# HIV 30 Years Later: Where We Were and Where We're Going

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## Disclosure

- The speaker has no conflicts of interest to disclose

## Learning Objectives for Pharmacists

1. List recent changes in the Department of Health and Human Services (DHHS) HIV Guidelines.
2. Identify differences between tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF).
3. Discuss updates regarding HIV Pre-exposure Prophylaxis (PrEP).
4. Identify potential new antiretroviral (ARV) mechanisms of action and routes of administration.
5. Discuss opportunities for Pharmacist integration within an ambulatory care HIV/ID clinic.

## Learning Objectives for Pharmacy Technicians

1. List recent changes in the DHHS HIV Guidelines.
2. Identify differences between tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF).
3. Discuss updates regarding HIV Pre-exposure Prophylaxis (PrEP).

## HIV Terminology

- CD4 or T Cells – normal CD4 500 – 1,500 cells
- VL or HIV RNA-viral load
- ND HIV RNA – non detectable viral load (< 20 copies/ml)
- ART (antiretroviral therapy)/ARVs (antiretrovirals)
- STR (single tablet regimens)
- HAART (highly active ART)-A.K.A. "the cocktail"
- GART-genotype (resistance testing)
- Phenotype- resistance testing reserved if known or suspected complex drug-resistance mutation patterns
- HLA-B*5701- done prior to initiation of Abacavir
- Trofile – done prior to initiation of Maraviroc

## History of HIV

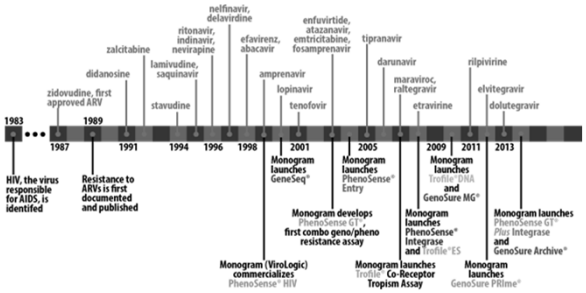
- 1981
  - IBM released first PC
  - Cost of a gigabite of data storage approximately $500,000 ($0.03 today)
  - Avg pharmacists salary ≈ $35,000/yr
  - **June 5th- MMWR describes the unusual occurrence of Pneumocystis carinii pneumonia (PCP) in MSM**
- 1982
  - CDC coins the term "AIDS"
- 1984
  - Renata came to the US
- 1985
  - HIV confirmed as cause of AIDS
- 1987
  - FDA Published regulations which require screening all blood and plasma collected in the U.S. for HIV antibodies

https://www.fda.gov/forpatients/illness/hivaids/history/default.htm

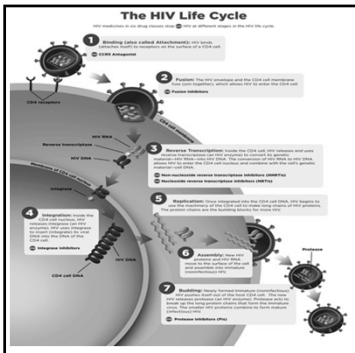
# History of HIV Treatment

- 1987
  - AZT (zidovudine, Retrovir®), a nucleoside analogue reverse transcriptase inhibitor (NRTI) – **1st antiretroviral** approved by the FDA. The recommended dose is one 100mg capsule every four hours *around the clock.*
- 1995
  - Saquinavir -1st protease inhibitor (PI)
- 1996
  - Nevirapine -1st non nucleoside reverse transcriptase inhibitor (NNRTI)
  - Highly Active Antiretroviral Therapy (**HAART**) AKA "The cocktail"
- 2006
  - Atripla - 1st single table regimen (**STR**)
- 2007
  - Raltegravir – 1st integrase inhibitor (INSTI)

https://www.fda.gov/forpatients/illness/hivaids/treatment/ucm118915.htm




Timeline slide developed by Monogram Biosciences, a world leader in HIV testing




https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/73/the-hiv-life-cycle

# HIV Replication

https://www.youtube.com/watch?v=PdzFvxfDGbg

Boehringer Ingelheim, (Producer). (2003).

