rapid ART may provide a sustainable solution for the challenges that limit implementation in the US. We began piloting our Pharmacist-Driven RAPID (PHARM-D RAPID) ART Protocol in January 2019
- Study Aim:** To evaluate a novel model for rapid ART implementation driven by Infectious Disease Clinical Pharmacists and its effect on clinical outcomes, including time to HIV viral suppression

METHODS

- Study Design:** We conducted a preliminary retrospective analysis comparing clinical outcomes of PNDWH prior to (1/2017 to 12/2017) and post-implementation (1/2019 to 12/2019) of our PHARM-D RAPID ART Protocol
- Study Site:** The Miriam Hospital Infectious Diseases & Immunology Center is a large, urban Ryan White-funded clinic providing care for >80% of persons with HIV in Rhode Island (over 1,800 patients)
- Statistical Analysis:** Bivariate analyses were conducted using a Student t-test, Wilcoxon rank sum, Chi-square, or Fisher exact test, as appropriate

Pre-Implementation	Post-Implementation
<ul style="list-style-type: none"> Visit 1: Intake visit upon diagnosis confirmation <ul style="list-style-type: none"> Intake team of RN with outreach worker or social worker as needed No RAPID ART 	<ul style="list-style-type: none"> Visit 1: Intake visit upon diagnosis confirmation <ul style="list-style-type: none"> Comprehensive intake team with RN, clinical pharmacists, social worker, outreach worker, and pharmacy liaisons RAPID ART
<ul style="list-style-type: none"> Visit 2: Provider visit and ART initiation 	<ul style="list-style-type: none"> Visit 2: Provider visit and follow-up labs

Role of the Pharmacist



RESULTS

Our PHARM-D RAPID ART Protocol significantly reduced time to HIV viral suppression by 48 days and reduced out-of-pocket costs to patients by \$488,398 annually

Table 1. Baseline Demographics

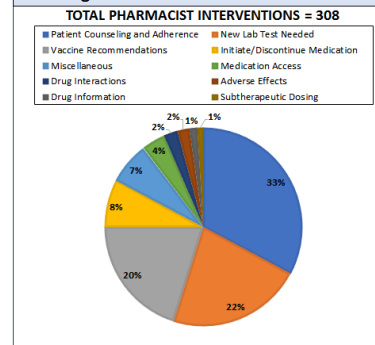
Variable	Pre-Implementation (N=55)	Post-Implementation (N=48)	Overall (N=103)	P-Value
Age (years)				
Median	37 (25-50)	31 (27-45)	33 (26-47)	0.326
Sex at Birth				
Male	48 (87.3)	40 (83.3)	88 (85.4)	0.572
Female	7 (12.7)	8 (16.7)	15 (14.6)	
Ethnicity				
Non-Hispanic	37 (67.3)	36 (75.0)	73 (70.9)	0.389
Hispanic	18 (32.7)	12 (25.0)	30 (29.1)	
Race				
White	31 (56.4)	27 (56.3)	58 (56.3)	0.195
Black	12 (21.8)	16 (33.3)	28 (27.2)	
Other	12 (21.8)	5 (10.4)	17 (16.5)	
Language				
English	45 (81.8)	39 (81.3)	84 (81.5)	0.199
Spanish	6 (10.9)	5 (10.4)	11 (10.7)	
Other	4 (7.3)	4 (8.3)	8 (7.8)	
Insurance Status				
Insured	37 (67.3)	40 (83.3)	77 (74.8)	0.061
Uninsured	18 (32.7)	8 (16.7)	26 (25.2)	
Risk Factor				
MSM	30 (54.5)	27 (56.3)	57 (55.3)	0.861
Substance Use				
Yes	26 (47.3)	29 (60.4)	55 (53.4)	0.182
No	29 (52.7)	19 (39.6)	48 (46.6)	
Mental Health Diagnosis				
Yes	27 (49.1)	27 (56.3)	54 (52.4)	0.470
No	28 (50.9)	21 (43.7)	49 (47.6)	
Baseline CD4 Cell Count				
<200 cells/mm ³ or AIDS Defining Illness*				
Yes	15 (27.3)	8 (17.0)	23 (22.5)	0.217
No	40 (72.7)	39 (83.0)	79 (77.5)	
Median (IQR)†	424 (191-552)	500 (355-605)	451 (250-578)	
Baseline HIV-1 RNA				
≤100,000 copies/mL	31 (56.4)	35 (72.9)	66 (64.1)	0.082
>100,000 copies/mL	24 (43.6)	13 (27.1)	37 (35.9)	
Median (IQR) (copies/mL)	4.88 (4.16-5.59)	4.52 (3.96-5.09)	4.73 (4.14-5.23)	

Table 2. Clinical Outcomes

Clinical Outcome	Pre-Implementation (N=55)	Post-Implementation (N=48)	P-Value
Time to HIV Viral Suppression (days)†	81 (79)	33 (16)	<0.001
Time to Medication Initiation (days)	17 (20)	0 (1)	<0.001
Time to First Scheduled Provider Visit (days)	15 (16)	21 (14)	0.007

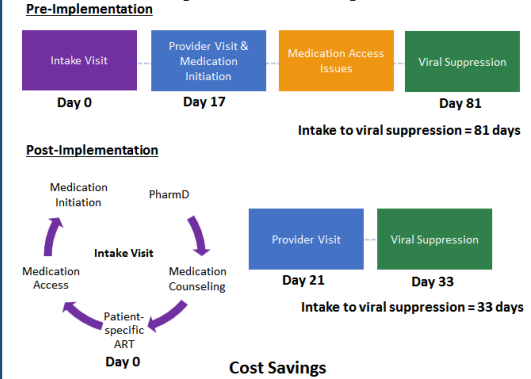
Table 1. Data presented in n (%) or median (IQR)
*HIV-1, 1 person with unknown CD4 cell count
Table 2. Data reported in mean (standard deviation). †Viral suppression defined as HIV RNA <200 copies/mL, time represented as days from intake visit
†IQR in pre-implementation group and 47 in post-implementation group

Figure 1. Pharmacist Interventions



RESULTS

Figure 2. Workflow Diagram



- Access issues were preemptively resolved in 61% of PHARM-D RAPID patients, which reduced potential out-of-pocket costs to PNDWH by a total of \$45,840 on first medication fill and \$488,398 annually; out-of-pocket costs can delay ART initiation

CONCLUSIONS

- Pharmacist-driven rapid initiation of ART significantly decreased time to viral suppression by 48 days (>50%) and time to initiation of ART by 17 days. Our protocol helped patients avoid \$488,398 annually on out-of-pocket ART costs and was not associated with any adverse outcomes
- Clinical pharmacists play an integral role in the care of persons with HIV by providing patient counseling and education; recommendations for screening, vaccinations, and laboratory monitoring; and resolution of drug-drug interactions and medication access issues
- This model may help overcome some of the barriers to implementation cited by previous studies and prevent potential provider burn out
- Data collection is ongoing to evaluate retention in care measures, factors associated with HIV viral suppression, and sustainability beyond 1 year
- Our PHARM-D RAPID protocol demonstrates a novel way to reduce time to HIV viral suppression for PNDWH thereby reducing risk of HIV transmission, an important component of our statewide efforts to achieve 90-90-90 goals

Acknowledgments: This research was supported in part by NIH/NIAD under R25AI140490. Thank you to our multidisciplinary team, including our pharmacy liaisons, clinic social workers, nurses, outreach workers, and providers

RAPID Initiation of ART

Reduce fear and stigma

Accessible treatment for all

PLWH are empowered

Improve confidence in healthcare team

Decrease barriers to care



INTRO TO ARVs

Clinical Resources

- DHHS HIV Guidelines
 - Available at: <http://aidsinfo.nih.gov/guidelines>
 - Adult, adolescent, pediatric, and pregnancy guidelines for treatment, guidelines for prophylaxis for HIV and OI, drug-drug information resource
- IAS-USA HIV Treatment and HIV Resistance
 - Available at: <https://www.iasusa.org/guidelines>
- Stanford Database for HIV Resistance
 - Available at: <https://hivdb.stanford.edu/>
- University of Liverpool HIV drug-interaction database
 - Available at: www.hiv-druginteractions.org

ARV Classes

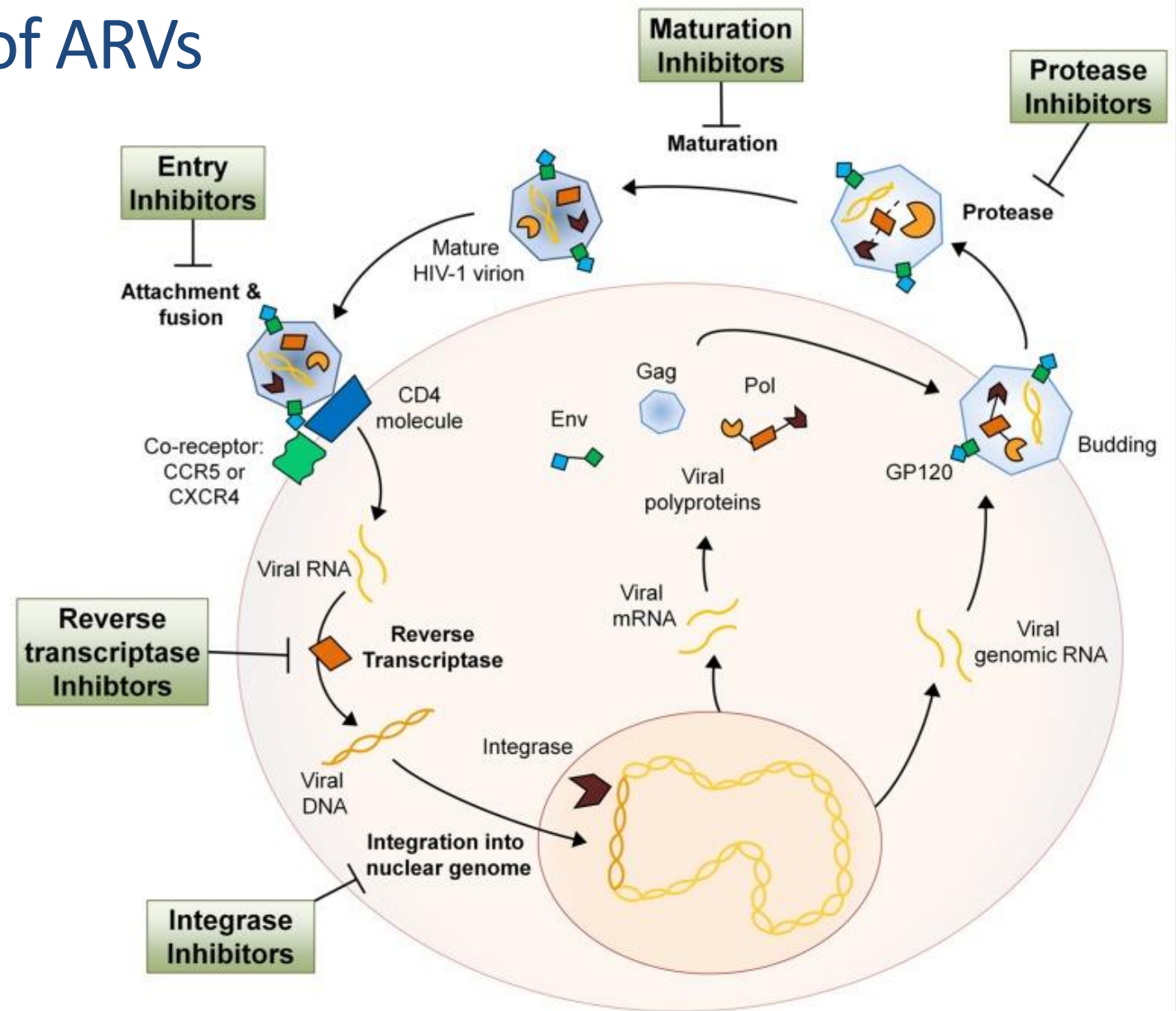
- Entry inhibitors*
 - CCR5 inhibitors, fusion inhibitors, post-attachment inhibitors
- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**
- Integrase strand transfer inhibitors (INSTIs)
 - PK-boosted INSTIs**
 - Non-boosted INSTIs
- Protease inhibitors (PIs)**

