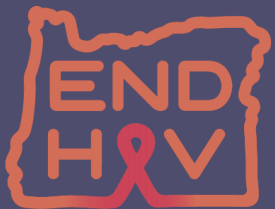


# HIV Treatment Update

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# Disclosures

3-Letter Abbreviation	Generic Name	Brand Name	ARV Class
3TC	Lamivudine	Epivir	NRTI
3TC / ABC	Lamivudine / Abacavir	Epzicom	NRTI
3TC / AZT	Lamivudine / Zidovudine	Combivir	NRTI
3TC / AZT / ABC	Lamivudine / Zidovudine / Abacavir	Trizivir	NRTI
3TC / TDF	Lamivudine / Tenofovir DF	Cimduo	NRTI
3TC / TDF / EFV	Lamivudine / Tenofovir DF / Efavirenz	Symfi & Symfi Lo	NRTI + NNRTI
ABC	Abacavir	Ziagen	NRTI
ABC / DTG / 3TC	Abacavir / Dolutegravir / Lamivudine	Triumeq	NRTI + InSTI
ATV	Atazanavir	Reyataz	PI
AZT (or ZDV)	Zidovudine	Retrovir	NRTI
CAB	Cabotegravir	Vocabria	InSTI
d4T	Stavudine	Zerit	NRTI
ddI (or ddI-EC)	Didanosine	Videx EC	NRTI
DOR	Doravirine	Pifeltro	NNRTI
DRV	Darunavir	Prezista	PI
DTG	Dolutegravir	Tivicay	InSTI
DTG / 3TC	Dolutegravir / Lamivudine	Dovato	InSTI + NRTI
DTG / RPV	Dolutegravir / Rilpivirine	Juluca	InSTI + NNRTI
EFV	Efavirenz	Sustiva	NNRTI
ETR	Etravirine	Intelence	NNRTI

# ARV Abbreviations

## ARV Classes:

Abbreviation	ARV Class
EI	Entry Inhibitor
InSTI	Integrase Inhibitor
NRTI	Nucleos(t)ide Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
PE	Pharmacokinetic Enhancer

3-Letter Abbreviation	Generic Name	Brand Name	ARV Class	3-Letter Abbreviation
FPV	Fosamprenavir	Lexiva	PI	Qday - BID
FTC / TAF	Emtricitabine / Tenofovir ALAFENAMIDE	Descovy	NRTI	Qday
FTC / TAF / BIC	Emtricitabine / Tenofovir alafenamide / bictegravir	Biktarvy	NRTI + InSTI	Qday
FTC / TAF / EVG / COBI	Emtricitabine / Tenofovir ALAFENAMIDE / Elvitegravir / Cobicistat	Genvoya	NRTI + InSTI + booster	Qday
FTC / TAF / RPV	Emtricitabine / Tenofovir ALAFENAMIDE / Rilpivirine	Odefsey	NRTI + NNRTI	Qday
FTC / TDF	Emtricitabine / Tenofovir DF	Truvada	NRTI	Qday
FTC / TDF / DOR	Emtricitabine / Tenofovir DF / doravirine	Delstrigo	NRTI + NNRTI	Qday
FTC / TDF / EFV	Emtricitabine / Tenofovir DF / Efavirenz	Atripla	NRTI + NNRTI	Qday
FTC / TDF / EVG / COBI	Emtricitabine / Tenofovir DF / Elvitegravir / Cobicistat	Stribild	NRTI + InSTI + booster	Qday
FTC / TDF / RPV	Emtricitabine / Tenofovir DF / Rilpivirine	Complera	NRTI + NNRTI	Qday
LPV/r	Lopinavir / Ritonavir	Kaletra	PI	Qday - BID
MVC	Maraviroc	Selzentry	EI	BID
NVP	Nevirapine	Viramune	NNRTI	BID
RAL	Raltegravir	Isentress	InSTI	BID
RPV	Rilpivirine	Edurant	NNRTI	Qday
RTV	Ritonavir	Norvir	PI	Qday - BID
TAF	Tenofovir Alafenamide	Vemlidy*	NRTI	Qday
TDF	Tenofovir DF	Viread	NRTI	Qday
TFV	Tenofovir (DF or AF)	n/a	NRTI	

# ARV Abbreviations

Brand Name	3-Letter Abbreviation	Generic Name	ARV Class
Atripla	FTC / TDF / EFV	Emtricitabine / Tenofovir DF / Efavirenz	NRTI + NNRTI
Biktarvy	FTC / TAF / BIC	Emtricitabine / Tenofovir alafenamide / bictegravir	NRTI + InSTI
Cabenuva	CAB / RPV	Cabotegravir / Rilpivirine IM Injection	InSTI + NNRTI
Cimduo	3TC / TDF	Lamivudine / Tenofovir DF	NRTI
Combivir	3TC / AZT	Lamivudine / Zidovudine	NRTI
Complera	FTC / TDF / RPV	Emtricitabine / Tenofovir DF / Rilpivirine	NRTI + NNRTI
Delstrigo	FTC / TDF / DOR	Emtricitabine / Tenofovir DF / doravirine	NRTI + NNRTI
Descovy	FTC / TAF	Emtricitabine / Tenofovir ALAFENAMIDE	NRTI
Dovato	DTG / 3TC	Dolutegravir / Lamivudine	InSTI + NRTI
Epzicom	3TC / ABC	Lamivudine / Abacavir	NRTI
Genvoya	FTC / TAF / EVG / COBI	Emtricitabine / Tenofovir ALAFENAMIDE / Elvitegravir / Cobicistat	NRTI + InSTI + booster
Juluca	DTG / RPV	Dolutegravir / Rilpivirine	InSTI + NNRTI
Odefsey	FTC / TAF / RPV	Emtricitabine / Tenofovir ALAFENAMIDE / Rilpivirine	NRTI + NNRTI
Stribild	FTC / TDF / EVG / COBI	Emtricitabine / Tenofovir DF / Elvitegravir / Cobicistat	NRTI + InSTI + booster
Symfi & Symfi Lo	3TC / TDF / EFV	Lamivudine / Tenofovir DF / Efavirenz	NRTI + NNRTI
Triumeq	ABC / DTG / 3TC	Abacavir / Dolutegravir / Lamivudine	NRTI + InSTI
Trizivir	3TC / AZT / ABC	Lamivudine / Zidovudine / Abacavir	NRTI
Truvada	FTC / TDF	Emtricitabine / Tenofovir DF	NRTI

# Nomenclature

- TFV = either tenofovir formulation (TDF or TAF)
- / means it's a combination tablet OR boosted regimen

# Goals

Review the newer concepts related to “when to start” treatment for HIV infection

Identify the currently preferred antiretroviral (ARV) regimens

Discuss the place in therapy of the Integrase Inhibitor class and the new “dual therapy” regimens