CDC

April 24, 1998 / Vol. 47 / No. RR-5

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

*Recommendations and Reports*

**Report of the NIH Panel to Define Principles of Therapy of HIV Infection**

**and**

**Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents**

https://aidsinfo.nih.gov/guidelines/archive/adult-and-adolescent-guidelines

# History of HIV Guidelines Updates

**Monday, November 10, 2003**
•Main Guideline PDF (1.51M)
**Monday, July 14, 2003**
•Main Guideline PDF (1.5M)
**Monday, February 4, 2002**
•Main Guideline PDF (1.8M)
**Monday, August 13, 2001**
•Main Guideline PDF (460K)
**Monday, April 23, 2001**
•Main Guideline PDF (393K)
**Monday, February 5, 2001**
•Main Guideline PDF (400K)
**Friday, January 28, 2000**
•Main Guideline PDF (469K)
**Wednesday, May 5, 1999**
•Main Guideline PDF (334K)
**Tuesday, December 1, 1998**
•Main Guideline PDF (230K)
**Wednesday, June 17, 1998**
•Main Guideline PDF (400K)
**Friday, April 24, 1998**
•Main Guideline PDF (723K)

**Monday, November 3, 2008**
•Main Guideline PDF (1.5 MB)
**Friday, April 4, 2008**
•Abacavir Announcement PDF (26 KB)
**Tuesday, January 29, 2008**
Main Guideline PDF (1.7 MB)
**Tuesday, August 7, 2007**
•Nelfinavir Announcement PDF (30 KB)
**Monday, April 30, 2007**
•Entecavir Supplement PDF (19 KB)
**Tuesday, October 10, 2006**
•Main Guideline PDF (2.4 MB)
**Thursday, May 4, 2006**
•Main Guideline PDF (3.4M)
**Thursday, October 6, 2005**
•Main Guideline PDF (2.1M)
**Thursday, April 7, 2005**
•Main Guideline PDF (2.3M)
**Friday, October 29, 2004**
•Main Guideline PDF (1.4M)
**Tuesday, March 23, 2004**
Main Guideline PDF (1.0M)

**Thursday, January 28, 2016**
•Main Guideline PDF (1.21 MB)
**Wednesday, April 8, 2015**
•Main Guideline PDF (1.21 MB)
**Thursday, November 13, 2014**
•Main Guideline PDF (2.2 MB)
**Thursday, May 1, 2014**
•Main Guideline PDF (1.21 MB)
**Tuesday, February 12, 2013**
•Main Guideline PDF (1.5 MB)
**Tuesday, September 18, 2012**
•EVG/COBI/TDF/FTC Update PDF (125 KB)
**Tuesday, March 27, 2012**
•Main Guideline PDF (3.8 MB)
**Friday, October 14, 2011**
•Main Guideline PDF (2.9 MB)
**Tuesday, August 16, 2011**
•Rilpivirine Update PDF (24 KB)
**Monday, January 10, 2011**
•Main Guideline PDF (4.0 MB)
**Tuesday, December 1, 2009**
•Main Guideline PDF (1.82 MB)

https://aidsinfo.nih.gov/guidelines/archive/adult-and-adolescent-guidelines

## When to start ART

- CR is a 29 yo man with newly diagnosed HIV. Renal and hepatic function are WNL. Not taking any medications, vitamins, or herbals.
  - HIV + 5/2017- **HV VL 63,075, CD4 767/29%**
  - HCV + 5/2017- HCV VL 498, 829
  - Buttock abscess-MRSA 5/2017
  - **HLA-B*5701-Negative 6/7/2017**
  - Active IVDU- heroin