*Not recommended in initial therapy

**Recommended in certain clinical situations

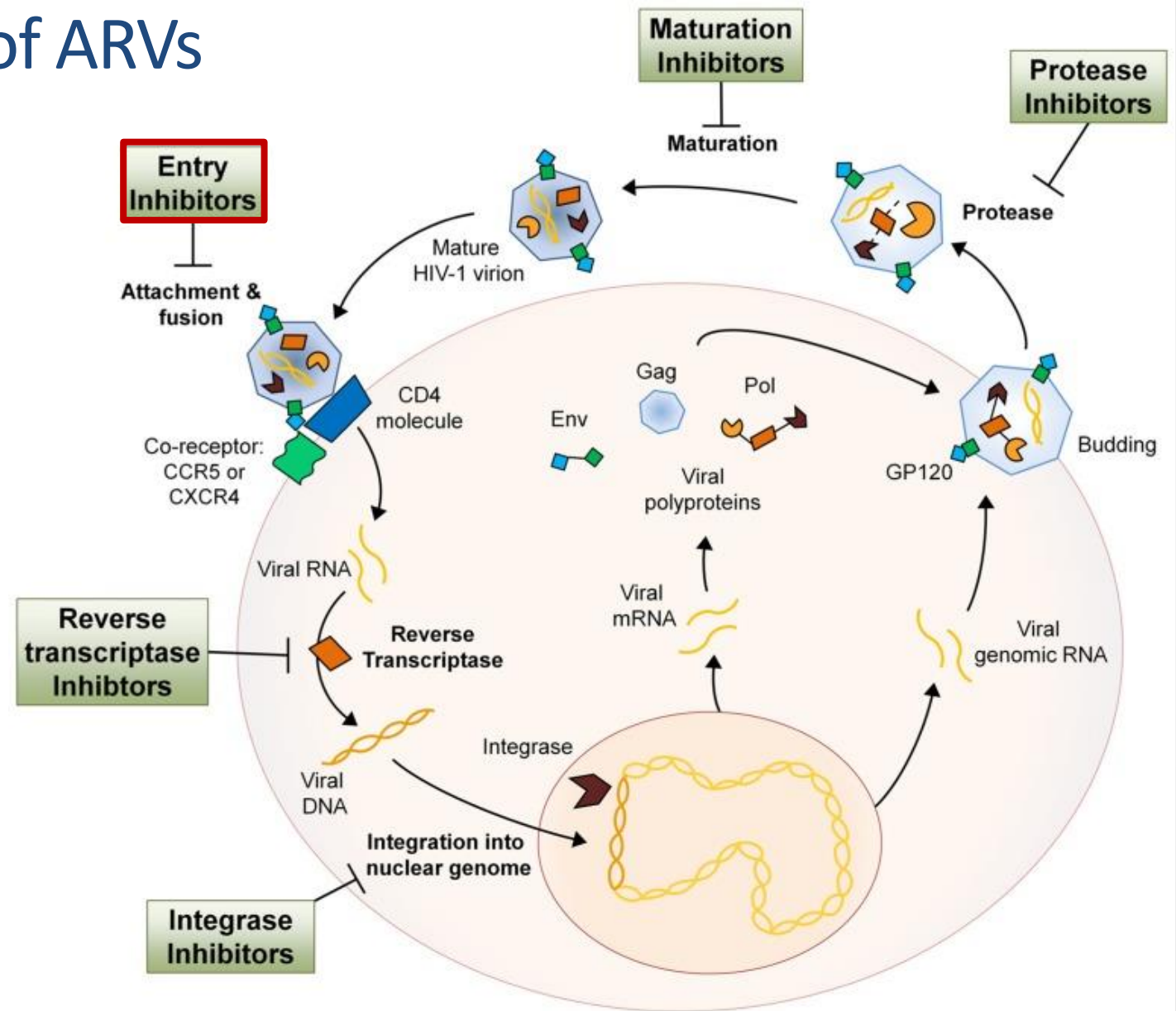
Mechanism of Action of ARVs

- Entry inhibitors
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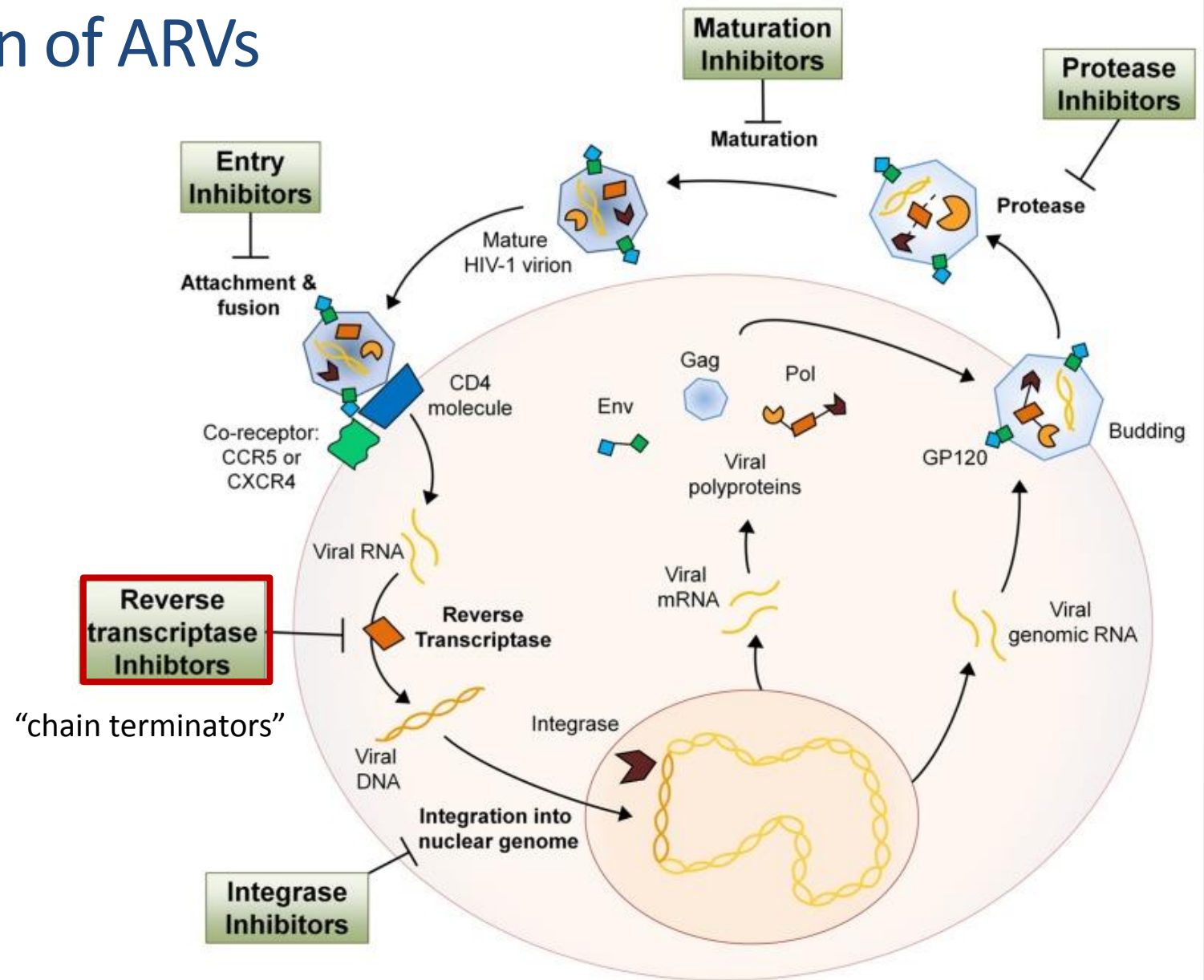
Not For First-Line Use

Generic	Administration	Brand	Abbreviation	Mechanism of Action
Maraviroc	Oral	Selzentry	MVC	CCR5 Inhibitor
Enfuvirtide	Intramuscular injection	Fuzeon	ENF, T20	Fusion inhibitor
Ibalizumab	Intravenous	Trogarzo	IBA	Post-attachment inhibitor, monoclonal antibody
Fostemsavir	Oral	Rukobia	FTR	Attachment inhibitor

Entry Inhibitors

Mechanism of Action of ARVs

- Entry inhibitors
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- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
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NRTIs

Generic	Brand	Abbreviation
Abacavir	Ziagen	ABC
Lamivudine	Epivir	3TC
Emtricitabine	Emtriva	FTC
Tenofovir disoproxil fumarate	Viread	TDF
Tenofovir alafenamide	Vemlidy	TAF
Didanosine	Videx	ddI
Stavudine	Zerit	D4T
Zidovudine	Retrovir	AZT or ZDV


Nucleoside Reverse Transcriptase Inhibitors

First-Line NRTIs

Generic	Brand	Abbreviation
Abacavir	Ziagen	ABC
Lamivudine	Epivir	3TC
Emtricitabine	Emtriva	FTC
Tenofovir disoproxil fumarate	Viread	TDF
Tenofovir alafenamide	Vemlidy	TAF
Didanosine	Videx	ddI
Stavudine	Zerit	D4T
Zidovudine	Retrovir	AZT or ZDV


Nucleoside Reverse Transcriptase Inhibitors

NRTI Combination Products: Make up part of a regimen

Generic	Brand	Abbreviation	Combination Product (Brand)
Abacavir	Ziagen	ABC	
Lamivudine	Epivir	3TC	 Epzicom
Emtricitabine	Emtriva	FTC	
Tenofovir disoproxil fumarate	Viread	TDF	
Tenofovir alafenamide	Vemlidy	TAF	
Didanosine	ddl	Videx	
Stavudine	D4T	Zerit	
Zidovudine	Retrovir	AZT or ZDV	


Nucleoside Reverse Transcriptase Inhibitors

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Emtricitabine	Emtriva	FTC	
Tenofovir disoproxil fumarate	Viread	TDF	 Cimduo
Tenofovir alafenamide	Vemlidy	TAF	
Didanosine	ddl	Videx	
Stavudine	D4T	Zerit	
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Tenofovir alafenamide	Vemlidy	TAF	
Didanosine	ddl	Videx	
Stavudine	D4T	Zerit	
Zidovudine	Retrovir	AZT or ZDV	

Nucleoside Reverse Transcriptase Inhibitors

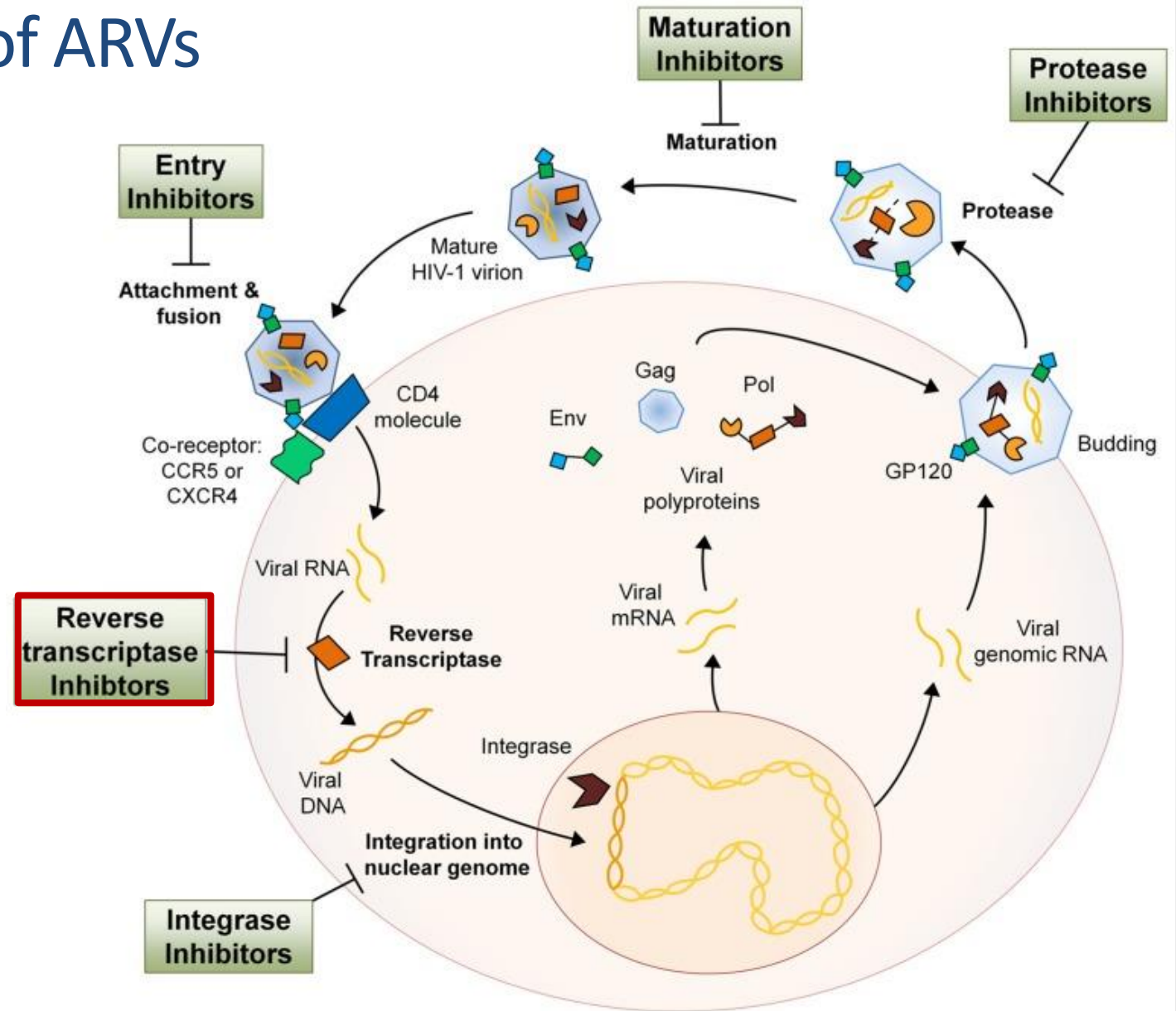
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Tenofovir alafenamide	Vemlidy	TAF	
Didanosine	ddl	Videx	
Stavudine	D4T	Zerit	
Zidovudine	Retrovir	AZT or ZDV	

Nucleoside Reverse Transcriptase Inhibitors

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- Entry inhibitors
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- Protease inhibitors (PIs)



NNRTIs

Generic	Brand	Abbreviation
<u>First Generation NNRTIs</u>		
Efavirenz	Sustiva, component of Atripla ^{1**} , Symfi ^{1**} , Symfi Lo ^{1**}	EFV
Nevirapine	Viramune	NVP
<u>Second Generation NNRTIs</u>		
Doravirine	Pifeltro, component of Delstrigo ^{1**}	DOR
Rilpivirine	Edurant, component of Odefsey ^{1*} , Complera ^{1**} , Juluca ¹	RPV
Etravirine	Intelence	ETR

¹Single Tablet Regimen (STR)

*Contains TAF

**Contains TDF

Non-Nucleoside Reverse Transcriptase Inhibitors

NNRTIs: Consider Using First-Line in Certain Situations

Generic	Brand	Abbreviation
<u>First Generation NNRTIs</u>		
Efavirenz	Sustiva, component of Atripla ^{1**} , Symfi ^{1**} , Symfi Lo ^{1**}	EFV
Nevirapine	Viramune	NVP
<u>Second Generation NNRTIs</u>		
Doravirine	Pifeltro, component of Delstrigo ^{1**}	DOR
Rilpivirine	Edurant, component of Odefsey ^{1*} , Complera ^{1**} , Juluca ¹	RPV
Etravirine	Intelence	ETR

¹Single Tablet Regimen (STR)

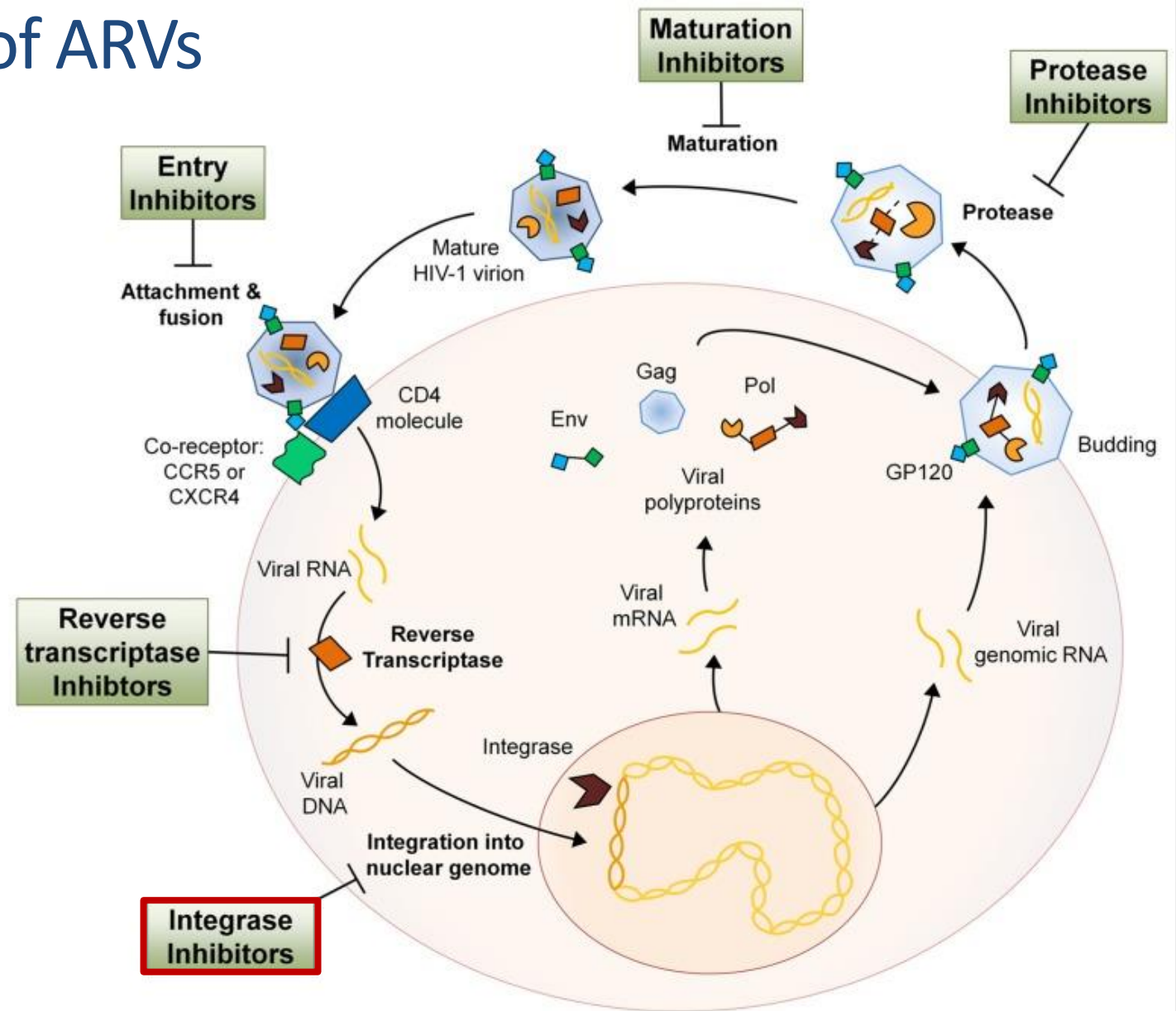
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Non-Nucleoside Reverse Transcriptase Inhibitors

Mechanism of Action of ARVs

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- Integrase strand transfer inhibitors (INSTIs)
- Protease inhibitors (PIs)



INSTIs

Generic	Brand(s)	Abbreviation
<u>First Generation INSTIs</u>		
Raltegravir ¹	Isentress, Isentress HD	RAL
Elvitegravir ²	Component of Stribild**, Genvoya*	EVG
<u>Second Generation INSTIs</u>		
Dolutegravir	Tivicay, component of Triumeq, Dovato Juluca (not for first line use)	DTG
Bictegravir ²	Component of Biktarvy*	BIC

Integrase Strand Transfer Inhibitors ("Integrase Inhibitors")