# When to Start Updates

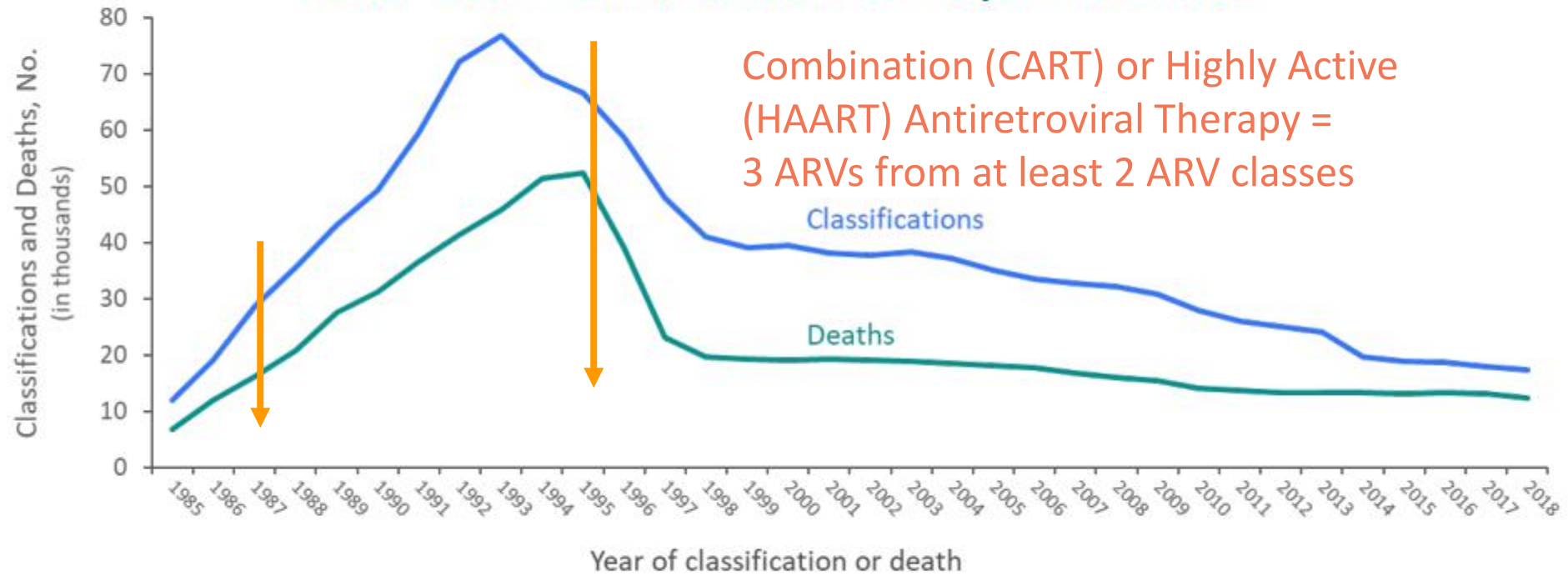
# Goals of Treatment

- Maximally and durably suppress plasma HIV RNA
- Restore and preserve immunologic function
- Reduce HIV-associated morbidity and prolong the duration and quality of survival
- Prevent transmission (MTCT, TasP)

Adapted from DHHS HIV/AIDS Treatment Guidelines for Adults and Adolescents: [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov) (last update: 28 Jan 2016)

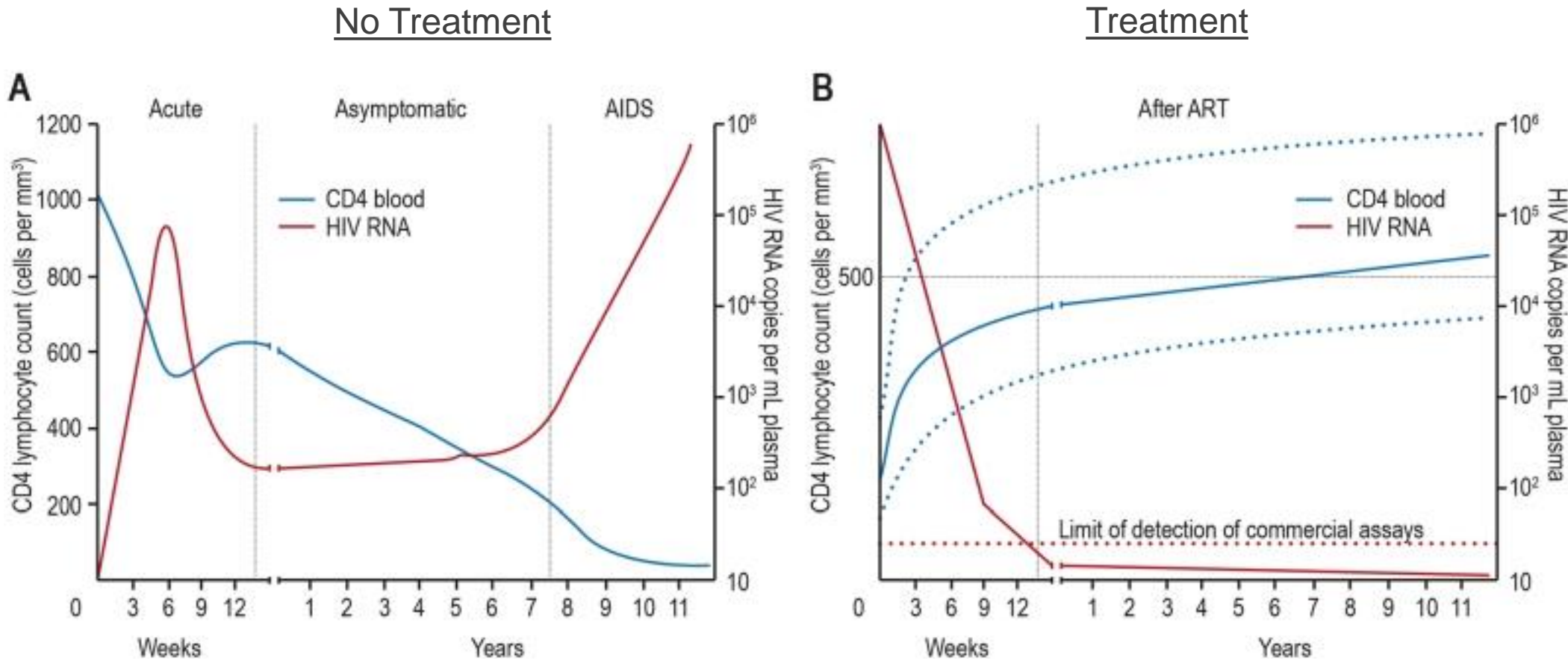


## Stage 3 (AIDS) Classifications and Deaths of Persons with Diagnosed HIV Infection Ever Classified as Stage 3 (AIDS) among Adults and Adolescents 1985–2018—United States and 6 Dependent Areas



Note. Deaths of persons with HIV infection, stage 3 (AIDS) may be due to any cause.

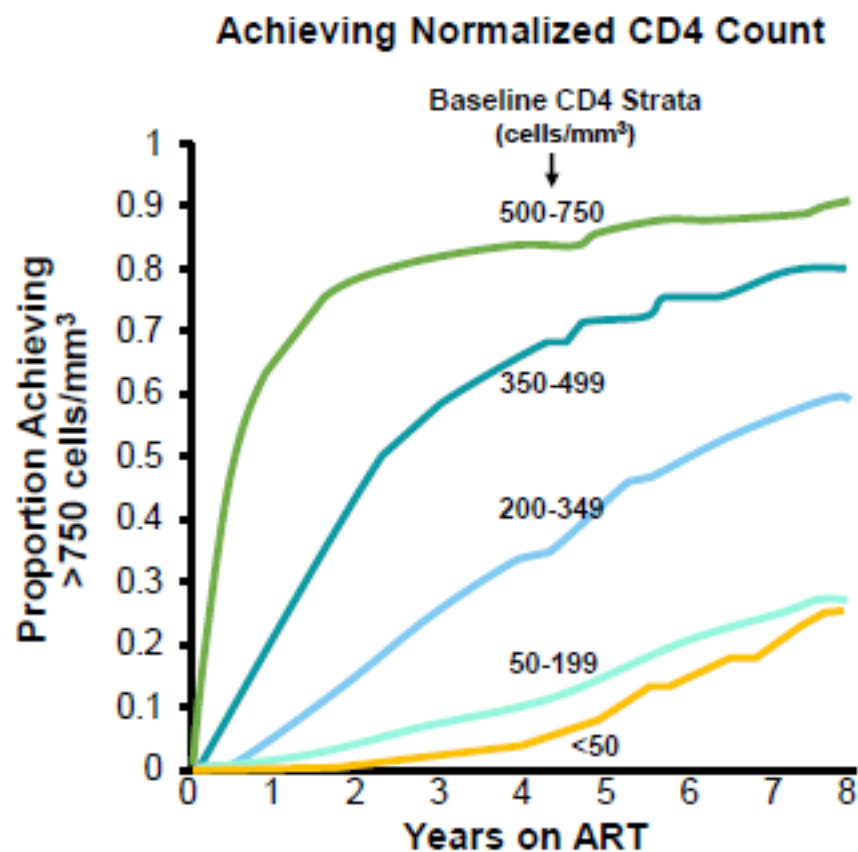
# HIV Progression Without vs With ARV Treatment