## When to start ART

- 1998
  - CD4 < 500 cells/mm3, HIV RNA > 20,000 copies/ml, or symptomatic (AIDS, thrush)
- 2000
  - CD4 < 350 cells/mm3, HIV RNA > 55,000 copies/ml, or symptomatic
- 2001
  - CD4 < 350 cell/mm3, HIV RNA - any value, or symptomatic
  - CD4 > 350 cell/mm3 if HIV RNA > 55,000 copies/ml
- 2004
  - CD4 < 350 cells/mm3, HIV RNA – any value, symptomatic
  - CD4 > 350 cells/mm3 if HIV RNA > 100,000 copies/ml
- 2011
  - CD4 between 350 and 500 cells mm3
- 2013
  - ART recommended for ALL HIV positive individuals

https://aidsinfo.nih.gov/guidelines/archive/adult-and-adolescent-guidelines

## Should CR start ART?

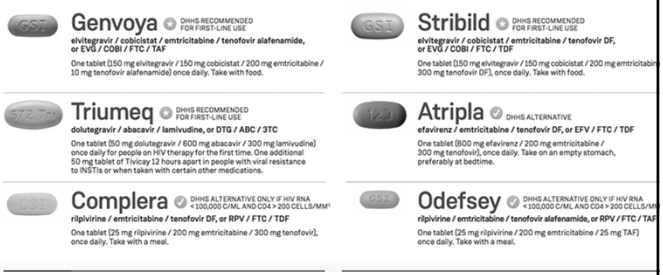
- Yes
- No

## Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents- July 14, 2016

| Generic name | Brand name |
|---|---|
| Dolutegravir/abacavir/lamivudine (**if HLA B-5701 is negative**) | Triumeq |
| Dolutegravir plus either tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine | Tivicay plus Truvada or Descovy |
| Elvitegravir/cobiciststat/tenofovir alafenamide/emtricitabine | Genvoya |
| Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine | Stribild |
| Raltegravir plus either tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine | Isentress plus Truvada or Descovy |
| Darunavir/ritonavir plus either tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine | Prezista/Norvir plus Truvada or Descovy |

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/37/whats-new-in-the-guidelines-

## Single Tablet Regimens (STR)




Used with permission from Positively Aware, 21st Annual HIV Drug Guide

## Multiple Tablet Regimens

**Integrase based**

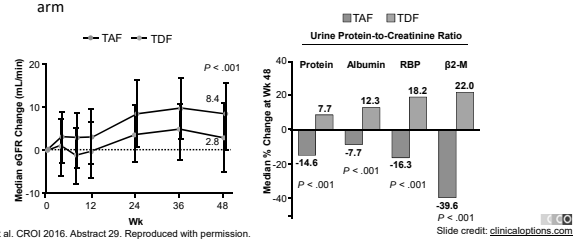
- Tivicay/Truvada or Descovy
- Isentress/Truvada or Descovy

**Protease based**

- Prezista 800 mg/r/Truvada or Descovy

## GS-1089: Renal Outcomes With Switch From TDF- to TAF Containing ART

- No proximal renal tubulopathy or Fanconi syndrome in either arm




Gallant JE, et al. CROI 2016. Abstract 29. Reproduced with permission.

Slide credit: clinicaloptions.com

## What regimen should CR start?

- Stribild
- Genvoya
- Triumeq
- Complera
- Odefsey
- Prezista/r/Truvada or Descovy
- Isentress/Truvada or Descovy
- Tivicay/Truvada or Descovy