¹Not available as fixed-dose combination product

²Only available as fixed-dose combination product

*Contains TAF

**Contains TDF

First-Line INSTIs

Generic	Brand(s)	Abbreviation
<u>First Generation INSTIs</u>		
Raltegravir ¹	Isentress, Isentress HD	RAL
Elvitegravir ²	Component of Stribild**, Genvoya*	EVG
<u>Second Generation INSTIs</u>		
Dolutegravir	Tivicay, component of Triumeq, Dovato Juluca (not for first line use)	DTG
Bictegravir ²	Component of Biktarvy*	BIC

Integrase Strand Transfer Inhibitors ("Integrase Inhibitors")

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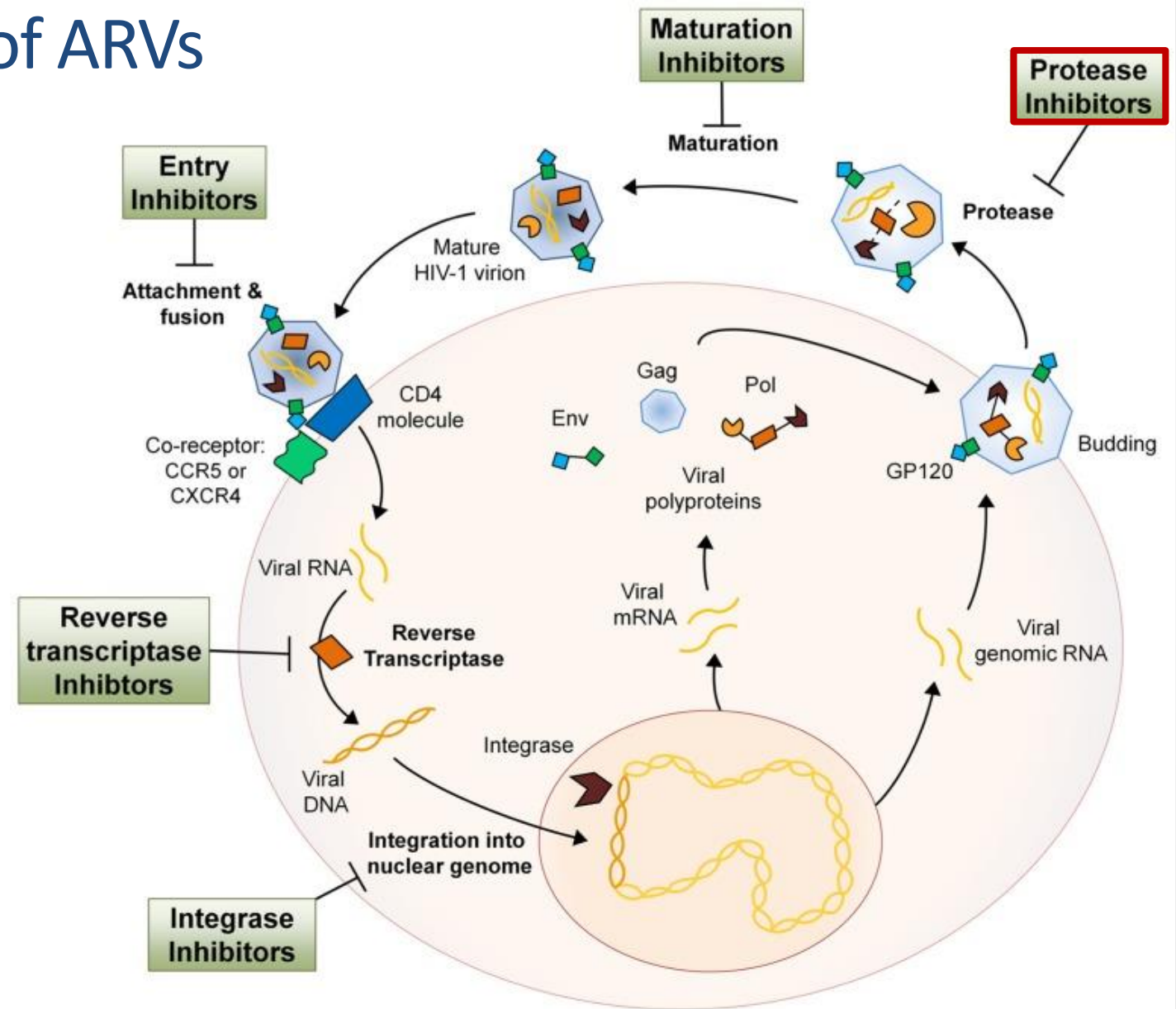
²Only available as fixed-dose combination product

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Pharmacokinetic Enhancers

“Boosters”

- **Ritonavir** and **cobicistat** are strong **CYP3A4 inhibitors** that are given in combination with **PIs** and the INSTI, **elvitegravir**
- Boosters inhibit the metabolism of PIs and elvitegravir to improve the pharmacokinetic/pharmacodynamic profile of these medications
- **This results in:**
 - Higher concentrations of PI or EVG
 - Less frequent dosing
 - Improved adherence
 - Decreased resistance
 - High potential for drug-drug interactions

The following products contain boosters:

- Norvir (RTV)
- Prezcofix (DRV/c)
- Evotaz (ATV/c)
- Symtuza (DRV/c/TAF/FTC)
- Stribild (EVG/c/TDF/FTC)
- Genvoya (EVG/c/TAF/FTC)

PIs

Generic	Brand	Abbreviation
Atazanavir plus ritonavir	Reyataz + Norvir	ATV/r
Atazanavir/cobicistat	Evotaz	ATV/c
Darunavir plus ritonavir	Prezista + Norvir	DRV/r
Darunavir/cobicistat	Prezcobix, component of Symtuza ¹	DRV/c
Fosamprenavir	Lexiva	FPV
Indinavir	Crixivan	IDV
Lopinavir/ritonavir	Kaletra	LPV/r
Nelfinavir	Viracept	NFV
Saquinavir	Forovase	SQV
Lopinavir/ritonavir	Kaletra	LPV/r

Protease Inhibitors

¹Single Tablet Regimen (STR)



PIs: Consider Using First-Line in Certain Situations

Generic	Brand	Abbreviation
Atazanavir plus ritonavir	Reyataz + Norvir	ATV/r
Atazanavir/cobicistat	Evotaz	ATV/c
Darunavir plus ritonavir	Prezista + Norvir	DRV/r
Darunavir/cobicistat	Prezcobix, component of Symtuza ¹	DRV/c
Fosamprenavir	Lexiva	FPV
Indinavir	Crixivan	IDV
Lopinavir/ritonavir	Kaletra	LPV/r
Nelfinavir	Viracept	NFV
Saquinavir	Forovase	SQV
Lopinavir/ritonavir	Kaletra	LPV/r

Protease Inhibitors

¹Single Tablet Regimen (STR)

PI Combination Products: Make up Part of a Regimen

Generic	Brand	Abbreviation	Combination Product
Atazanavir plus ritonavir	Reyataz + Norvir	ATV/r	
Atazanavir/cobicistat	Evotaz	ATV/c	
Darunavir plus ritonavir	Prezista + Norvir	DRV/r	
Darunavir/cobicistat	Prezcobix, component of Symtuza¹	DRV/c	
Fosamprenavir	Lexiva	FPV	
Indinavir	Crixivan	IDV	
Lopinavir/ritonavir	Kaletra	LPV/r	
Nelfinavir	Viracept	NFV	
Saquinavir	Forovase	SQV	
Lopinavir/ritonavir	Kaletra	LPV/r	

Protease Inhibitors

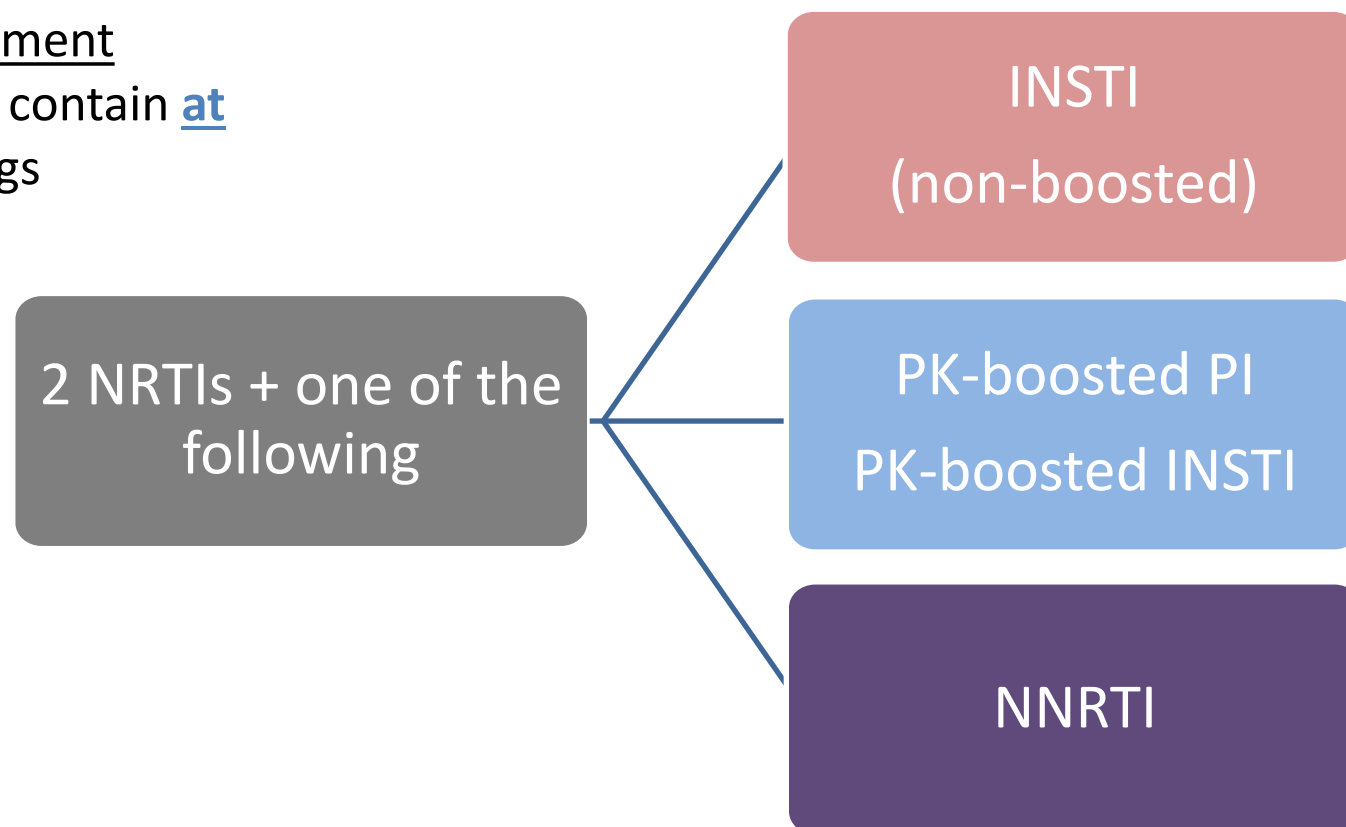
¹Single Tablet Regimen (STR)

A close-up photograph of two hands, one from a person with a darker skin tone and one from a person with a lighter skin tone, gently holding a pink awareness ribbon. The ribbon is a looped shape, commonly used to represent HIV/AIDS awareness. The background is a soft, out-of-focus light color.

BUILDING AN ARV REGIMEN

Building an ARV Regimen

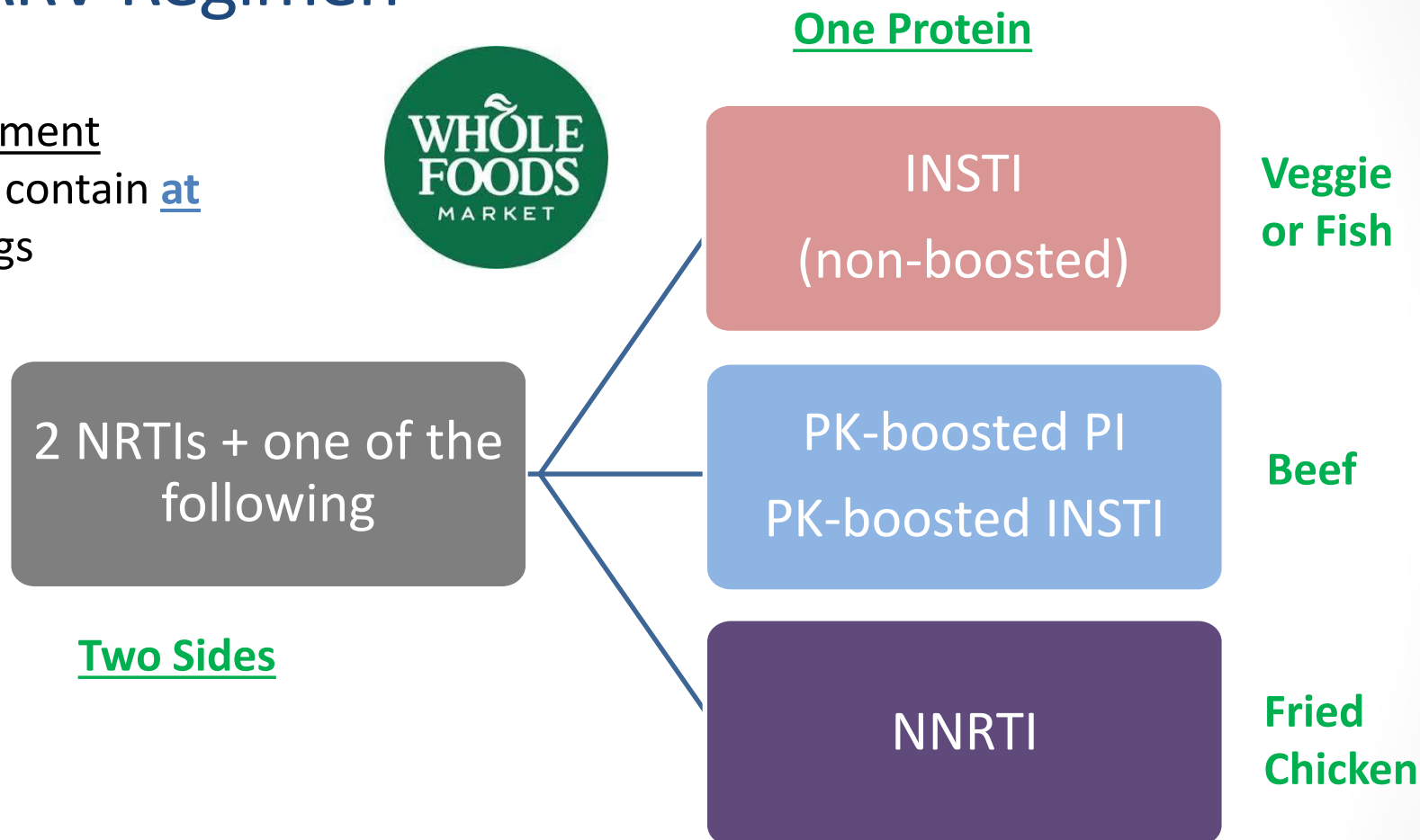
First-line HIV treatment regimens typically contain at least 3* active drugs



*One first-line regimen only contains 2 active drugs

Building an ARV Regimen

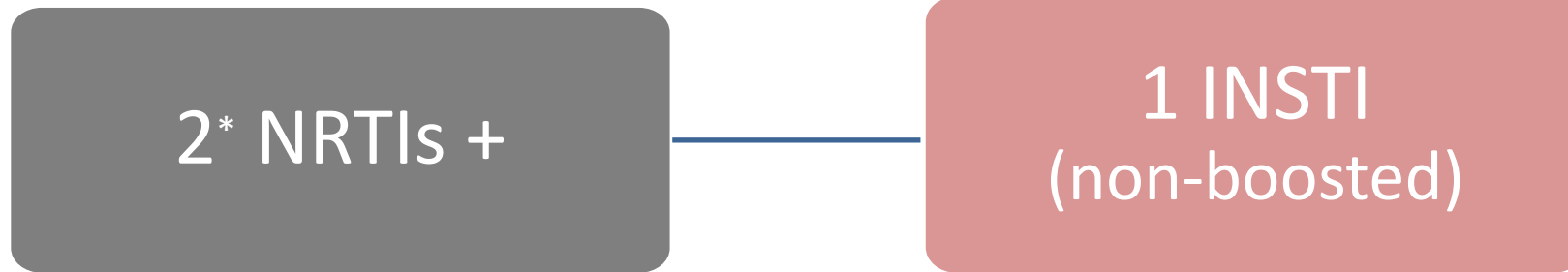
First-line HIV treatment regimens typically contain at least 3* active drugs