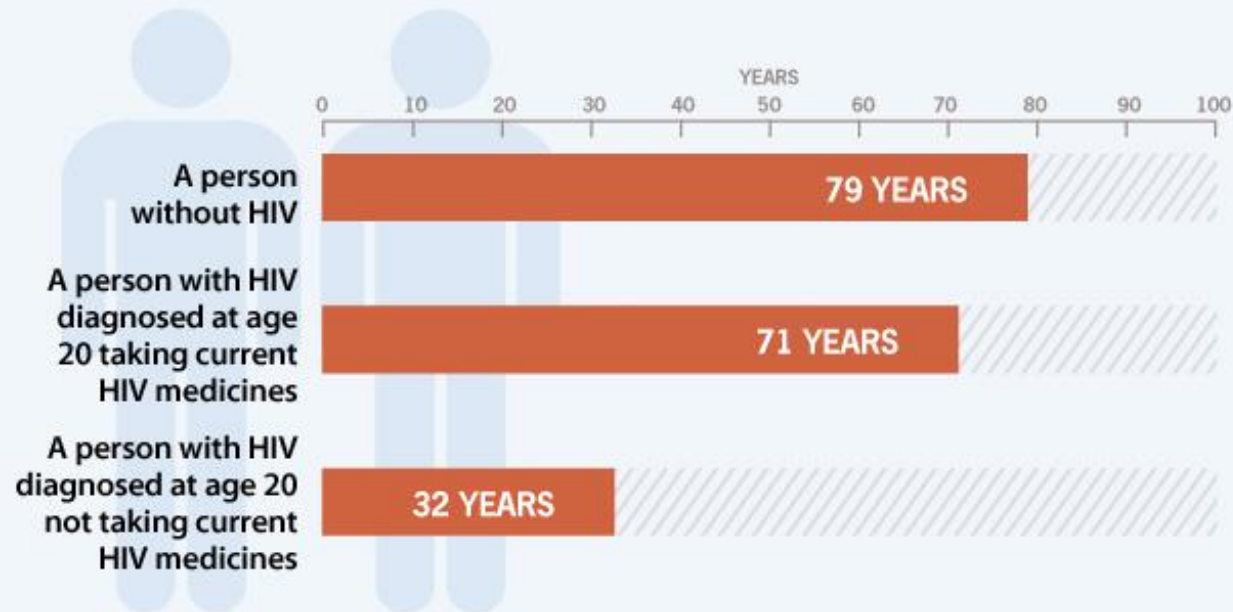
Adapted by *Microbial Cell* from: Maartens G, Celum C, and Lewin SR. *Lancet* 2014;384:258-71  
 Available at: <http://microbialcell.com/figure-5-hiv-aids-pandemic/>

## HOPS Cohort: ART Initiation and Achieving CD4 Normalization

- CD4 trajectories in the HOPS Cohort after  $\geq 3$  years of ART (n=1327) (1996-2012)
  - CD4 normalization ( $>750$  cells/mm<sup>3</sup>)
- After 7.9 years of follow-up, progressively higher CD4 at ART initiation was associated with
  - Greater gains in CD4
  - Greater likelihood of CD4 normalization (baseline CD4 and hazard ratio for achieving CD4 normalization with ART)
    - 500-750 cells/mm<sup>3</sup>: 12.78 ( $P<0.001$ )
    - 350-499 cells/mm<sup>3</sup>: 7.02 ( $P<0.001$ )
    - 200-349 cells/mm<sup>3</sup>: 3.16 ( $P<0.001$ )
    - Reference: 0-49 cells/mm<sup>3</sup>: 1.0
  - Increased survival rates



# HIV Medicines Help People with HIV Live Longer (Average years of life)



SOURCE: National Vital Statistics Reports, 2012; PLoS One, 2013; and Journal of the American Medical Association, 1993.



**CDC**  
*Vitalsigns*<sup>TM</sup>

[www.cdc.gov/vitalsigns/HIV-AIDS-medical-care](http://www.cdc.gov/vitalsigns/HIV-AIDS-medical-care)



## Risk of HIV Transmission With Undetectable Viral Load by Transmission Category

Transmission Category	Risk for People Who Keep an Undetectable Viral Load
Sex (oral, anal, or vaginal)	Effectively no risk
Pregnancy, labor, and delivery	1% or less <sup>†</sup>
Sharing syringes or other drug injection equipment	Unknown, but likely reduced risk
Breastfeeding	<b>Substantially reduces, but does not eliminate risk.</b> Current recommendation in the United States is that mothers with HIV should <i>not</i> breastfeed their infants.

<sup>†</sup> The risk of transmitting HIV to the baby can be 1% or less if the mother takes HIV medicine daily as prescribed throughout pregnancy, labor, and delivery and gives HIV medicine to her baby for 4-6 weeks after giving birth.

# WHEN To Start Treatment

## Panel's Recommendations for Initiating Antiretroviral Therapy in Treatment-Naive Patients

### Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality **(AI)** and to prevent the transmission of HIV to others **(AI)**.
- 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

DHHS HIV/AIDS Treatment Guidelines for Adults and Adolescents: [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov) (last update: 18 Dec 2019)