## How do we and the patient choose a regimen?

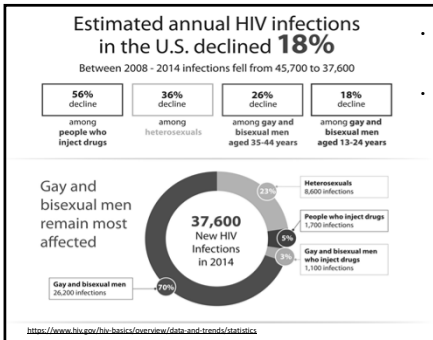
- Resistance testing
- HLA-B5*701 test
- Base line viral load
- Renal and hepatic function
- Allergy history
- Current medications – lots of drug interactions with ARVs
- Concomitant disease states (HCV, HLD)
- Insurance coverage/copay coverage
- Discuss immediate AEs
- Discuss long term AEs
- Show patient the pills of all possible regimens


**PrEP**
the ongoing use of HIV antiretroviral medications by an HIV-negative person to reduce their risk of getting HIV

## PrEP

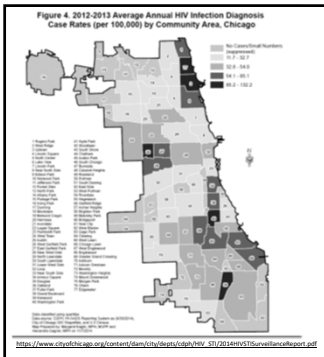
- At the end of 2014, an estimated 1,107,700 adults and adolescents were living with HIV in the US.
- An estimated 166,000 (15%) had not been diagnosed.
- Among people aged 13-24, an estimated 51% (31,300) of those living with HIV at the end of 2013 did not know their status.

https://www.cdc.gov/hiv/statistics/overview/ataglance.html




https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics

- **African Americans represented 12% of the US population, but accounted for 45% (17,670) of HIV diagnoses.**
- **Hispanics/Latinos represented about 18% of the US population, but accounted for 24% (9,290) of HIV diagnoses.**




https://www.cityofchicago.org/content/dam/city/depts/cdph/HIV_STI/2014HIVSTISurveillanceReport.pdf

**Prevalance**
19,510 people with HIV in 2014
81% men, 19% women
50% black, 20% Hispanic/Latino

**New Diagnosis**
903 people in 2015

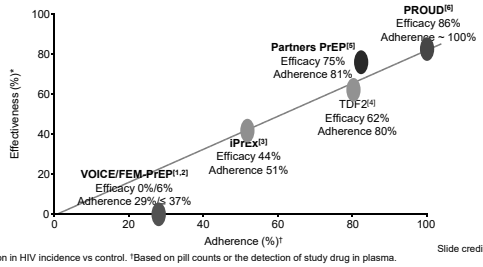
## Who should receive PrEP?

CR's new girlfriend is 23 yo. She prostitutes and uses drugs but does not inject. She uses condoms, but not always. She has an IUD to prevent pregnancy. No medical issues and she is not taking any medications.

Is she a PrEP candidate?

- Yes
- No

## Select Daily Oral TDF/FTC PrEP Trials: Effectiveness Improves With Adherence




*Reduction in HIV incidence vs control. †Based on pill counts or the detection of study drug in plasma.

Slide credit: clinicaloptions.com

**Summary of Guidance for PrEP Use**

| | Men Who Have Sex With Men | Heterosexual Women and Men | Injection Drug Users |
|---|---|---|---|
| **Detecting substantial risk of acquiring HIV infection:** | • Sexual partner with HIV<br>• Recent bacterial STD<br>• High number of sex partners<br>• History of inconsistent or no condom use<br>• Commercial sex work | • Sexual partner with HIV<br>• Recent bacterial STD<br>• High number of sex partners<br>• History of inconsistent or no condom use<br>• Commercial sex work<br>• Lives in high-prevalence area or network | • HIV-positive injecting partner<br>• Sharing injection equipment<br>• Recent drug treatment (but currently injecting) |
| **Clinically eligible:** | • Documented negative HIV test before prescribing PrEP<br>• No signs/symptoms of acute HIV infection<br>• Normal renal function, no contraindicated medications<br>• Documented hepatitis B virus infection and vaccination status | | |
| **Prescription** | Daily, continuing, oral doeses of TDF/FTC (Truvada), ≤90 day supply | | |
| **Other services:** | • Follow-up visits at least every 3 months to provide:<br>• HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STD symptom assessment<br>• At 3 months and every 6 months after, assess renal function<br>• Every 6 months test for bacterial STDs | | |
| | • Do oral/rectal STD testing | • Assess pregnancy intent<br>• Pregnancy test every 3 months | • Access to clean needles/ syringes and drug treatment services |

