THE STATE OF HIV TREATMENT

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The University of Kansas School of Medicine - Wichita
The average time between HIV infection and diagnosis decreased 17% in the United States from 3 years and 7 months in 2011 to 3 years in 2015, according to data released by the CDC.
HIV Cascade of Care: Who is at risk of dropping out of care?

HIV Care Continuum, United States, 2014

An estimated 1.1 million people are living with HIV in the United States.

- Diagnosed: 85%
- Receiving Care: 62%
- Retained in Care: 48%
- Virally Suppressed: 49%

CDC website. HIV in the United States: At A Glance.
Life Expectancy Now Near Normal in North America and Europe

New research, which retrospectively analyzed data from 88,504 patients starting treatment over three-year periods between 1996 and 2010, life expectancy:

- Rose by nine years for woman
- Rose by ten years for men

This means that a 20 year-old person living with HIV in these regions, starting treatment after 2008, can now expect to live to 78.

Source: Published: May 10, 2017. DOI:https://doi.org/10.1016/S2352-3018(17)30066-8
In the United States…

Fast Facts

More than 1.1 million people in the U.S. are living with HIV today

New HIV Diagnoses in the US

- Number of new HIV diagnoses in the US was 39,782
  - 32,131 adult and adolescent males (13 years or older)
  - 7,529 adult and adolescent females
  - 122 children younger than 13 years[^a]

HIV Trends in the US

• Southern states experience the greatest burden of infection and deaths
  – Southern US is home to nearly 37% of the country's population, but these states account for more than half of all new HIV diagnoses (52%) and deaths among persons diagnosed with HIV (49%)

• Racial disparities in HIV infection continue with African Americans most impacted
  – African American make up just 12% of the US population, accounted for 45% of all new HIV diagnoses in 2015

• HIV diagnoses among youth continue to rise
  – Number of new HIV diagnoses among all persons in the US decreased by 18% between 2008 and 2015, new diagnoses among youth (aged 13 to 24 years) increased by 2%
1 in 20

1 in 48

1 in 48

1 in 227

1 in 132

1 in 880

1 in 2

1 in 6

1 in 11

1 in 4

The overall lifetime risk of HIV in the United States is 1 in 99.

African-American men have highest lifetime risk of HIV of all races and ethnicities (1 in 20).

African-American MSM (1 in 2) and Hispanic MSM (1 in 4) have even higher lifetime risk of HIV.

Racial disparities along the HIV care continuum might reflect differences in access to and use of health care and treatment.
Sexual activity continues into older age: be prepared to screen and treat

Key results

- 40% of women aged 65-74 years report that they are sexually active.
- <20% of women aged 75-85 years report that they are sexually active.
- Decline in sexual activity may result from physical problems and lack of available partners.
- Menopause symptoms can cause vaginal dryness and painful intercourse but can be treated with lubricants and hormonal therapy.
- Older women are at risk for HIV and sexually transmitted infections (STIs) and need counseling for screening and prevention.
- Medical conditions in the patient or partner may affect sexuality through fears of hurting a partner during sexual activity, physical barriers, and side effects of medications.
- Providers should acknowledge the importance of sexuality and openly discuss these issues with patients.

Sexual activity continues into older age: be prepared to screen and treat

Takeaway

• Sexual health in older women is rarely studied or addressed by physicians.

Why this matters

• Sexual history is infrequently addressed in older women, despite treatable challenges.
• Physicians lack training in caring for this aspect of older women.

The difference is in the denominators • All people living with HIV (includes persons with diagnosed and undiagnosed infection) is used as the denominator for the prevalence-based continuum. People living with diagnosed HIV is the denominator used for the diagnosis-based continuum.

Figure 1: Prevalence-based HIV Care Continuum, 2015

<table>
<thead>
<tr>
<th>Step</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed</td>
<td>86%</td>
</tr>
<tr>
<td>Receipt Of Care</td>
<td>63%</td>
</tr>
<tr>
<td>Retained In Care</td>
<td>49%</td>
</tr>
<tr>
<td>Viral Suppression</td>
<td>51%</td>
</tr>
</tbody>
</table>

Figure 2: Diagnosis-based HIV Care Continuum, 2015

<table>
<thead>
<tr>
<th>Step</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt Of Care</td>
<td>73.4%</td>
</tr>
<tr>
<td>Retained In Care</td>
<td>57.2%</td>
</tr>
<tr>
<td>Viral Suppression</td>
<td>59.8%</td>
</tr>
</tbody>
</table>

Linked to Care

- In 2016, 75.9% of persons receiving a diagnosis of HIV were linked to care within 1 month.
- Defined as linked to care within 1 month of HIV diagnosis.