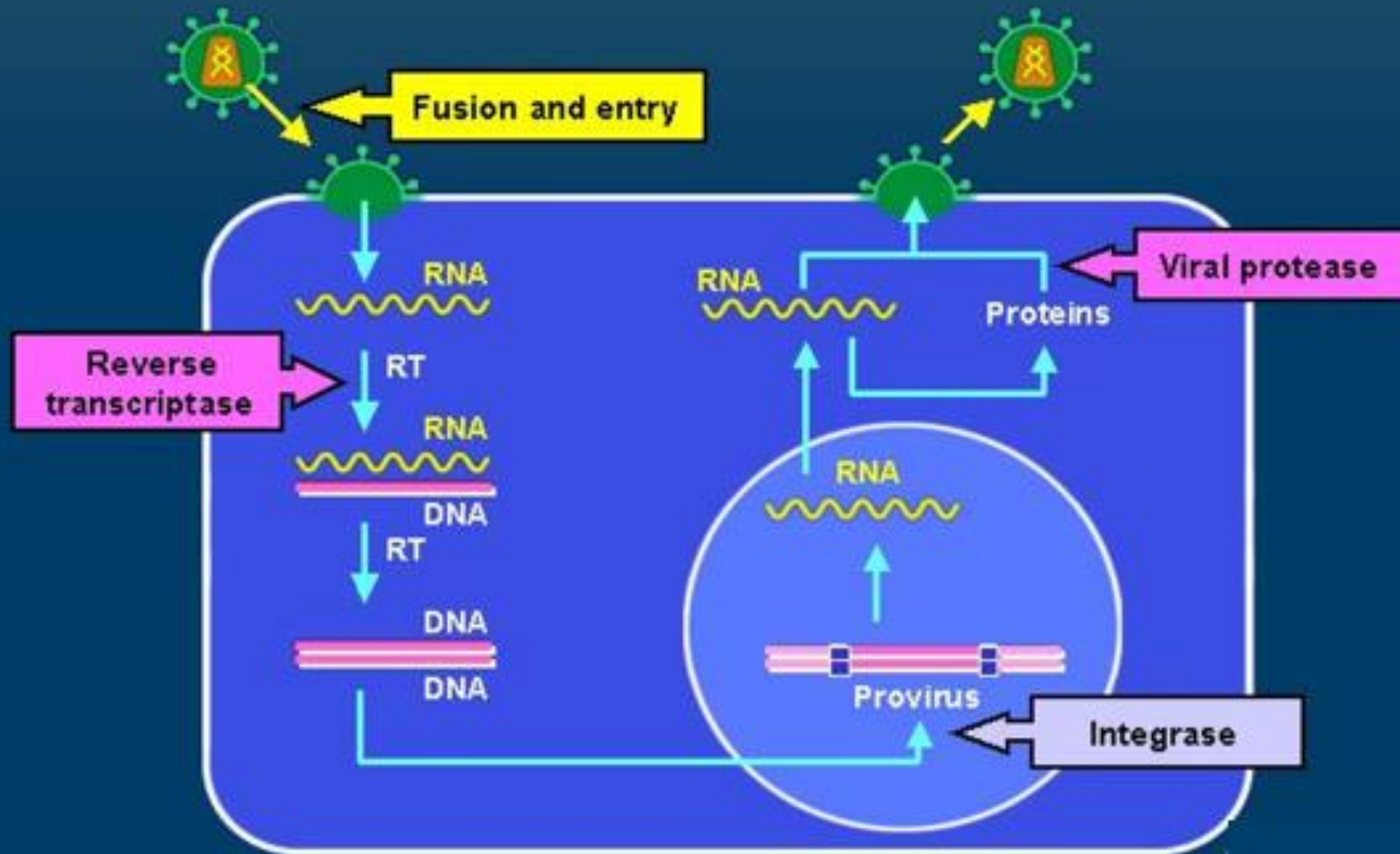
# WHEN To Initiate Treatment

- Rapid ARV Initiation
  - Always during pregnancy
  - When resources and workflows are in place to do so for everyone who accepts it
- Delayed ARV Initiation
  - In presence of some Opportunistic Infections
    - Risk of Immune Reconstitution Syndrome (IRIS)

# What to Start Updates



# HIV Replication

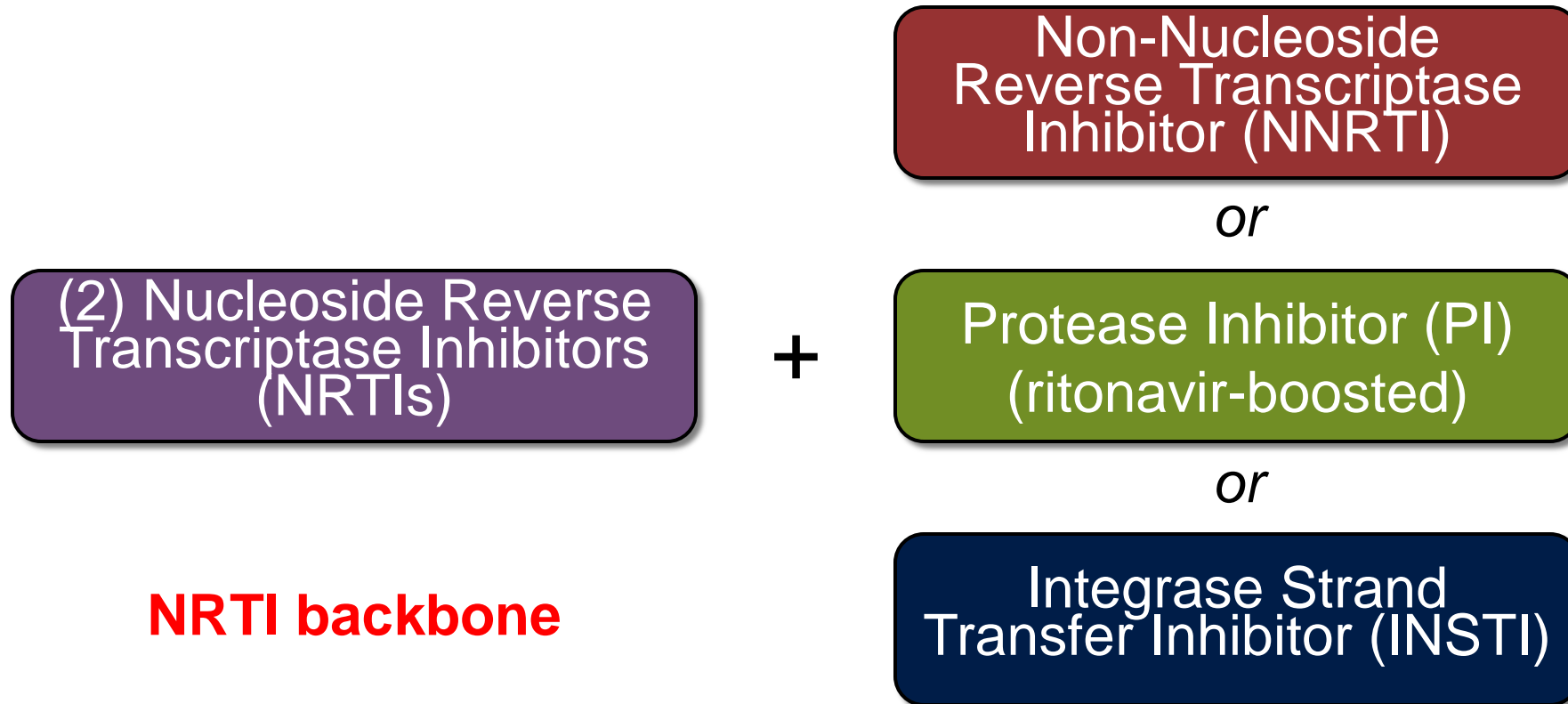


# Overview of Antiretrovirals

<p><b>Nucleoside Reverse Transcriptase Inhibitors (NRTIs):</b></p> <p>Abacavir      Stavudine            Didanosine      Tenofovir DF/AF            Emtricitabine      Zidovudine            Lamivudine</p>	<p><b>Integrase Inhibitors (InSTI):</b></p> <p>Bictegravir            Dolutegravir            Elvitegravir            Raltegravir            Cabotegravir</p>
<p><b>Protease Inhibitors (PIs):</b></p> <p>Atazanavir      Lopinavir/ritonavir            Darunavir      Nelfinavir            Fosamprenavir      Saquinavir            Indinavir      Tipranavir</p>	<p><b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):</b></p> <p>Delavirdine      Etravirine            Doravirine      Nevirapine            Efavirenz      Rilpivirine</p>
<p><b>Entry Inhibitors (EI):</b></p> <p>Enfuvirtide            Maraviroc            Ibalizumab            Fostemsavir</p>	<p><b>Pharmacokinetic Enhancers (“Boosters”):</b></p> <p>Cobicistat            Ritonavir (also a protease inhibitor)</p>