*One first-line regimen only contains 2 active drugs

Building an ARV Regimen

DHHS Recommended Initial Regimens for Most Patients



Fish/veggie = “healthy option”

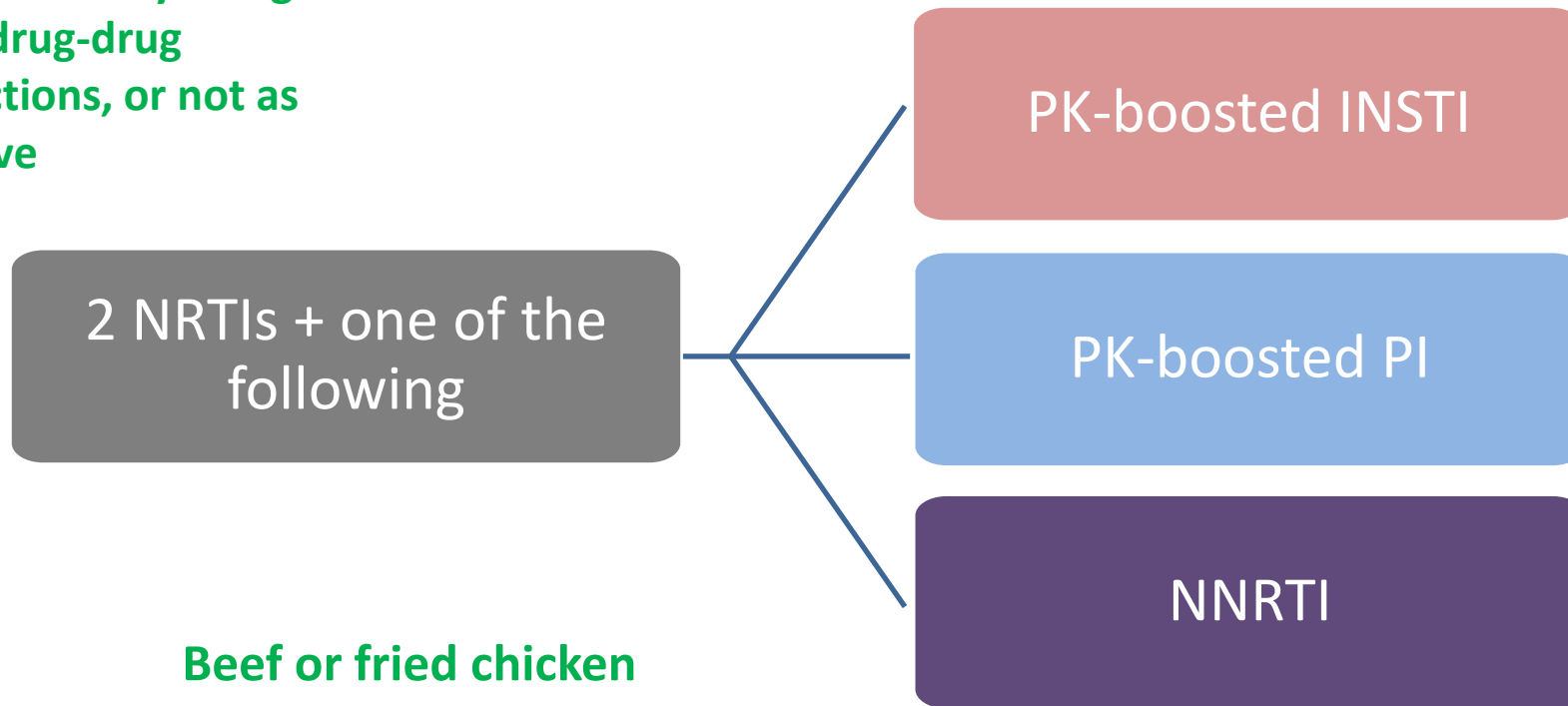
First-line regimens are all INSTI based!

*One regimen only contains **1 NRTI**

Building an ARV Regimen

DHHS Regimens to Consider in Certain Clinical Situations

Not as “healthy” long-term, drug-drug interactions, or not as effective



These regimens are effective and tolerable but have some disadvantages when compared with first-line regimens, or have less supporting data from randomized clinical trials

The Shift to INSTI-Based Regimens

- INSTIs have high rates of virologic suppression and often greater tolerability than PIs and NNRTIs








Study	INSTI	Comparator(s)	Follow-up	Efficacy
STARTMRK	RAL	Efavirenz	192 weeks	Raltegravir superior to efavirenz
ACTG A5257	RAL	Darunavir/ritonavir Atazanavir/ritonavir	96 weeks	Raltegravir superior to darunavir/r Raltegravir superior to atazanavir/r
GS-102	EVG	Efavirenz	144 Weeks	Elvitegravir non-inferior to efavirenz
GS-103	EVG	Atazanavir/ritonavir	144 Weeks	Elvitegravir non-inferior to atazanavir/ritonavir
WAVES	EVG	Atazanavir/ritonavir	48 Weeks	Elvitegravir superior to atazanavir/ritonavir in women
SINGLE	DTG	Efavirenz	48 Weeks	Dolutegravir superior to efavirenz
FLAMINGO	DTG	Darunavir/ritonavir	48 Weeks	Dolutegravir superior to darunavir/ritonavir
ARIA	DTG	Atazanavir/ritonavir	48 Weeks	Dolutegravir superior to atazanavir/ritonavir in women
GS-US-380-1489	BIC	Dolutegravir	48 Weeks	Bictegravir non-inferior to dolutegravir
GS-US-380-1480	BIC	Dolutegravir	48 Weeks	Bictegravir non-inferior to dolutegravir



DHHS RECOMMENDED INITIAL REGIMENS FOR MOST PEOPLE WITH HIV

Initiation of Antiretroviral Therapy








DHHS Recommendations (Adults & Adolescents)

DHHS Panel's Recommended Initial Regimens for <u>Most</u> People with HIV		
Generic (Abbreviation)	Brand	Pill Burden
Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)	Biktarvy	
Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)	Triumeq	
Dolutegravir/lamivudine (AI) (DTG/3TC)	Dovato	
Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)	Tivicay + Descovy	
Dolutegravir + tenofovir disoproxil fumarate/emtricitabine (AI) (DTG + TDF/FTC*)	Tivicay + Truvada	
Raltegravir + tenofovir alafenamide/emtricitabine (BI) (RAL + TAF/FTC*)	Isentress + Descovy	
Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)	Isentress + Truvada	

Initiation of Antiretroviral Therapy

DHHS Recommendations (Adults & Adolescents)








“tegravir” = integrase inhibitor

DHHS Panel’s Recommended Initial Regimens for <u>Most</u> People with HIV		
Generic (Abbreviation)	Brand	Pill Burden
Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)	Biktarvy	
Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)	Triumeq	
Dolutegravir/lamivudine (AI) (DTG/3TC)	Dovato	
Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)	Tivicay + Descovy	
Dolutegravir + tenofovir disoproxil fumarate/emtricitabine (AI) (DTG + TDF/FTC*)	Tivicay + Truvada	
Raltegravir + tenofovir alafenamide/emtricitabine (BI) (RAL + TAF/FTC*)	Isentress + Descovy	
Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)	Isentress + Truvada	

Initiation of Antiretroviral Therapy

DHHS Recommendations (Adults & Adolescents)








Dual NRTI backbone

DHHS Panel's Recommended Initial Regimens for <u>Most</u> People with HIV		
Generic (Abbreviation)	Brand	Pill Burden
Bictegravir/ tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)	Biktarvy	
Dolutegravir/ abacavir/lamivudine (AI) (DTG/ABC/3TC)	Triumeq	
Dolutegravir/lamivudine (AI) (DTG/3TC)	Dovato	
Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)	Tivicay + Descovy	
Dolutegravir + tenofovir disoproxil fumarate/emtricitabine (AI) (DTG + TDF/FTC*)	Tivicay + Truvada	
Raltegravir + tenofovir alafenamide/emtricitabine (BI) (RAL + TAF/FTC*)	Isentress + Descovy	
Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)	Isentress + Truvada	

Initiation of Antiretroviral Therapy

DHHS Recommendations (Adults & Adolescents)

Single NRTI backbone
'Two-drug' regimen

DHHS Panel's Recommended Initial Regimens for <u>Most</u> People with HIV		
Generic (Abbreviation)	Brand	Pill Burden
Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)	Biktarvy	
Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)	Triumeq	
Dolutegravir/ lamivudine (AI) (DTG/3TC)	Dovato	
Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)	Tivicay + Descovy	
Dolutegravir + tenofovir disoproxil fumarate/emtricitabine (AI) (DTG + TDF/FTC*)	Tivicay + Truvada	
Raltegravir + tenofovir alafenamide/emtricitabine (BI) (RAL + TAF/FTC*)	Isentress + Descovy	
Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)	Isentress + Truvada	




Single Tablet Regimens (STR)

“We combined all your medications into ONE convenient dose!”



Initiation of Antiretroviral Therapy












DHHS Recommendations (Adults & Adolescents)

DHHS Panel's Recommended Initial Regimens for <u>Most</u> People with HIV (Single Tablet Regimens)		
Generic (Abbreviation)	Brand	Pill Burden
Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)	Biktarvy	
Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)	Triumeq	
Dolutegravir/lamivudine (AI) (DTG/3TC)	Dovato	



DHHS RECOMMENDED INITIAL REGIMENS IN CERTAIN CLINICAL SITUATIONS

DHHS Panel's Recommended Initial Regimens in Certain Clinical Situations








Boosted INSTI + 2 NRTIs	Brand	Pill Burden
Elvitegravir/cobicistat/tenofovir AF/emtricitabine (EVG/c/TAF/FTC)	Genvoya	
Elvitegravir/cobicistat/tenofovir DF/emtricitabine (EVG/c/TDF/FTC)	Stribild	
Boosted PI + 2 NRTIs		
Darunavir/cobicistat/tenofovir AF/emtricitabine (DRV/c/TAF/FTC)	Symtuza	
Darunavir/cobicistat + tenofovir/emtricitabine (DRV/c + TDF (or TAF)/FTC*)	Prezcobix + Truvada (or Descovy)	
Darunavir + ritonavir + tenofovir/emtricitabine (DRV/r + TDF (or TAF)/FTC*)	Prezista + Norvir + Truvada (or Descovy)	
Atazanavir/cobicistat + tenofovir/emtricitabine (ATV/c + TDF (or TAF)/FTC*)	Evotaz + Truvada (or Descovy)	
Atazanavir + ritonavir + tenofovir/emtricitabine (ATV/r + TDF (or TAF)/FTC*)	Reyataz + Norvir + Truvada (or Descovy)	
NNRTI + 2 NRTIs		
Efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC*)	Atripla**	
Rilpivirine/tenofovir AF/emtricitabine (RPV/TAF/FTC)	Odefsey	
Rilpivirine/tenofovir DF/emtricitabine (RPV/TDF/FTC)	Complera	
Doravirine/tenofovir DF/lamivudine (DOR/TDF/3TC)	Delstrigo	
Doravirine + tenofovir AF/emtricitabine (DOR + TAF/FTC*)	Pifeltro + Descovy	

*May substitute 3TC for FTC

**Additionally, Symfi, Symfi Lo, Sustiva plus Descovy, Sustiva plus Cimduo

Initiation of Antiretroviral Therapy

DHHS Recommendations (Adults & Adolescents)

DHHS Panel's Recommended Initial Regimens in <u>Certain Clinical Situations</u> (Single Tablet Regimens)		
Boosted INSTI + 2 NRTIs	Brand	Pill Burden
Elvitegravir/cobicistat/tenofovir AF/emtricitabine (EVG/c/TAF/FTC)	Genvoya	
Elvitegravir/cobicistat/tenofovir DF/emtricitabine (EVG/c/TDF/FTC)	Stribild	
Boosted PI + 2 NRTIs		
Darunavir/cobicistat/tenofovir AF/emtricitabine (DRV/c/TAF/FTC)	Symtuza	
NNRTI + 2 NRTIs		
Efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC)	Atripla*	
Rilpivirine/tenofovir AF/emtricitabine (RPV/TAF/FTC)	Odefsey	
Rilpivirine/tenofovir DF/emtricitabine (RPV/TDF/FTC)	Complera	
Doravirine/tenofovir DF/lamivudine (DOR/TDF/3TC)	Delstrigo	

*Additionally, Symfi, Symfi Lo



INTERNATIONAL ANTIVIRAL SOCIETY – USA PANEL

Initiation of Antiretroviral Therapy

Recommendations - International Antiviral Society, USA Panel

Recommended Initial Regimens

- Bictegravir/TAF/emtricitabine (Ala)
- Dolutegravir/abacavir/lamivudine (Ala)
- Dolutegravir plus TAF/emtricitabine (Ala)

- BIC and DTG do not require boosting, have a high barrier to resistance, and are part of regimens with a low pill burden and toxicity
- TAF results in fewer tenofovir-associated renal and bone toxic effects

When Initial Regimens Are Not an Option

- Darunavir* plus tenofovir/emtricitabine (Ala)
- Efavirenz/TDF/emtricitabine (Ala)
- Elvitegravir/cobi/tenofovir/emtricitabine (Ala)
- Raltegravir plus tenofovir/emtricitabine (Ala)
- Rilpivirine plus tenofovir/emtricitabine (Ala)

*Boosted with ritonavir or cobicistat

- RAL is well tolerated with few drug interactions, but has a low barrier to resistance and a high pill burden
- EVG has a lower barrier to resistance and requires boosting, resulting in more drug interactions



PROCESS FOR SELECTING INITIAL ART

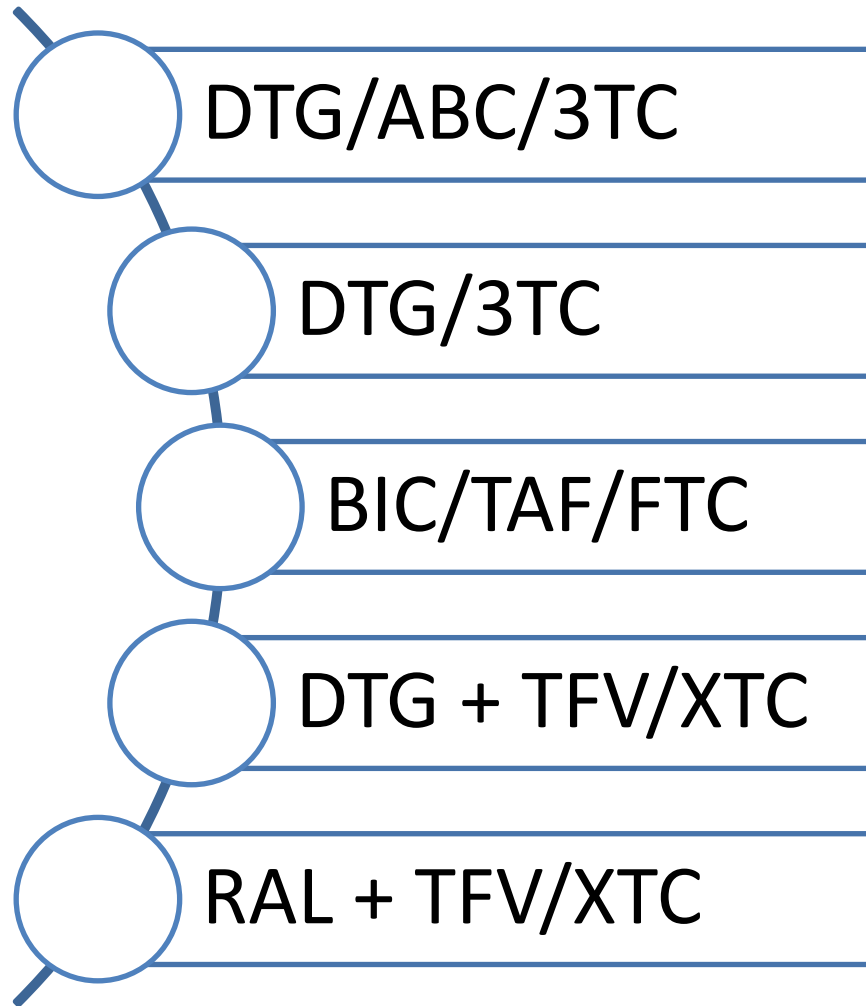
Process for Selecting Initial ART

- **Regimen efficacy**
 - Guidelines recommendations, superiority data?
- **Drug resistance**
 - Transmitted resistance 10-17%
 - Prevalence: **NNRTIs > NRTIs > PIs > INSTI**
 - If genotype pending, use DTG-, BIC-, or PI-based regimens (strongest barrier to resistance)
- **Pretreatment labs and considerations**
 - i.e. RPV: only if CD4 >200, HIV RNA <100,000
 - DTG/3TC only if HIV RNA <500,000
 - **HBV status**
 - HLA-B*5701 status
 - Childbearing potential, pregnancy status
- **Comorbidities, comedications**
 - Potential for adverse effects or **drug-drug interactions** (most common with boosters and PIs), renal dosing or hepatic dosing
- **Adherence potential**
 - Pill burden, dosing frequency, food restrictions (RPV, EVG/c, PIs must be administered with food), side-effect profile

A close-up photograph of two hands, one from a person with a darker skin tone and one from a person with a lighter skin tone, gently holding a pink awareness ribbon. The ribbon is a looped shape, commonly used to represent HIV/AIDS awareness. The background is a soft, out-of-focus light color.