Source: US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States —2014: a clinical practice guideline.

https://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf

## Should CR's girlfriend initiate PrEP?

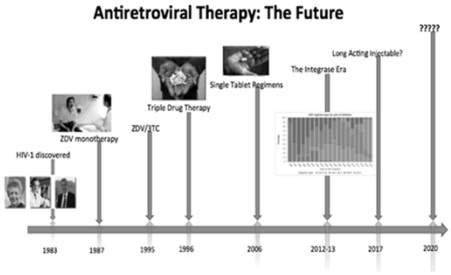
- Yes
- No

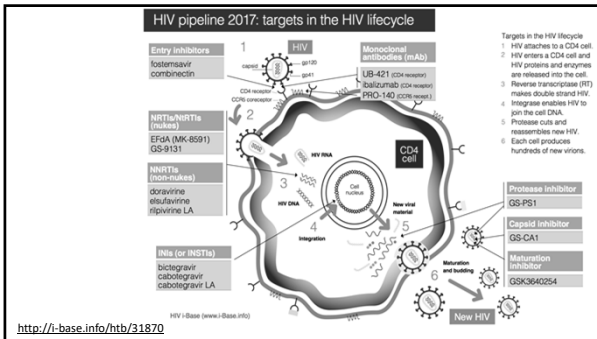
## CDC: Time to Achieving Protection on PrEP

- Time from initiation of daily TDF/FTC to maximal protection against HIV infection is unknown
- No scientific consensus on what intracellular concentrations are protective for either drug or the protective contribution of each drug in specific body tissues
- TDF and FTC PK vary by tissue
- Preliminary PK data on lead-time to achieve maximal intracellular TFV-DP concentrations with daily TDF dosing:
  - **Blood: ~ 20 days**
  - **Rectal tissue: ~ 7 days**
  - **Cervicovaginal tissues: 20 days**
  - Penile tissues: no data

https://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf

Slide credit: clinicaloptions.com




http://i-base.info/htb/31870

## HIV Treatment Pipeline

**Integrase Inhibitors**

- Bictegravir (phase III): QD unboosted INSTI coformulated with FTC/TAF
- Cabotegravir (phase IIb): Long-acting injectable for treatment or PrEP

**NNRTIs**

- Doravirine (phase III): Active against some forms of resistant virus, better tolerated than EFV
- Rilpivirine (phase IIb): Long-acting injectable version for treatment or PrEP

**Entry Inhibitors**

- Ibalizumab (phase III): Monoclonal antibody that binds to CD4, given by IV infusion every 2 wks
- Fostemsavir (phase IIb): Attachment inhibitor: binds to gp120

**NRTIs**

- MK-8591 (EFdA) (phase Ib): Translocation inhibitor, long-acting oral dosing

**Protease Inhibitors**

- DRV/COBI/FTC/TAF (phase III): QD single-tablet regimen

## Investigational Agents

- Bictegravir/FTC/TAF vs Dolutegravir-Containing Regimens for Treatment-Naive Pts
  - QD unboosted INSTI coformulated with FTC/TAF
  - 92% vs. 93% achieved VL < 50 copies/ml
  - Less nausea
- Doravirine/3TC/TDF vs EFV/FTC/TDF for Treatment-Naive Pts
  - NNRTI with unique resistance profile
  - Less drug interactions
  - Less CNS AEs
  - 84% vs. 81% achieved VL < 50 copies/ml