# DHHS Antiretroviral Therapy Guidelines

## Traditional Preferred Initial Therapy Regimen Classes

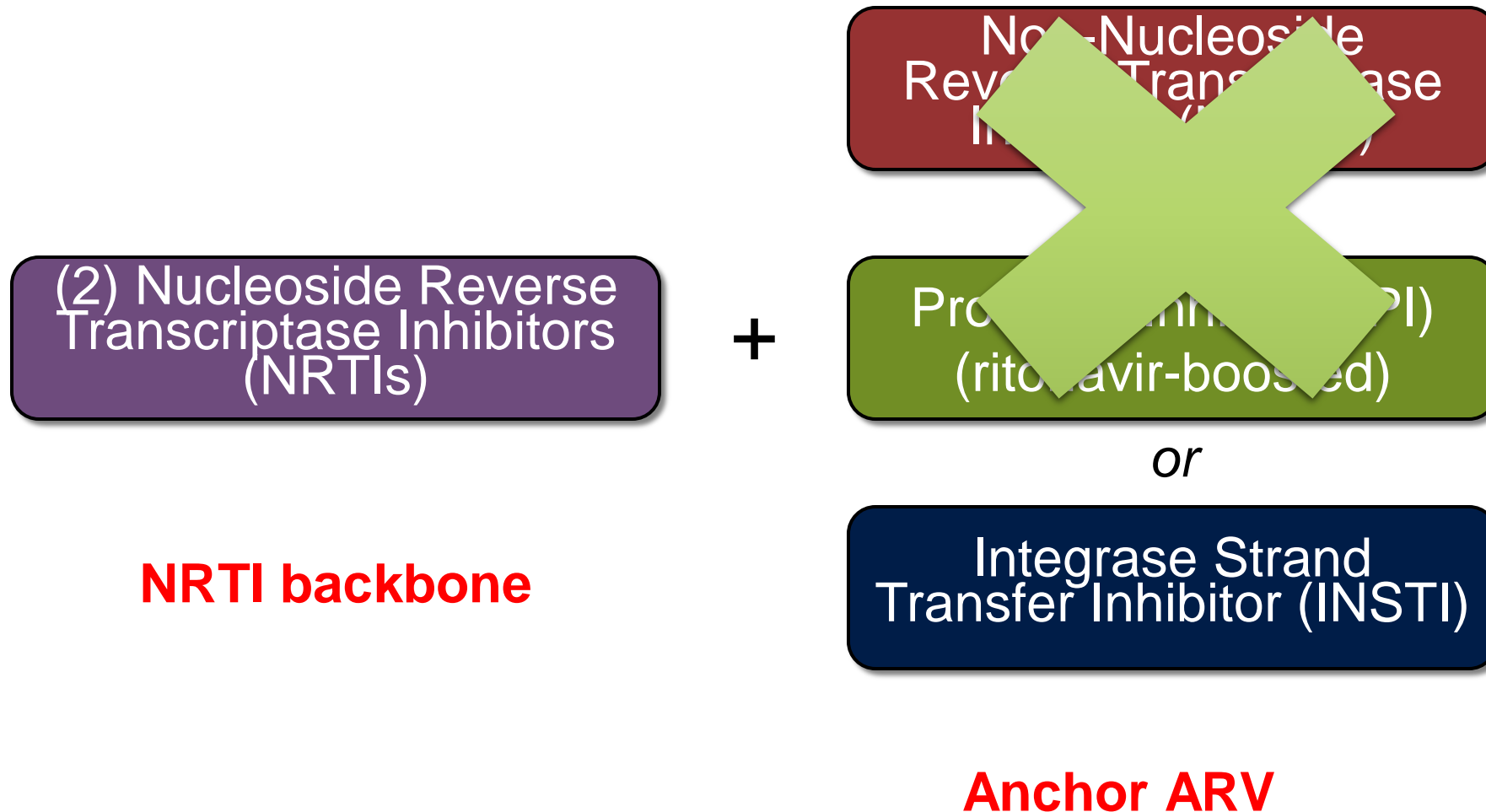


**NRTI backbone**

**Anchor ARV**

# DHHS Antiretroviral Therapy Guidelines

## Traditional Preferred Initial Therapy Regimen Classes



# Recommended Initial Regimens for **Most People**

- 2 NRTIs + Integrase Inhibitor (InSTI)

- Single Tablet Regimen Options

- 3TC / ABC<sup>1</sup> / DTG (AI) = Triumeq<sup>®</sup>

- FTC / TAF / BIC (AI) = Biktarvy<sup>®</sup>

- Two Tablet Regimen Options

- FTC / TFV + DTG (AI)

- FTC / TFV + RAL

- w/TDF (BI), w/TAF (BII)

<sup>1</sup>Only for those negative for the HLA-B\*5701 allele

- 1 NRTI + 1 InSTI

- 3TC / DTG<sup>2</sup> (AI) = Dovato<sup>®</sup>

<sup>2</sup>Only for those with VL < 500,000 copies/mL, no Hep B coinfection, and resistance testing is completed

# Recommended Initial Regimens in **Certain Clinical Situations**

- 2 NRTIs + Integrase Inhibitor (InSTI)
  - FTC / TFV / EVG / COBI (BI)
    - w/TDF = Stribild<sup>®</sup>
    - w/TAF = Genvoya<sup>®</sup>
- 2 NRTIs + Protease Inhibitor (PI)
  - FTC / TFV + DRV + [RTV or COBI] (AI)
    - FTC / TAF / DRV / COBI = Symtuza<sup>®</sup>

Adapted from DHHS HIV/AIDS Treatment Guidelines for Adults and Adolescents: [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov) (last update: 18 Dec 2019)