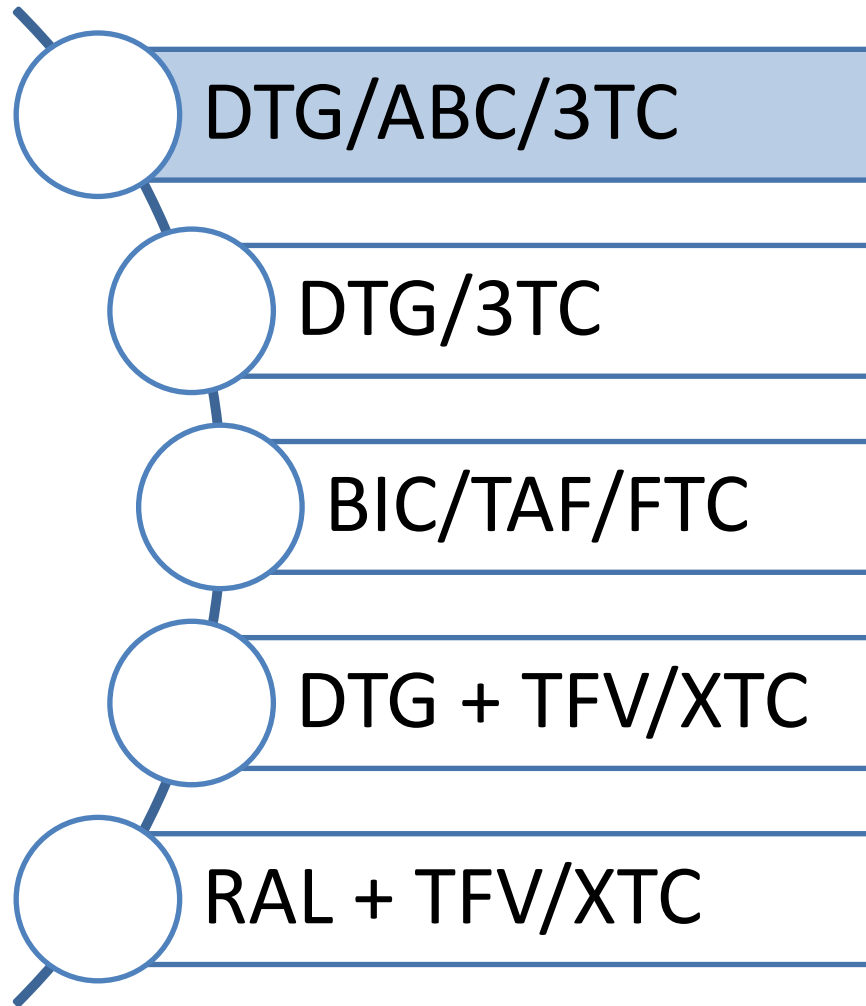
SELECTING A FIRST-LINE REGIMEN

Selecting a First-Line Regimen



TFV= TAF or TDF
XTC = FTC or 3TC

Selecting a First-Line Regimen



Triumeq

TFV= TAF or TDF
XTC = FTC or 3TC

Triumeq



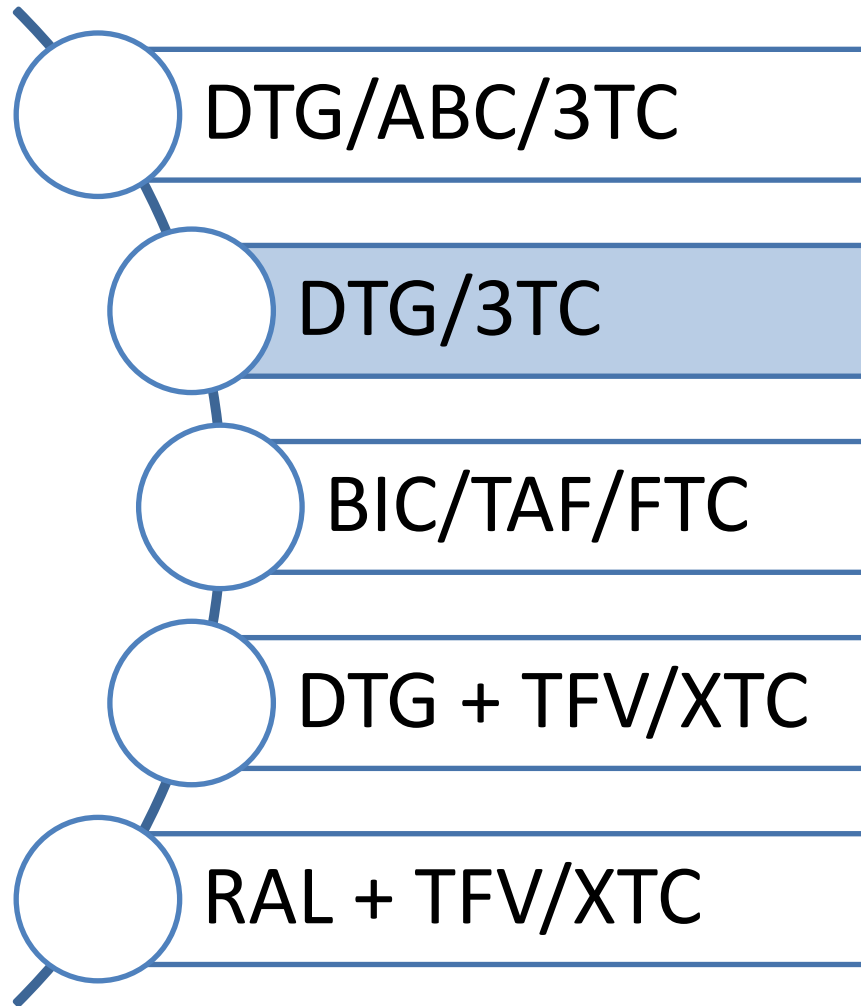
(Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg)

- Fallen out of favor for persons who are newly diagnosed with HIV outside of being a **preferred STR in women who are pregnant** and living with HIV
- Can be given without dose adjustment with rifabutin
- Cannot be rapidly initiated due to several limitations
 - Requires testing for HLA-B*5701 allele prior to initiation (abacavir hypersensitivity)
 - Does not adequately cover HBV co-infection (regimen lacks tenofovir)
- Largest pill size as a STR
- Controversial association between abacavir and cardiovascular risk

Abacavir and CV Risk

- Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D):
 - 33,000 patients, observational study, **RR 1.91** (95% CI, 1.5-2.42) with ABC
 - Increased risk with PIs (darunavir and lopinavir/ritonavir) also
- Several additional studies show conflicting results
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association
- **Guidelines state to use caution or avoid** in patients with known high CV risk

Selecting a First-Line Regimen

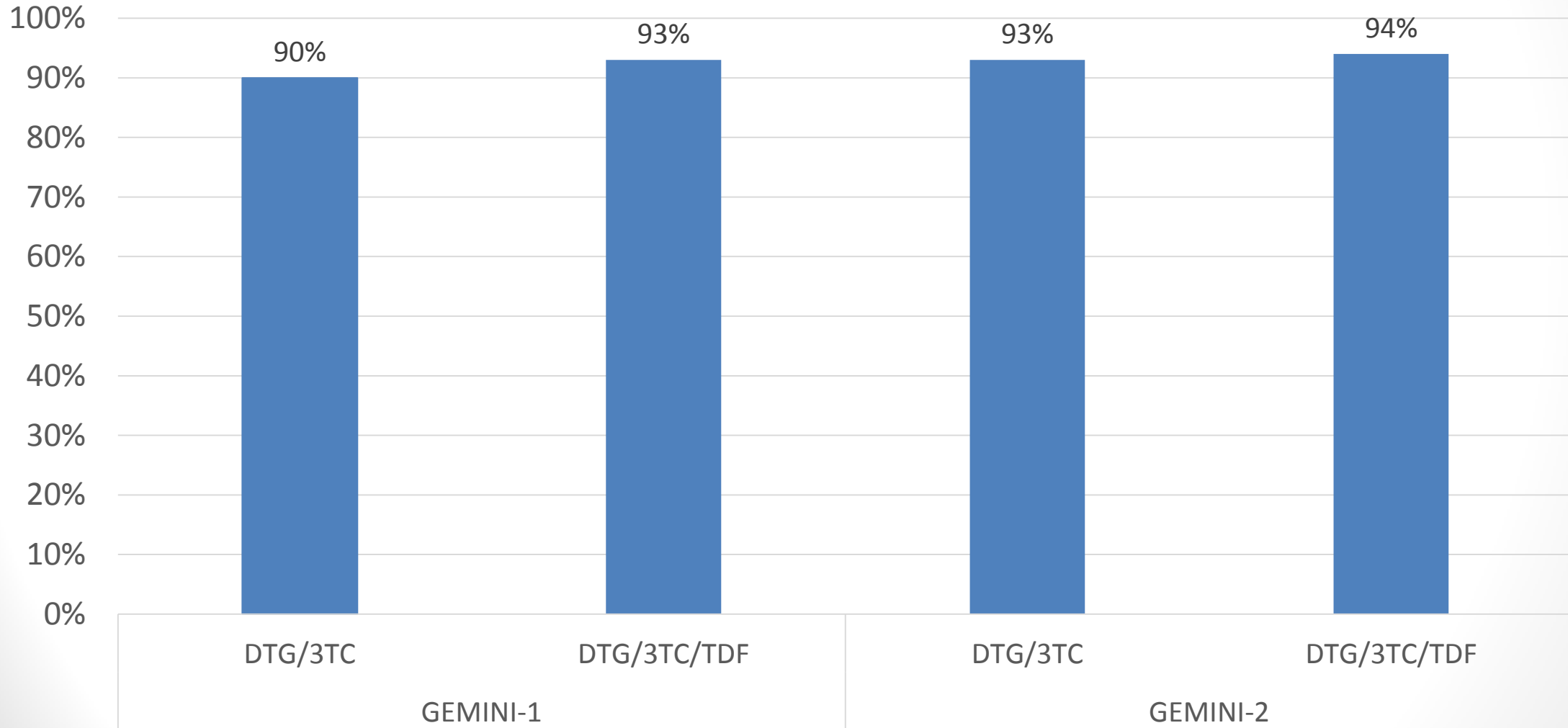


Dovato

TFV= TAF or TDF
XTC = FTC or 3TC

Results from GEMINI-1 and GEMINI-2

Virologic Success at 48 weeks



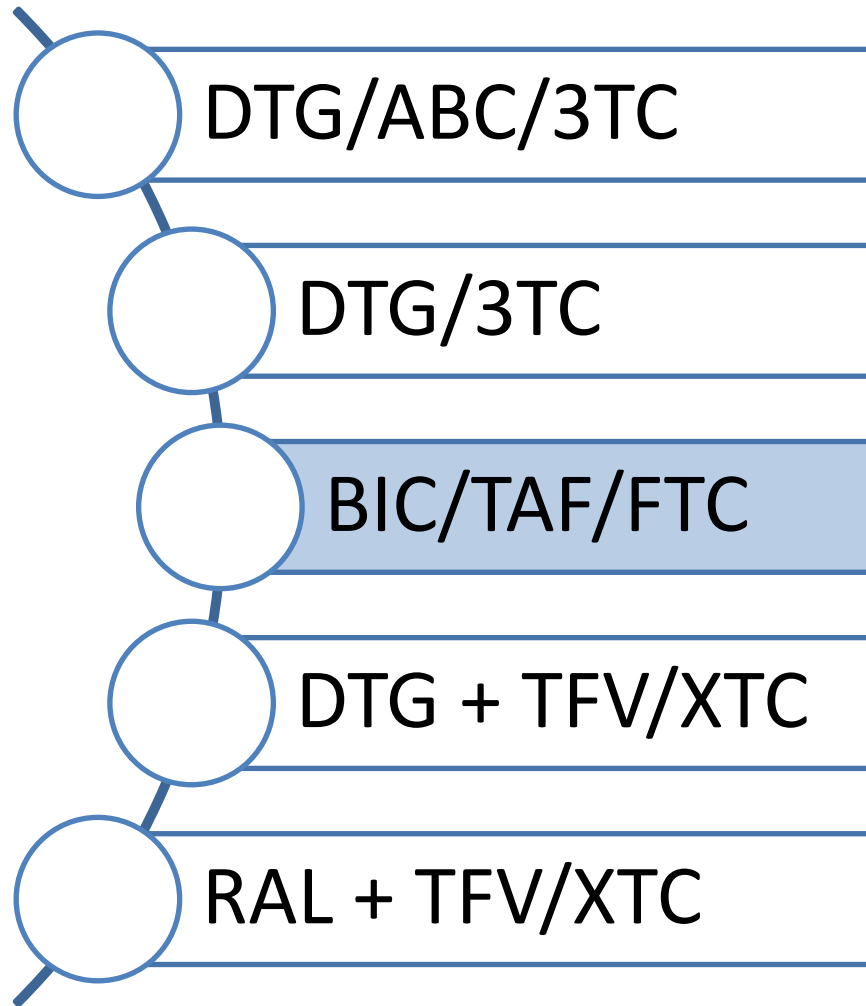
Dovato



(Dolutegravir 50 mg/lamivudine 300 mg)

- Garnering more attention as an option for **newly-diagnosed persons (or switch)**, especially in an aging population with HIV
- Cannot be rapidly initiated
 - Requires baseline viral load, genotype
 - Does not adequately cover HBV co-infection (regimen lacks tenofovir)
- Has potential benefits when compared to other two-drug regimen DTG/RPV (Juluca)
- Medium pill size as a STR
- Avoid if potential for poor adherence, and **carefully review resistance history** prior to switch
- Can be given without dose adjustment with rifabutin
- Consider for those with baseline kidney or bone dysfunction or for those with high cardiovascular risk