## Cabotegravir (Latte-2)

- Integrase inhibitor as both oral tablet and long-acting (LA) injectable formulation
- Cabotegravir-LA (made w/ nanocrystals of drug) has half-life of 21-50 days
- Similar drug-resistance profile to dolutegravir
- Combined intramuscular injection containing two long-acting formulations (cabotegravir + rilpivirine) is currently in phase 3 study for maintenance therapy
- 87% in IM injections Q4 weeks, 94% in IM injections Q8 weeks, and 84% in the oral therapy groups maintained viral suppression
- Cabotegravir-LA is also being studied as PrEP therapy

1. Zhou T et al. A long-acting nanoformulated cabotegravir prodrug for improved antiretroviral therapy. CROI 2017

## Ibalizumab TMB-301 Study

- Humanized antibody that attaches to the CD4 receptor to block HIV from entering the CD4 cell.
- Everyone had to have had a strain of HIV that was still sensitive to at least one drug for their optimized background regimen (OBR).
- Current ART followed by addition of ibalizumab IV at day 7, 14, 21, then Q 2 weeks for a total of 24 weeks.
- At day 14, the OBR was added
- By week 24, the average decrease in viral load was 55% for those with a 1 log reduction and 48% for those with a 2 log reduction.
- Side effects included dizziness, weakness, fatigue, nausea, vomiting, diarrhea,and rash.
- A new intra-muscular injection is also being studied.

S Lewis, et al. Long-Acting Ibalizumab in Patients with Multi-Drug resistant HIV-1: A 24-Week Study. 2017 CROI, Seattle. Abstract 449LB

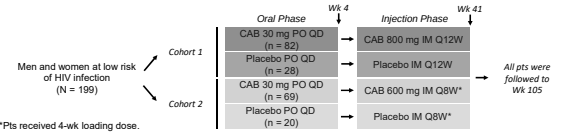
# PrEP Studies

- **MTN023/IPM 030:** randomized, double-blind, placebo-controlled phase IIa trial of a **dapivirine vaginal ring** for HIV prevention in uninfected, sexually active US adolescents 15-17 yrs of age (N = 96)[3]
  - At Wk 24, similar rates of grade ≥ 2 AE between study groups; 87% of plasma samples (taken at 2, 4, 12, 24 wks) showed dapivirine levels suggestive of adherence; 95% of returned rings had residual dapivirine levels suggestive of adherence
- **Pluspills:** open-label demonstration study of **FTC/TDF PO QD** + support for HIV prevention in uninfected, sexually active adolescents 15-19 yrs of age in South Africa (N = 148)[2]
  - Adherence decreased over time and with less frequent study visits; at Wk 12 (monthly visits), 54% had plasma TDF levels of ≥ 10 ng/mL; at Wk 48 (visits every 3 mos), 38% had plasma TDF levels of ≥ 10 ng/mL
- **Opposites Attract:** international, prospective cohort study assessing the incidence of linked HIV transmission in MSM serodiscordant couples when **HIV-infected partner on ART and virologically suppressed** (N = 343 couples; 591 CYFU; 16,889 acts of CLAI)[1]
  - For HIV-infected partner, HIV-1 RNA undetectable for 95% of CYFU
  - No linked infections; 3 infections occurring during study contracted from outside partners

1. Bavinton BR, et al. IAS 2017. Abstract TUAC0506LB. 2. Gill K, et al. IAS 2017. Abstract TUAC0207LB. 3. Bunge K, et al. IAS 2017. Abstract TUAC0206LB.