# Integrase Inhibitors - EFFICACY

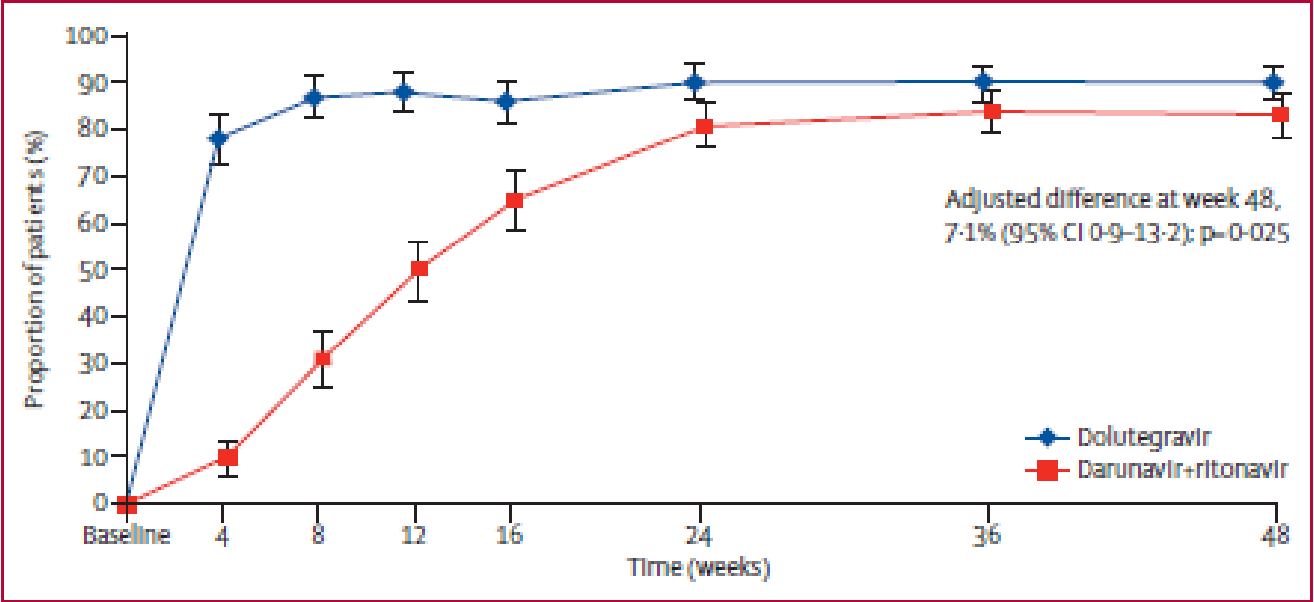
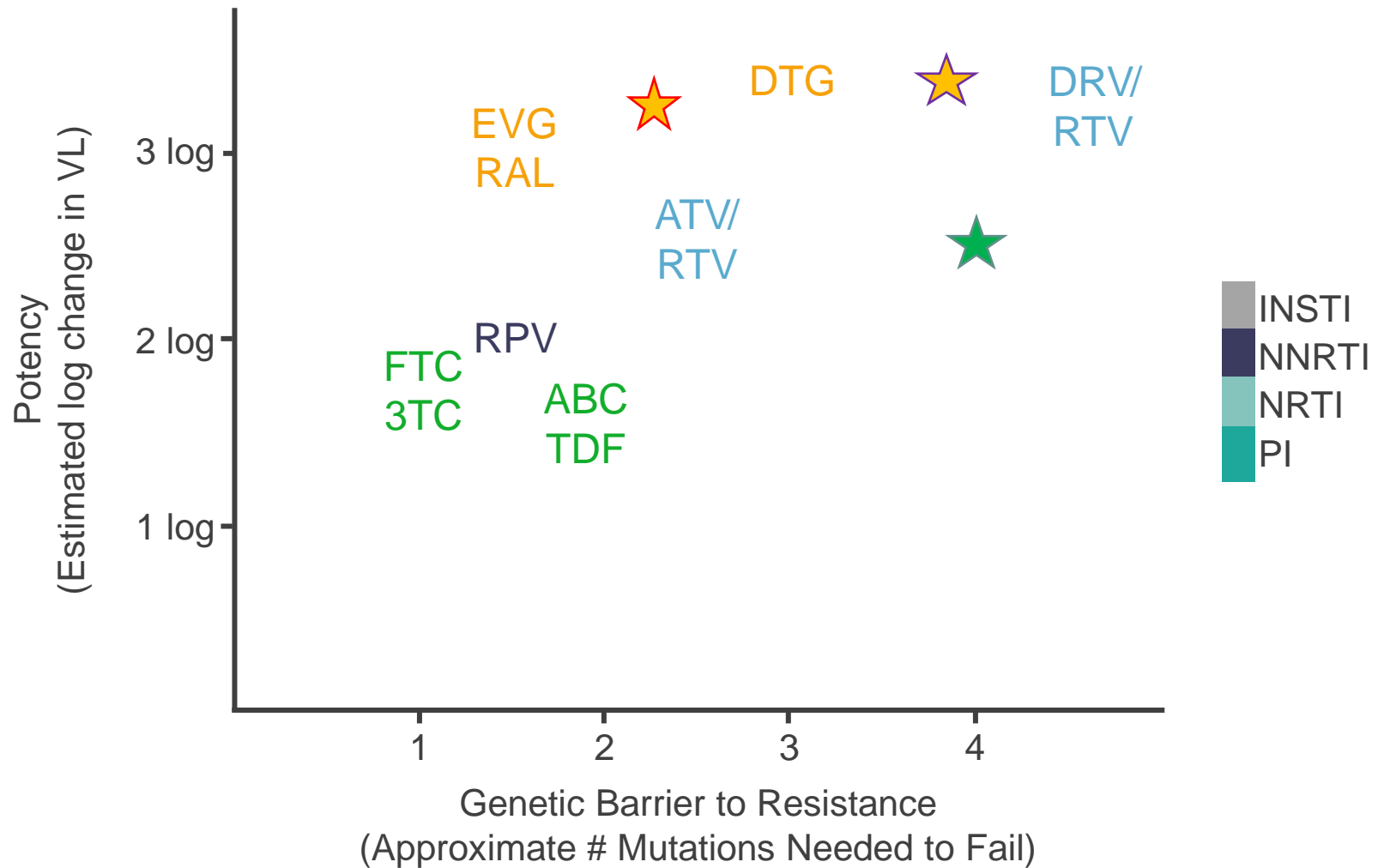


Figure 2: Proportion of patients (95% CI) with HIV-1 RNA of less than 50 copies per mL by visit. Error bars indicate 95% CIs.

## FLAMINGO: DTG vs DRV + RTV in Treatment Naïve

Clotet et al. *Lancet* 2014; 383:2222-2231.

# Genetic Barrier to Resistance for Specific ARVs





# Integrase Inhibitors

- Inhibits the “strand transfer” phase of HIV DNA integration into the host DNA
  - Raltegravir (Isentress<sup>®</sup> and Isentress HD<sup>®</sup>; RAL)
  - Elvitegravir (in Genvoya<sup>®</sup> and Stribild<sup>®</sup>; EVG)
  - Dolutegravir (Tivicay<sup>®</sup> and in Triumeq<sup>®</sup>; DTG)
  - Bictegravir (in Biktarvy<sup>®</sup>; BIC)

# Integrase Inhibitors

Potential Future Directions???:

\*Cabotegravir ORAL lead-in/bridge product available at community pharmacies

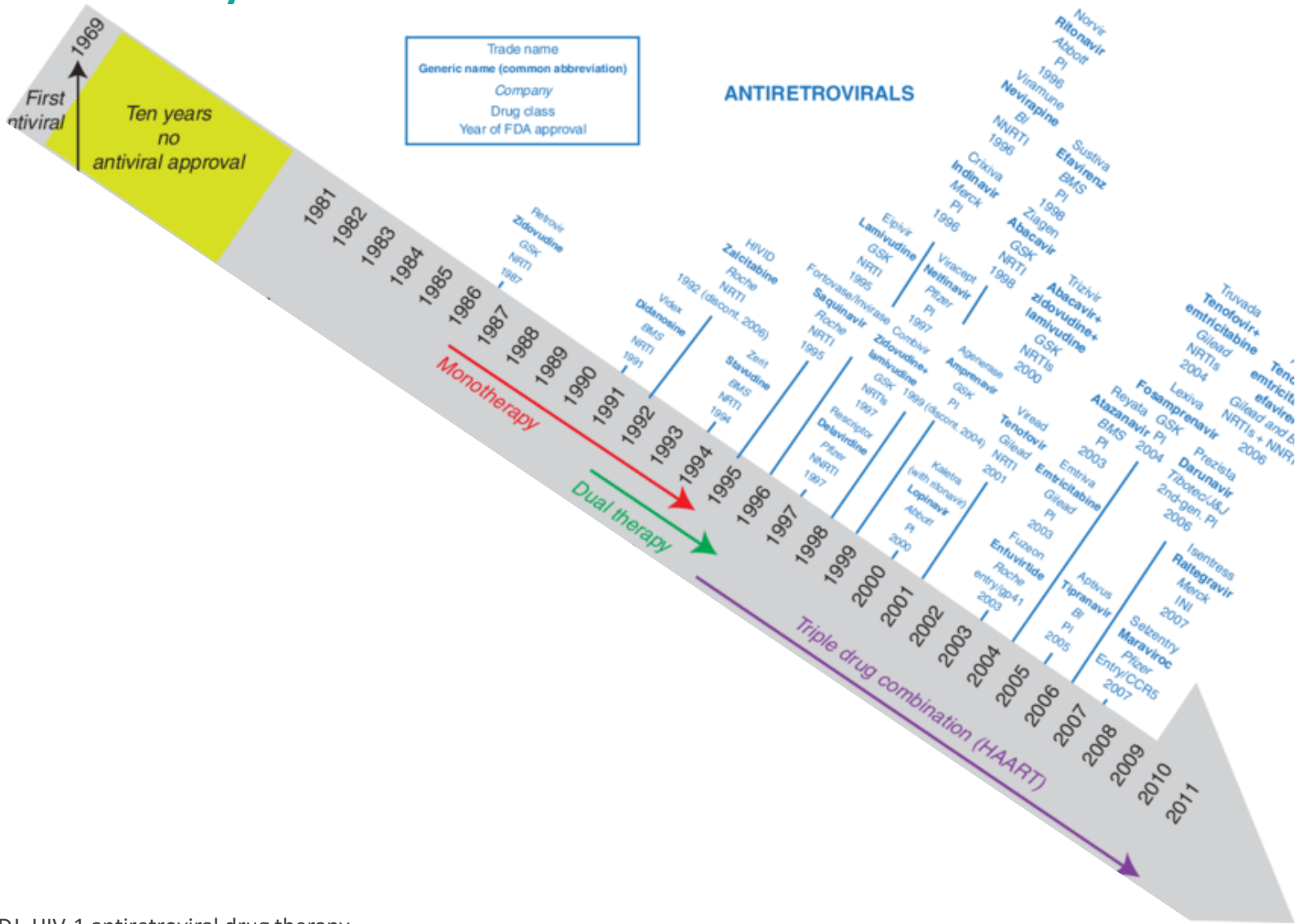
\*Community pharmacy injection of or space for injection of cabotegravir products?