Selecting a First-Line Regimen



Biktarvy

TFV= TAF or TDF
XTC = FTC or 3TC

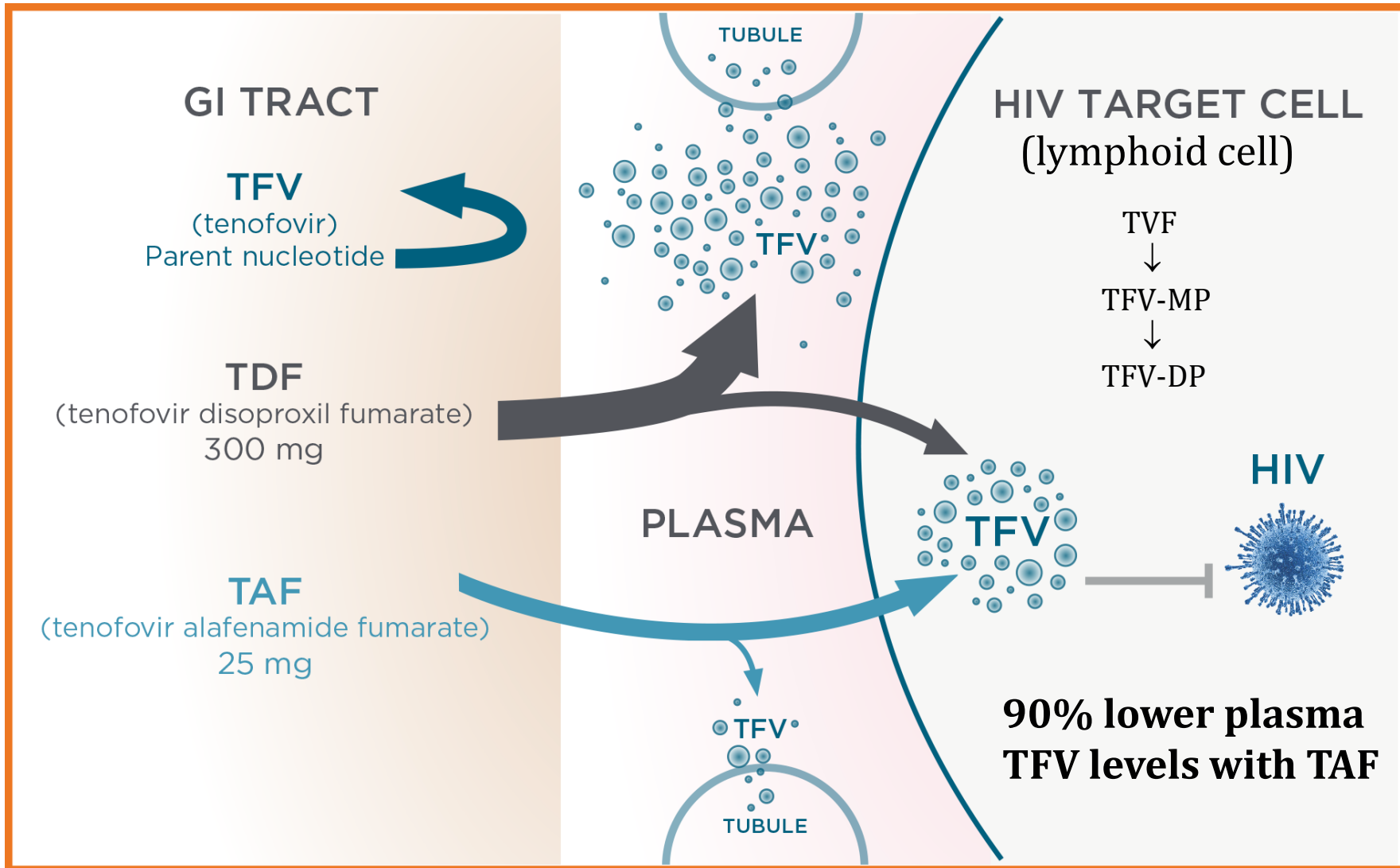
Biktarvy



(Bictegravir 50 mg/tenofovir AF 25 mg/emtricitabine 200 mg)

- Most commonly prescribed regimen for persons who are newly diagnosed with HIV (or switch)
- **Only first-line STR that is appropriate for rapid initiation**
 - No viral load restrictions
 - High barrier to resistance
 - Adequately treats HBV coinfection
- Smallest pill size as a first-line STR
- Insufficient data for use during **pregnancy** or in patients with **INSTI resistance**
- Consider avoiding in those with baseline renal or bone dysfunction
 - (No TFV>TAF>TDF)

Tenofovir alafenamide vs. Tenofovir disoproxil fumarate



TAF vs. TDF

Clinical Trials Data

- Studies 104/111: TAF-Based Regimen **Superior** to TDF Through 144 Weeks in Treatment-Naïve Patients
- Key Conclusions at 144 Weeks
 - TAF regimen statistically **superior virologic efficacy**
 - HIV-1 RNA <50 copies/mL difference: 4.2% (95% CI: 0.6-7.8%; P=.02), largely driven by discontinuations
 - Significantly fewer discontinuations due to AEs with TAF vs TDF
 - Significantly fewer discontinuations due to renal and bone AEs with TAF vs TDF (none in TAF arm)
 - Significantly smaller losses in spine and hip bone mineral density with TAF vs TDF
 - Significantly smaller decreases from baseline for renal parameters with TAF vs TDF

TAF vs. TDF

Not always interchangeable!


Use TAF or TFV-sparing	• Concern for renal/bone toxicity?
TAF or TDF	• ESRD?
TAF* or TDF	• PrEP?
TDF	• Pregnancy?
TDF	• DDIs (rifamycins, anti-seizure meds)
TAF or TDF	• Hepatitis B co-infection?

*Only approved for MSM and TGW

Selecting a First-Line STR: Summary

	Triumeq (DTG/ABC/3TC)	Dovato (DTG/3TC)	Biktarvy (BIC/TAF/FTC)
Rapid start	No	No	Yes
Requires HLA-B*5701	Yes	No	No
Viral load restrictions	No	Yes	No
Covers HBV co-infection	No	No	Yes (tenofovir component)
Tablet size	Large	Medium	Small
Administration	Without regard to meals	Without regard to meals	Without regard to meals
Considerations for renal dose adjustment	No renal dose adjustment required	No renal dose adjustment required	No renal dose adjustment required in ESRD; consider alternative in CKD
Bottom line	Not initiated frequently anymore outside of pregnancy	Consider in those with kidney or bone disorders or cardiovascular risk	Most frequently initiated regimen in persons newly diagnosed with HIV



Renal dose adjustment of 3TC/FTC in hemodialysis





Dose: elviteg-cobicistat-emtricit-tenofovir, 1 Tab, Oral, Once Daily

▼ Specific dosing guidelines are not available for this patient's level of renal impairment. The ordered dose is within the limits that do not consider renal impairment but otherwise match the patient's conditions.

▼ Renal adjustment note: Not recommended in patients with ESRD (CrCl <15 mL/min) who are NOT receiving hemodialysis. No adjustment required in patients with ESRD (CrCl <15 mL/min) who ARE receiving hemodialysis.

[Details](#)  



elviteg-cobicistat-emtricit-tenofovir (GENVOYA) 150-150-200-10 mg Tab tablet
 Prescription. New. [Remove](#)




Dose: abacavir-dolutegravir-lamivudine, 1 Tab, Oral, Once Daily

▼ This drug is not recommended for use in patients with this level of renal impairment (CrCl 0 - 49 mL/min).

▼ Warnings are based on assumed values for the following undetermined data.
Creatinine Clearance

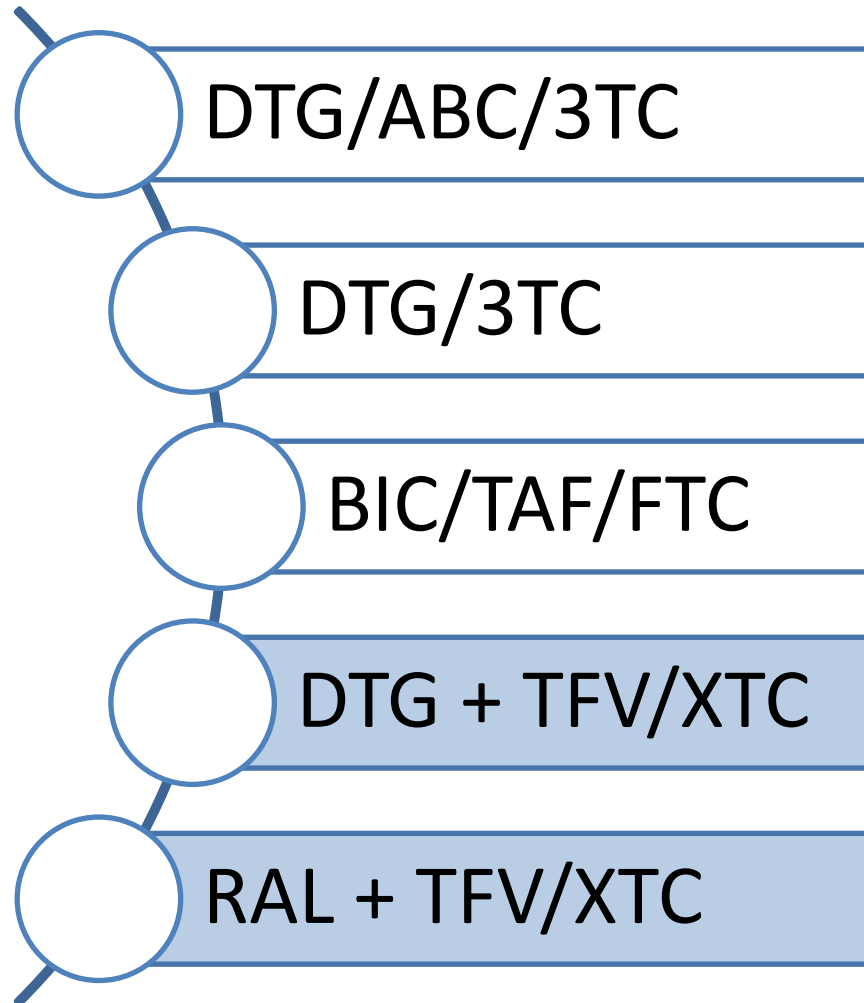
[Details](#)  

abacavir-dolutegravir-lamivudine (TRIUMEQ) 600-50-300 mg Tab tablet
 Prescription. New. [Remove](#)

Renal dose adjustment of 3TC/FTC in hemodialysis

- EVG/c/TAF/FTC
 - Phase 3b, open labeled, single armed study in 55 patients with ESRD on chronic HD
 - **Overall no major side effects**, 82% maintained viral suppression at 48 weeks, and 78% were more satisfied with single tablet regimen
- DTG/ABC/3TC
 - Case series of 6 PLWH simplified to STR of DTG/ABC/3TC 50-600-300 mg daily
 - All 6 maintained HIV RNA < 200 copies/mL
 - **No serious adverse effects reported**

Selecting a First-Line Regimen: Non-STRs



Tivicay + Descovy (or Truvada, Cimduo)

Isentress + Descovy (or Truvada, Cimduo)

TFV= TAF or TDF

XTC = FTC or 3TC

Initiation of First-Line Non-STRs

Tivicay plus Descovy
(or Truvada, Cimduo)



Isentress plus Descovy
(or Truvada, Cimduo)



- May be selected if persons develop **intolerance to bicitegravir**
 - May be selected if certain **drug-drug interactions** preclude the use of BIC/TAF/FTC (most often DTG 50 mg BID or RAL 800 mg BID plus TDF/XTC)
 - DTG 50 mg daily or RAL 400 mg BID plus TDF 300 mg/FTC 200 mg (or TDF 300 mg/3TC 300 mg) is a preferred regimen in **pregnant women** living with HIV
-
- May be selected if persons have **INSTI resistance** (requires DTG 50 mg BID)
 - Lower genetic barrier to resistance than BIC or DTG

INSTIs and Weight Gain

- Weight gain has been associated particularly DTG/BIC + TAF compared to EFV
- Trials have shows statistically significant weight gain; however overall absolute differences have not been clinically significant
- 10-40% of patients have experienced significant weight gain (> 10% of original weight)
- Phenomenon seems to be more prevalent in **women and black/Hispanic race, lower CD4 count, and higher HIV RNA**
- Overall significance of weight gain is controversial

Moorhouse M et al. IAS 2019. Mexico City, Mexico.

Kouanfack C et al. *N Engl J Med.* 2019;381:816-26.

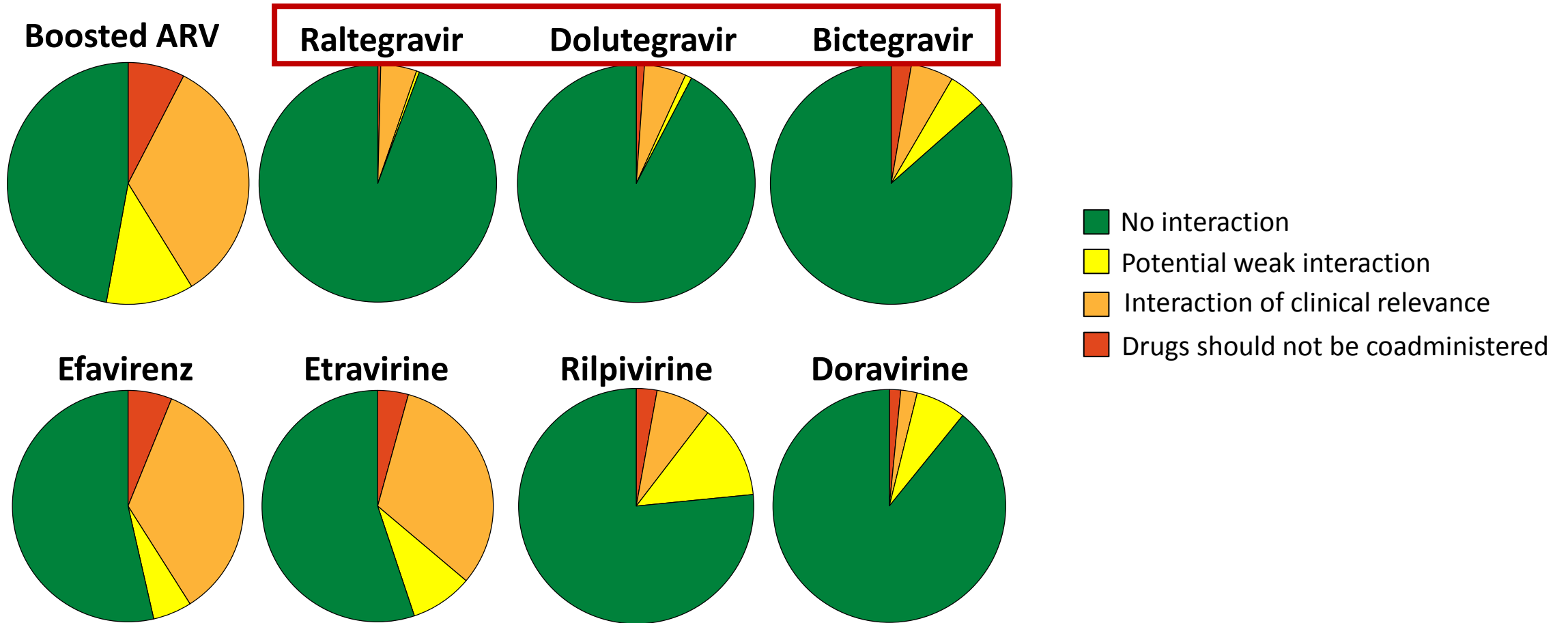
Norwood J et al. *J Acquir Immune Defic Syndr.* 2017;76(5):527-31

Sax PE et al. *Clin Infect Dis.* 2019;

Considerations for Clinical Practice

- Discuss association with patients
- Consider historical adherence patterns
- Review treatment history and prior genotypes for alternative agents
- Evaluate alternative agents for toxicities
- Assess current medications for drug-drug interactions