# HPTN 077: Cabotegravir for PrEP in Low-Risk Persons

- International, randomized, double-blind, placebo-controlled phase IIa study (N = 199)




- Grade ≥ 2 AEs significantly different between CAB and PBO during injection phase: injection-site pain (34% vs 2%; *P* < .0001), headache (15% vs 2%; *P* = .03)
  - Most injection-site reactions mild/moderate; 1 discontinuation due to injection-related AE
- 1 seroconversion (CAB cohort 1): detected 48 wks after final injection; CAB levels undetectable
- Participants in cohort 2 (600 mg IM Q8W) consistently met prespecified PK targets; this dose will be assessed in phase III studies

Landovitz R, et al. IAS 2017. Abstract TUAC0106LB. ClinicalTrials.gov. NCT02178800. Slide credit: clinicaloptions.com

# Pharmacist Integration in HIV Care

- Complete a PGY1 and PGY2 in HIV/ID or Ambulatory Care with extensive training in HIV
- Continuing education and understanding of the latest treatment regimens/Networking
  - MATEC trainings
  - Dinner programs
  - AAHIVP certification
  - IAS-USA (yearly in Chicago)
- Facilitate access to ARVs
  - Prior authorizations
  - Have ARVs in stock to ensure patients do not interrupt treatment
  - Offer and Activate co-pay cards
  - Encourage patient to fill ALL medications at same pharmacy
- Confidential area for counseling
- Call providers' offices to let them know when patients are not picking up ARVs every month
- Check for DIs with every refill and let providers know if significant DIs are identified
- Offer pill boxes (help pts with filling their pill boxes) and other adherence aids
- Ask permission to contact them monthly for refill reminders

# Take-home Points

- INSTI-based regimens are now the standard of care for initial therapy
- TAF/FTC is the preferred NRTI backbone for all regimens except
  DTG/ABC/3TC
- Switching from TDF to TAF increases bone density and eGFR and decreases proteinuria
- Drug development - long-acting regimens PO and IM for treatment of HIV and PrEP
- First protease inhibitor STR to be available soon

**UIC Locations**

**Family Center for Infectious Diseases**
UI Health Outpatient Care Center, Suite 3
1801 W. Taylor St.
Chicago, IL 60612
Hours: Monday to Friday, 9 am to 4 pm
To schedule an appointment, call 312.355.3785
**South Side (Englewood)**
1606 W. 63rd Street
Chicago, IL 60636
Hours: Mondays from 9 am to 4 pm
To schedule an appointment, call 312.259.4518
**New Age Services (NAS)**
1330 S. Kostner Ave.
Chicago, IL 60623
Hours: Tuesdays, 8 am to 2 pm
To schedule an appointment, call 312.259.4518
**Northwest Side (Humboldt Park)**
1610-12 N. Kedzie Ave.
Chicago, IL 60647
Hours: Thursdays, 9 am to 4 pm
To schedule an appointment, call 312.636.1222
**West Side (Austin)**
4754 W. Madison St.
Chicago, IL 60644
Hours: Wednesdays, 9 am to 4 pm
To schedule an appointment, call 312.259.4518
**North Side (Uptown)**
845 W. Wilson Ave.
Chicago, IL 60640
Hours: Monday to Friday, 9 am to 4 pm
To schedule an appointment, call 312.744-1935
**Southeast Side (South Chicago)**
8910 S. Commercial Ave.
Chicago, IL 60617
Hours: Wednesdays from 9 am to 4 pm
To schedule an appointment, call 773.356-5920

**Comprehensive HIV Care Clinics**

**University of Illinois – multiple sites (all have Pharm.Ds onsite)**
Ruth M Rothstein CORE center – Stroger Hospital (Pharm.Ds. onsite)
Howard Brown – multiple sites
South Suburban HIV/AIDS Regional Clinics (SSHARC) – multiple sites
Northstar Medical Center – Lakeview
Northwestern Memorial Hospital
Rush University Medical Center
University of Chicago
Saint Joseph Hospital
Open Door Health Center of Illinois - Aurora and Elgin
Christian Community Health center – multiple locations
Jesse Brown VA, Edward Hines, Jr. VA (Pharm.D onsite)

**HIV Education/Training**

Midwest AIDS Training and Education center (MATEC)