\*Other long-acting parenteral treatments

- Cabotegravir (Vocabria® and in Cabenuva®; CAB)
  - FDA Approval Jan 2021
    - Only as switch strategy for virologically suppressed patients
    - Long-acting injectable, combined with rilpivirine
  - Requires oral-lead in dosing before injection
  - Cabotegravir ORAL product is currently very limited distribution
    - May have people eventually who just want rilpivirine ORAL – **always check with at least the patient and make sure they understand NOT to take rilpivirine without the cabotegravir or other medication**
  - New drug application submitted to the FDA for PrEP
    - Single entity cabotegravir injection

# New “Dual Therapy” Options

# Antiretroviral History



Modified from: Arts EJ and Hazuda DJ. HIV-1 antiretroviral drug therapy. *Cold Spring Harb Perspect Med* 2012;2:a007161

# Common Dual Therapy Options in Cases of Viral Resistance or Intolerance / Inability to Use NRTIs

- InSTI + NNRTI
  - Dolutegravir / Rilpivirine (Juluca<sup>®</sup>)
    - Only approved for use as a switch strategy
  - Cabotegravir / Rilpivirine (Cabenuva<sup>®</sup>) INJECTION
    - Only approved for use as a switch strategy
- InSTI + 1 NRTI
  - Dolutegravir / Lamivudine (Dovato<sup>®</sup>)
    - Lamivudine is one of the most well tolerated NRTIs
- InSTI + PI
  - Dolutegravir + Darunavir / cobicistat (Prezcobix)

## Non-Nucleoside Reverse Transcriptase Inhibitors:

Drug Name	Dose	Side Effects	Comments
Rilpivirine (Edurant <sup>®</sup> , RPV)	25 mg daily	Less incidence of rash or CNS effects vs. efavirenz; may cause increased SCr but, no change in GFR	<u>Avoid with HIV VL &gt; 100,000 copies/mL or CD4 count &lt; 200 cells/mm<sup>3</sup> or high risk for poor adherence;</u> <u>ACID suppressant interactions,</u> <u>Take with food;</u> active against K103N mutation
Doravirine (Pifeltro <sup>®</sup> DOR)	100 mg daily	Sleep disturbance, dizziness, altered sensorium, suicidality/self-harm Neuropsych: EFV > RPV, DOR > ETR	With or without food  Active against K103N and possibly other mutations

# New Antiretrovirals with New Mechanisms of Action

# Attachment Inhibitor

- Fostemsavir (Rukobia<sup>®</sup>; FTR)
  - Approved July 2020
  - Prodrug – hydrolyzed to temsavir
  - 600 mg po BID
  - Potential Side Effects:
    - Nausea, diarrhea
    - Increased LFT's, SCr



# Attachment Inhibitor

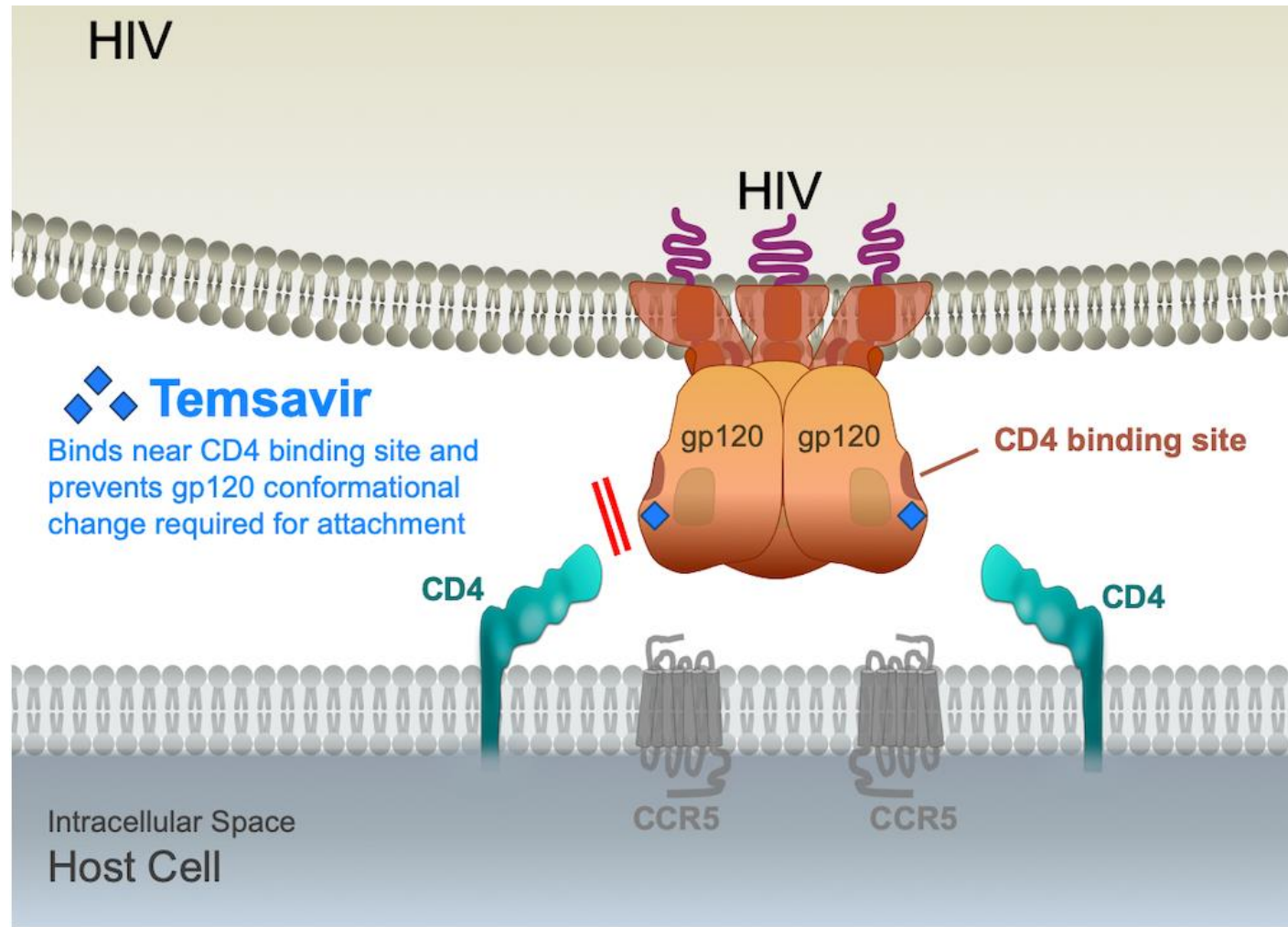


Figure 5 - Mechanism of Action of Attachment Inhibitors

The attachment inhibitor fostemsavir is hydrolyzed to its active form temsavir, which binds to HIV gp120 and prevents normal attachment of the host CD4 receptor with HIV gp120.