Drug-Drug Interaction Risk: Differences Among ARVs



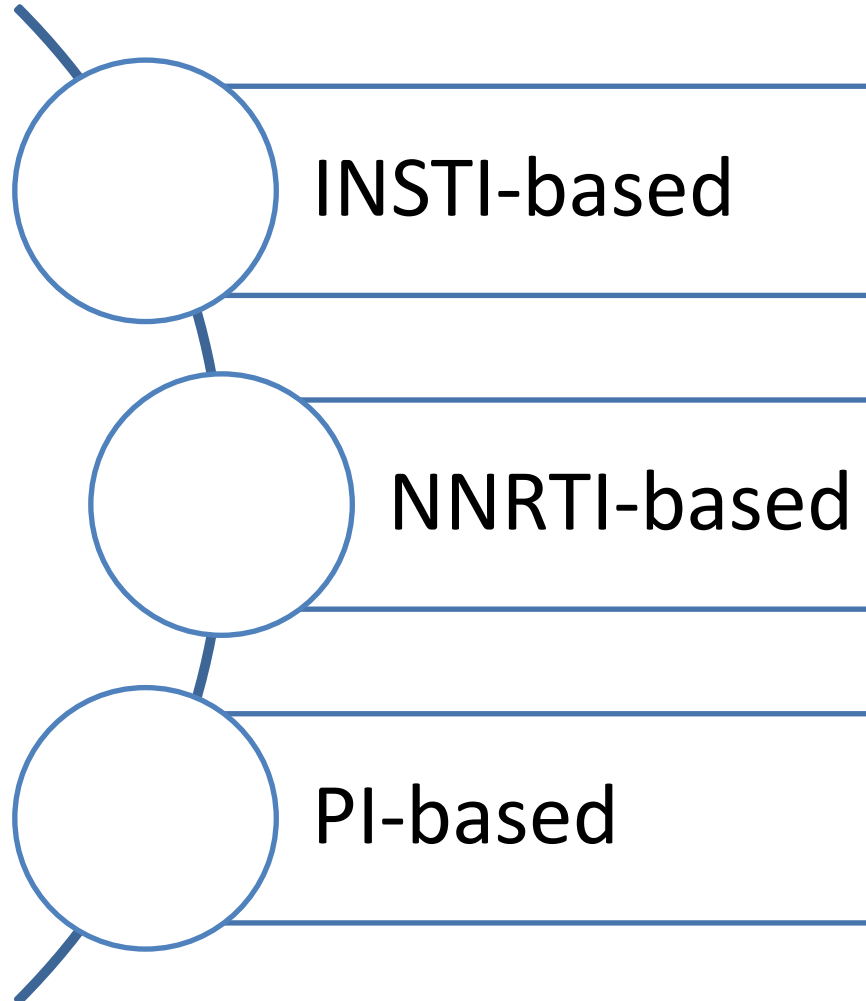
First-Line INSTI Drug-Drug Interactions

- **Polyvalent and divalent cations** and all INSTIs
 - Some can be given simultaneously with food
 - Separate by 12 hours is simplest thing to tell patients on daily supplements (more difficult with iron, need to look up specifics)
 - If frequent use of antacids, evaluate for cause, educate patient, consider H2-antagonist if using acutely
- **Metformin** and dolutegravir, bictegravir (less so)
- **Rifampin, antiepileptics** and all INSTIs (and TAF)

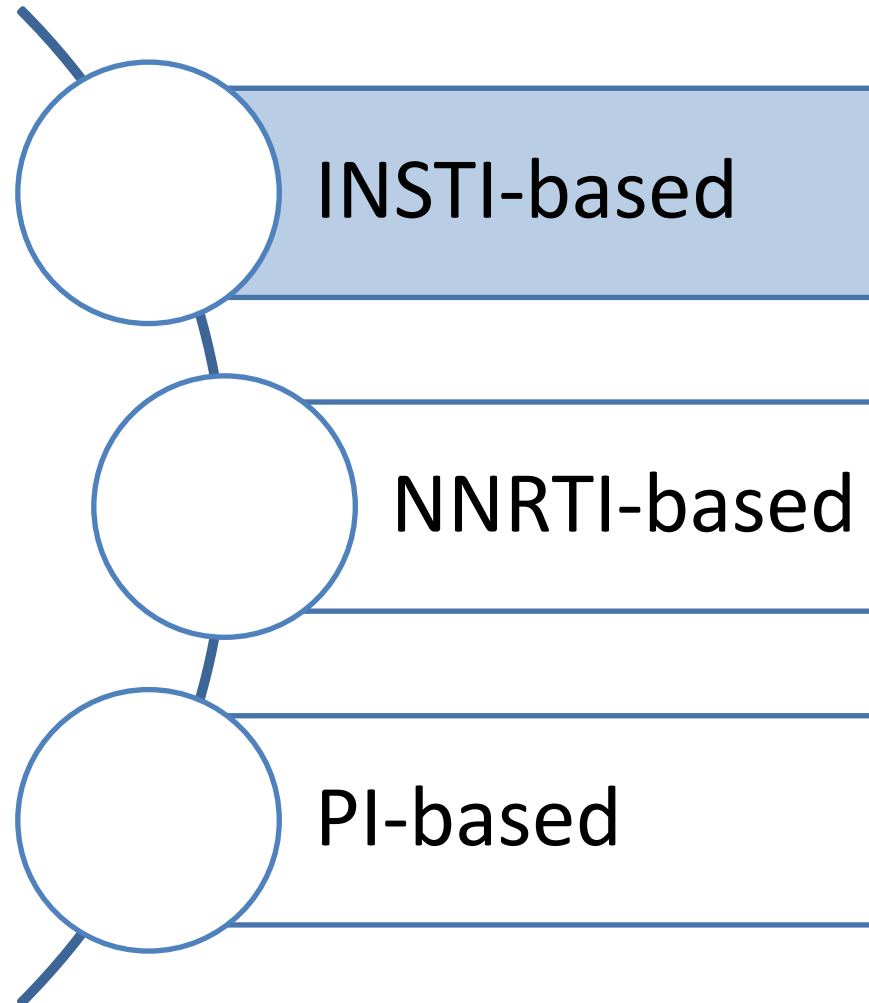
A close-up photograph of two hands, one from a darker-skinned person and one from a lighter-skinned person, gently holding a pink awareness ribbon. The ribbon is a symbol for breast cancer awareness. The background is a soft, out-of-focus light color.

SELECTING AN ALTERNATIVE REGIMEN

Selecting an Alternative Regimen



Selecting an Alternative Regimen



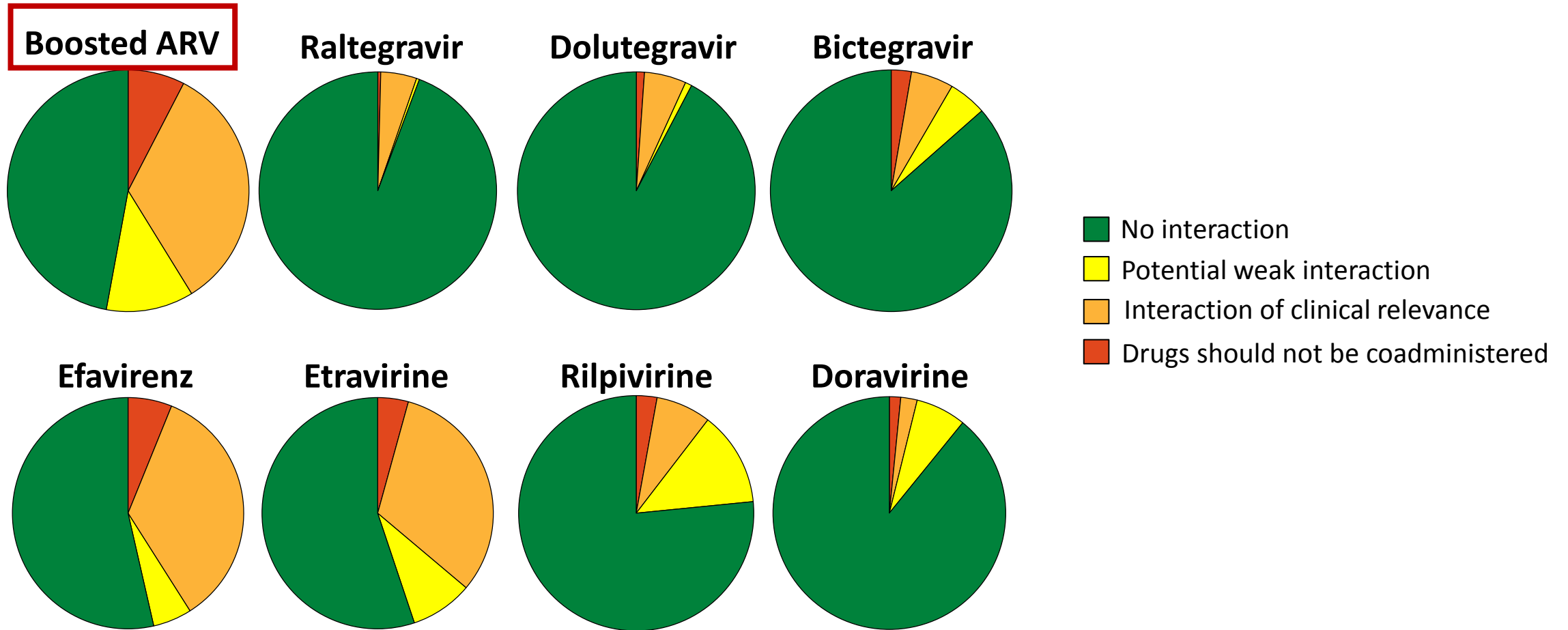
Genvoya or Stribild



(Elvitegravir 150 mg/cobicistat 150 mg/tenofovir/emtricitabine 200 mg)

- Removed from first-line regimens due to poorer tolerability (GI side-effects) and multiple drug-drug interactions
- Requires food for absorption
- Lower genetic barrier to resistance than BIC or DTG
- May be considered in persons with intolerance to other INSTIs

Drug-Drug Interaction Risk: Differences Among ARVs



INSTI Drug-Drug Interactions

EVG/c

To name a few....

- **Inhaled/intranasal/injectable/systemic steroids**
- **Hormonal contraceptives and hormone replacement therapy**
- **Statins**
- **Anticoagulants and antiplatelets**
- **Antidepressants/anxiolytics/antipsychotics**
- **Cardiac Medications**

INSTI Drug-Drug Interactions

EVG/c

- **Inhaled/intranasal/injectable/systemic steroids**

Beclomethasone, prednisone, and prednisolone preferred

- **Hormonal contraceptives and hormone replacement therapy**

Hormonal contraceptive should contain at least 30 mcg of ethinylestradiol

- **Statins**

Contraindicated with lovastatin, simvastatin, no more than atorvastatin 20 mg daily

- **Anticoagulants and antiplatelets**

Avoid DOACs, utilize warfarin or consider changing ARV regimen

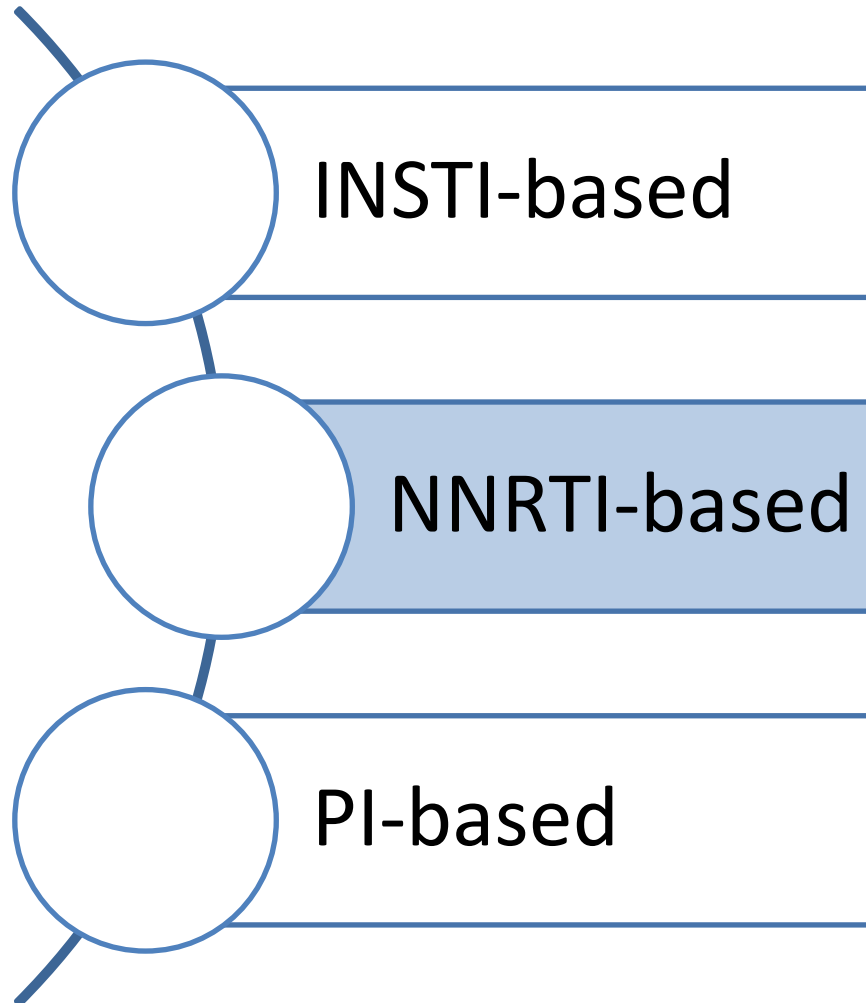
- **Antidepressants/anxiolytics/antipsychotics**

Initiate with lowest dose and titrate carefully

- **Cardiac Medications**

Consider beta-blockers such as atenolol, labetalol, nadolol; monitor for AEs with amlodipine

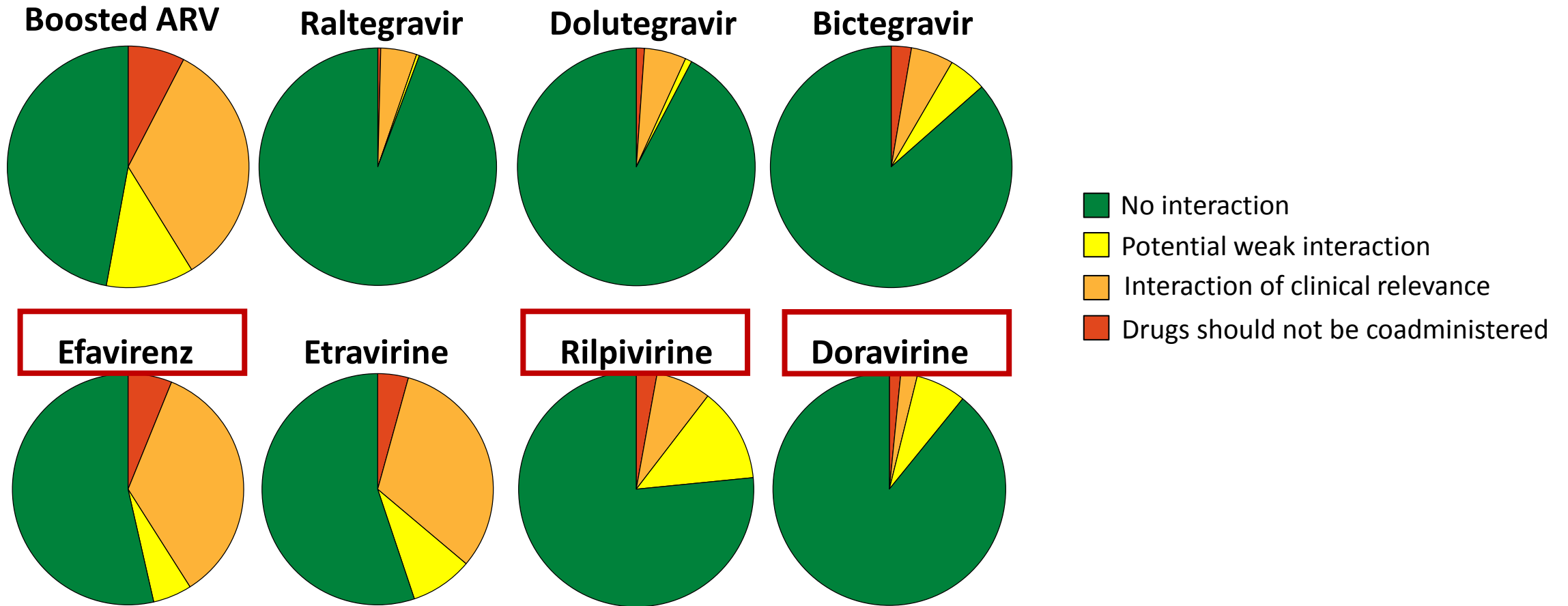
Selecting an Alternative Regimen



Selecting an NNRTI-Based Regimen: EFV vs. RPV vs. DOR

Efavirenz-based	Ralpivirine-based	Doravirine-based
<ul style="list-style-type: none"> Preferred in setting of HIV RNA >100,000 and CD4 count <200 when combined with XTC/TFV 	<ul style="list-style-type: none"> Higher incidence of failure when HIV RNA >100,000 and CD4 count <200; avoid use 	<ul style="list-style-type: none"> Preferred in setting of HIV RNA >100,000 and CD4 count <200; least amount of data
<ul style="list-style-type: none"> Higher incidence of neuropsychiatric side-effects, elevated cholesterol 	<ul style="list-style-type: none"> Lower incidence of neuropsychiatric side-effects, better tolerability 	<ul style="list-style-type: none"> Lower incidence of neuropsychiatric side-effects, better tolerability
<ul style="list-style-type: none"> CYP3A4 substrate; CYP3A4, CYP2C19 and UGT1A1 inducer; many drug-drug interactions 	<ul style="list-style-type: none"> CYP3A4 substrate; drug-drug interactions with acid-reducing medications 	<ul style="list-style-type: none"> CYP3A4 substrate; less potential for drug-drug interactions
<ul style="list-style-type: none"> Only coformulated with TDF 	<ul style="list-style-type: none"> Coformulations with TAF and TDF 	<ul style="list-style-type: none"> Only coformulated with TDF
<ul style="list-style-type: none"> Avoid if unknown HIV genotype or HIV genotype pending 		