Illustration by David H. Spach, MD

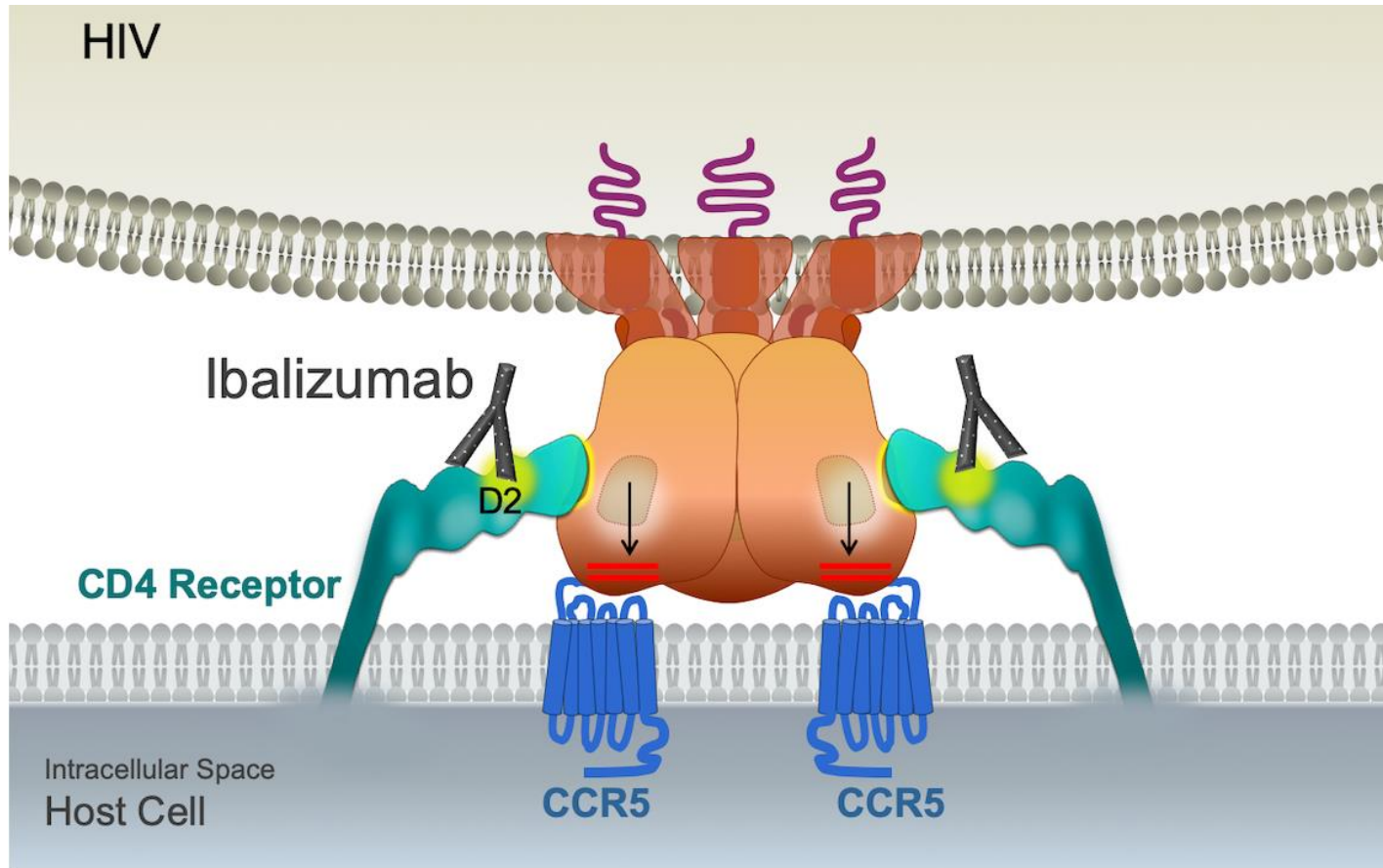
# POST-Attachment Inhibitor

- Ibalizumab-uiyk (Trogarzo<sup>®</sup>; IBA)
  - Approved March 2018
  - Monoclonal antibody
    - Induction: 2,000 mg x 1 dose over at least 30 minutes and with 1-hr post-dose observation
    - Maintenance: 800 mg q14 days over at least 15 minutes and with 15 min post-dose observation
    - Repeat induction dose if > 3 days late

# POST-Attachment Inhibitor

- Potential Side Effects
  - Diarrhea, dizziness, nausea, rash
  - Infusion reactions
- Drug-Drug Interactions
  - None known; none expected
- MOA: Binds to domain 2 of CD4 cell receptor; blocks interaction between gp120 and the CD4 cell coreceptors (both CCR5 and CXCR4)

# POST-Attachment Inhibitor



**Figure 6 - Mechanism of Action of CD4 Postattachment Inhibitors**

The CD4 postattachment inhibitor ibalizumab is a humanized monoclonal antibody that binds to the domain 2 region of the human CD4 cell receptor. This binding does not prevent attachment of HIV gp120 with the host CD4 receptor, but, through steric hindrance it prevents normal postbinding conformational changes in gp120 that are required for gp120-coreceptor binding.

Illustration by David H. Spach, MD

# Resources

# HIV / AIDS Resources

- [www.clinicalinfo.hiv.gov](http://www.clinicalinfo.hiv.gov)
  - HIV / AIDS Treatment Guidelines – ALL categories
    - Pediatric Treatment Guidelines
    - Perinatal Treatment Guidelines
    - Opportunistic Infection Prophylaxis and Treatment Guidelines
    - Pre- and Post- Exposure Guidelines
  - Includes Data on Drug – Drug Interactions
- [www.nccc.ucsf.edu](http://www.nccc.ucsf.edu)
  - HIV Telephone Consultation Service
  - Pre- AND Post- Exposure Prophylaxis Consultations
  - Perinatal HIV Consultation and Referral Service

# HIV / AIDS Resources –

- [www.hiv.uw.edu](http://www.hiv.uw.edu)
  - Comprehensive HIV care, treatment, and prevention information
  - National HIV Curriculum training course for providers
- [ORAETC.org](http://ORAETC.org)
  - Oregon AIDS Education and Training Center (AETC)
  - Resources by county
  - Provider consultations, mentoring, webinars, conferences

# HIV / AIDS Resources – Community Resources

- Care-Assist (Oregon's ADAP)
  - <http://www.oregon.gov/oha/ph/DiseasesConditions/HIVSTDViralHepatitis/HIVCareTreatment/CAREAssist/Pages/index.aspx>
- Partnership Project
  - <http://www.ohsu.edu/partnership>
  - Social Work and Nurse (RN) Case Management and Medical Navigator Services



# HIV / AIDS Resources – Community Resources

- HIV Alliance
  - [www.hivalliance.org](http://www.hivalliance.org)
  - Case management and other services
- CAP (Cascade AIDS Project)
  - [www.cascadeaids.org](http://www.cascadeaids.org)
  - Case management and other services
  - SW Washington general case management support

Let's end HIV in Oregon.

We can make it  
happen.  
The time is now.