Drug-Drug Interaction Risk: Differences Among ARVs



NNRTI Administration Concerns and DDIs

- Efavirenz (in Sustiva, Atripla, Symfi, Symfi Lo)
 - At bedtime on an **empty stomach** (food increases absorption, leading to higher side-effects)
 - CYP inducer, **decreases** levels of other medications
- Rilpivirine (in Edurant, Complera, Odefsey, Juluca)
 - **With high calorie meal**, requires acid for absorption
 - Avoid acid-reducing medications, **CONTRAINDICATED** with PPIs
- Doravirine (in Pifeltro, Delstrigo)
 - **No concerns**; can be taken with or without food and with acid-reducing medications

Efavirenz =



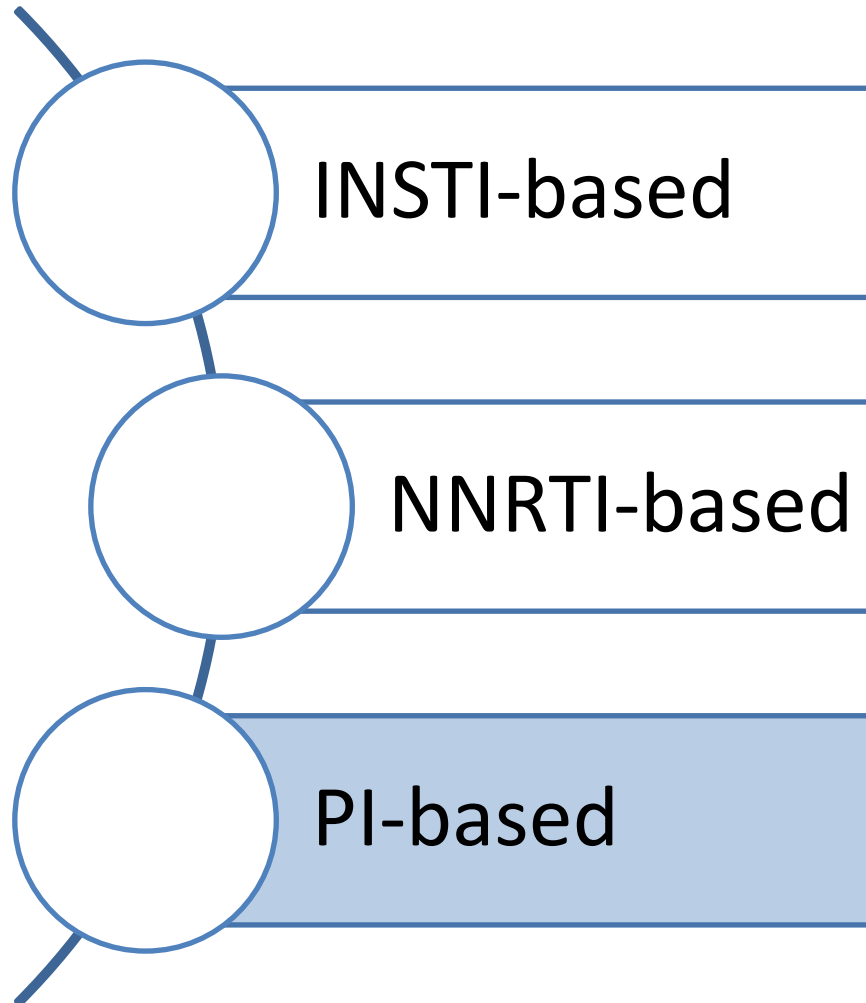
Rilpivirine =



Doravirine =



Selecting an Alternative Regimen



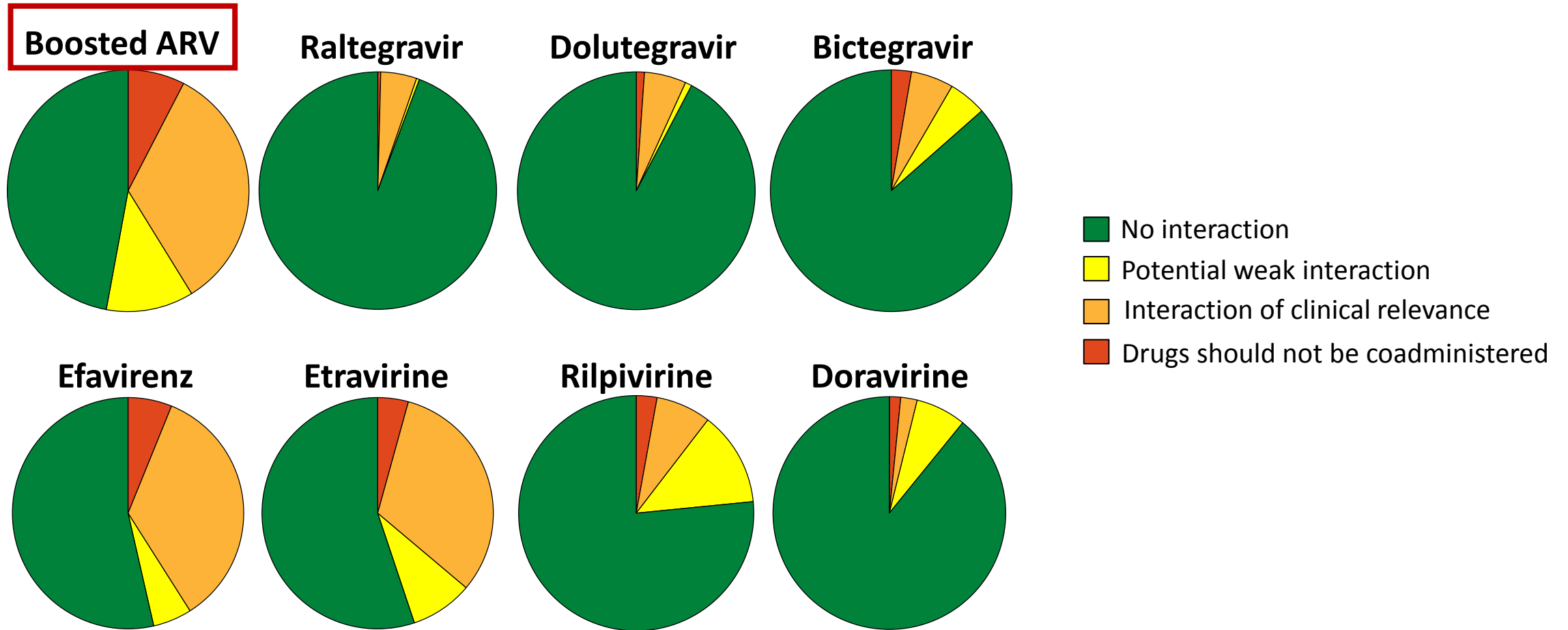
Selecting a PI-Based Regimen

ATV vs. DRV

Atazanavir-based	Darunavir-based
<ul style="list-style-type: none">• Administer with food, GI upset, dyslipidemia, many DDIs	
<ul style="list-style-type: none">• Acidic environment required for absorption; DDIs with acid-reducing agents in addition to typical DDIs (CYP3A4 and p-glycoprotein)	<ul style="list-style-type: none">• No DDIs with acid-reducing agents (inhibitor of CYP3A4 and p-glycoprotein)
<ul style="list-style-type: none">• High genetic barrier but lower genetic barrier than DRV	<ul style="list-style-type: none">• Higher genetic barrier, may be used in the setting of failure or if genotype pending
<ul style="list-style-type: none">• Indirect hyperbilirubinemia, jaundice, cholelithiasis, nephrolithiasis	<ul style="list-style-type: none">• Potentially higher cardiovascular risk, contains sulfonamide
<ul style="list-style-type: none">• Smaller combination tablet size	<ul style="list-style-type: none">• Available as a STR

- PIs mainly reserved for resistant HIV or poor adherence
- In general, boosted DRV is preferred over boosted ATV

Drug-Drug Interaction Risk: Differences Among ARVs



PIs, Boosters, and Drug-Drug Interactions

To name a few....

- **Inhaled/intranasal/injectable/systemic steroids**
- **Hormonal contraceptives and hormone replacement therapy**
- **Statins**
- **Anticoagulants and antiplatelets**
- **Antidepressants/anxiolytics/antipsychotics**
- **Cardiac Medications**

Not all PIs and boosters are created equal. Always look up specific recommendation!

Summary of Clinical Considerations for Alternative Agents

- **NNRTIs are typically used when patients have intolerance to INSTIs**
 - Of the three, DOR is the most appealing from a side-effect and PK/PD standpoint
 - Lowest barrier to resistance and highest incidence of transmitted resistance
- **PIs are typically reserved for when there is concern for poor adherence (to protect the integrase class) or in patients with multi-drug resistant HIV (limited treatment options)**
 - High barrier to resistance but use is limited by DDIs, adverse effects, and administration requirements
 - DRV is preferred agent
- **EVG/c may be selected when patients have intolerance to other INSTIs**
 - Low barrier to resistance, use is limited by DDIs, adverse effects, and administration requirements
 - May also consider NNRTI if possible in this scenario



ADDITIONAL GUIDELINE UPDATES

Dolutegravir use in Women of Childbearing Potential and Pregnancy

- Botswana birth surveillance study first reported increase in Neural Tube Defects (NTD) in patients on dolutegravir compared to those on alternative ART
 - Incidence of NTD in patients on DTG vs. any other ART: 0.30% vs. 0.10%
 - No birth defects were seen in those who started DTG during pregnancy
- Other studies have not found NTDs in patients taking DTG
- RAL remains preferred INSTI in those who are trying to conceive
- Insufficient data regarding BIC in pregnancy

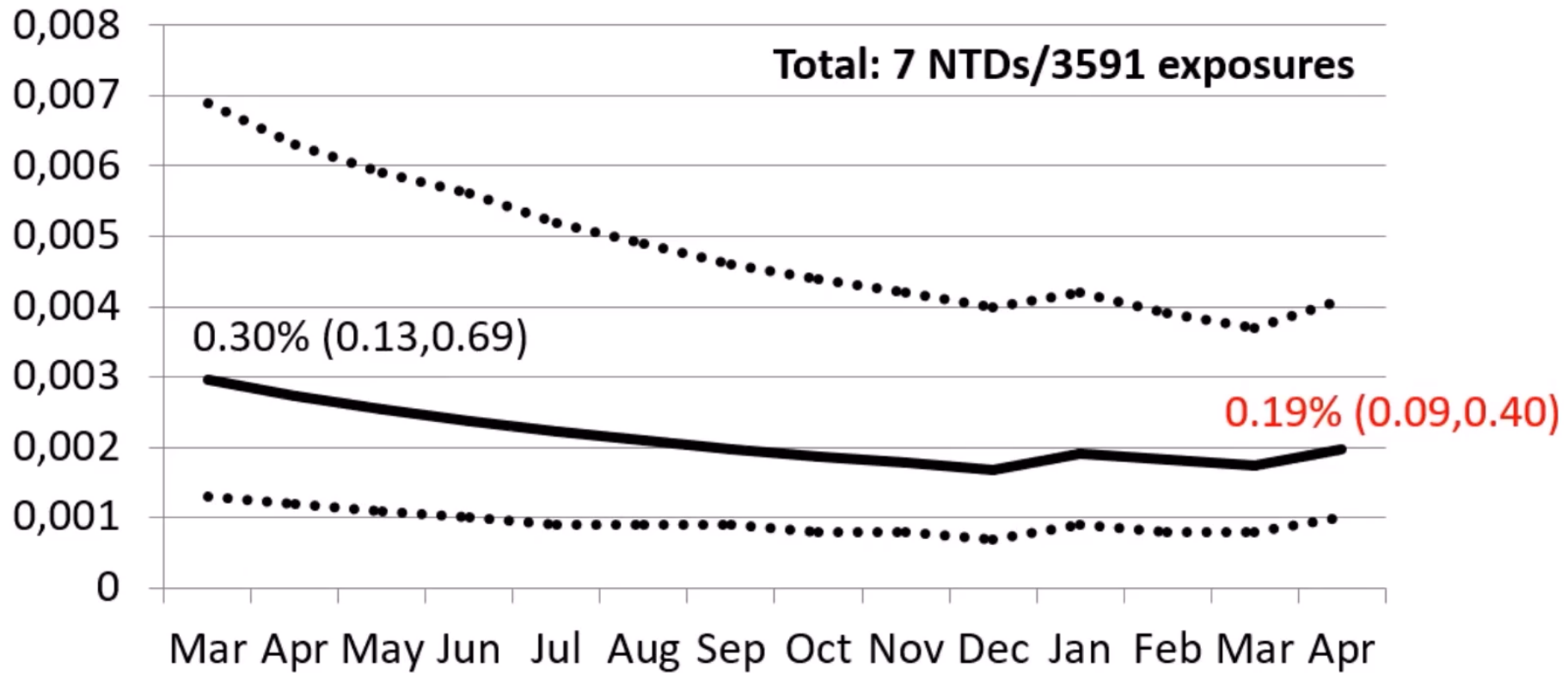
Summary of DHHS Recommendations on Dolutegravir

ART for treatment naïve pregnant patients	Continuing ART for patients suppressed and on well-tolerated regimen	ART for patients who have received ART in the past, but currently off treatment
Preferred	Continue	Preferred

New ART regimen for pregnant patients intolerant of/failing current ART	ART for non-pregnant patients trying to conceive
Preferred	Alternative

Updates from AIDS 2020

NTD Prevalence (95% CI) with DTG at conception, Apr 1, 2019-April 30, 2020



Considerations for DTG use in Women of Childbearing Potential

- Assess the patient's desire for pregnancy
- Discuss risks with patients
- Review treatment history and prior genotypes for alternative agents
- Consider adherence and ability to follow multiple tablet or BID regimen

Prophylaxis of Opportunistic Infections – Opportunities for Antibiotic Stewardship

- Primary Prophylaxis of Mycobacterium Avium Complex
 - MAC prophylaxis no longer recommended in those who immediately initiate ART
- Primary Prophylaxis of Pneumocystis Pneumonia and Toxoplasma gondii encephalitis
 - Okay to D/C if CD4 100-200 cells/mm³ with an undetectable viral load



NOVEL AGENTS

Fostemsavir (FTR)

- Attachment inhibitor that binds to gp120 to prevent viral attachment and CD₄ entry
 - No cross resistance to other classes of ART
- Ongoing phase 3 study of fostemsavir based salvage regimens in multi-drug resistant HIV (BRIGHTE)
 - 60% of patients in randomized cohort and 37% of patients in the non-randomized cohort had HIV RNA < 40 copies/mL at week 96
- Most common adverse events: nausea (4%), diarrhea (2%), and headache (2%)
- Received FDA approval for MDR HIV 07/2020

Injectable ART: Cabotegravir/Rilpivirine (CAB/RPV)

- Studied in treatment naïve subjects after 20 weeks of oral therapy (FLAIR) or for stable switch in suppressed patients (ATLAS)
- 48 week virologic suppression was similar for injectable compared to conventional ART
- 3 subjects in each study experienced confirmed virologic failure
 - FLAIR – all subjects developed RPV and INSTI resistance mutations
 - ATLAS – one subjects developed RPV/INSTI resistance; others had RPV resistance at baseline

Practical Considerations for use of CAB/RPV

- Initiation requires loading dose
- Agents are not co-formulated
- Screen for pre-existing resistance to RPV or INSTIs
- Rule out chronic HBV infection
- Ensure virologic suppressed before initiation
- Assess adherence to monthly clinic visits
- Oral lead-in period required

Thank you!

To all of the clinic staff and physicians, including

- Dr. Joseph Garland
- Pharmacy Liaisons
 - Melanie Ferreira
 - James Wisnaskas
- Clinic Nurses
- Clinic Social Workers
- Clinic Outreach Workers
- Research Team, including Dr. Karen Tashima

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