- Denominator is persons receiving a diagnosis of HIV in a measurement year; numerator is the number of persons who were linked to care within 1 month of HIV diagnosis.
- Because it has a different denominator, it cannot be directly compared to other steps.

See Table 1 on page 4 for additional details.

ND has seen an increase in reported HIV/AIDS case count*, North Dakota 1984-2018

*includes newly diagnosed (incident) cases as well as previously diagnosed persons living with HIV/AIDS moving to North Dakota for the first time.
The average age of those newly diagnosed with HIV/AIDS was 36 years in 2017.

HIV/AIDS Incidence by Age, North Dakota, 2018

Source: NDDoH Division of Disease Control
Risk factors for newly diagnosed HIV/AIDS cases
HIV Incidence by Risk Factor, North Dakota 2014-2018

Source: NDDoH Division of Disease Control
South Dakota HIV/AIDS Data 2018

- 32 Cases
  - 26 Male
  - 6 Female

- Risk Factors
  - MSM (56%)
  - HRH (28%)
  - IDU (13%)
  - MSM/IDU (3%)

- Ages
  - <18 (0%)
  - 18 – 24 (9%)
  - 25 – 39 (41%)
  - 40 – 59 (44%)
  - >60 (6%)

- Race
  - White (47%)
  - American Indian (28%)
  - Black (22%)
  - Other (3%)
HIV in South Dakota, 2009-2018
Goal of Routine HIV Screening

- HIV Screening
- HIV Diagnosis
- Link to Care
- Medical Care
- Prevention Services

Source: CDC
Most new HIV transmissions are from people who
  – do not know they have HIV infection
  – or are aware of infection but are not receiving care

March 18 early-release issue of the U.S. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report. Zihao Li, Ph.D., from the CDC in Atlanta, and colleagues estimated transmission rates in 2016 along the HIV continuum of care.
HIV Screening Test Options:

- **At point of care:**
  - A rapid HIV-1/2 antibody test or a rapid combination HIV-1/2 antibody and p24 antigen test; results available in 10-20 minutes

- **Follow-up:**
  - Confirmation of all HIV+ tests by an HIV1 and 2 discrimination test, Western Blot, or viral load
HIV Screening Test Options:

**Using a laboratory:**
- A combination HIV-1/2 antibody and p24 antigen test will identify HIV infection 1-2 weeks earlier than antibody test alone; results usually available in 1-2 days
- A conventional HIV-1/2 antibody test (typically an ELISA); results usually available in 1-2 days
HIV Testing: Current Algorithm

To “close the window”, current testing algorithm:

Advantages:
- RNA testing identifies patients with acute HIV
  - Averted missed diagnoses in 8 – 32% of HIV patients
- All antibody-positive specimens tested for HIV-2
- Same day turnaround

4th gen. immunoassay: HIV-1/HIV-2 antibodies and p24 antigen

Branson B, Stekler J. JID. 2012; MMWR June 21, 2013
Laboratory Testing for the Diagnosis of HIV Infection, Updated
CDC Recommendations, June 27, 2014.
INSTI HIV-1/HIV-2 Antibody Test

- Method: Flow-through
- Time to Results: 60 seconds
- Shelf life: 15 months
- Sample type: finger stick, venous whole blood or plasma
- Storage conditions: 35.6-86 degrees Fahrenheit
- Non-Reactive = 1 control spot
- Reactive = 2 spots control and test spots

Source: https://biolytical.com/products/insti-hiv-1hiv-2/
Point-of-Contact (Rapid) 4\textsuperscript{th} Generation HIV Testing

\textbf{Alere Determine HIV-1/2 Ag/Ab Combo}

- 4\textsuperscript{th} generation for fingerstick or venous whole blood, serum or plasma
- Can be used to detect acute (early) HIV infection before antibody detection
- Distinguish between the detection of p24 antigen and HIV antibodies
- Results in about 20 minutes

Caveat emptor!

- Although current algorithm more likely to detect HIV during routine screening, if acute HIV suspected, check immunoassay (IA) and HIV RNA

- If IA negative and HIV RNA low (<10,000), repeat RNA testing to r/o false positive result.

- If very recent exposure (<10-15 d), repeat testing 1-2 wks later, particularly if symptoms develop
We offer HIV testing to all patients.

If we fail to ask, ask us.
Reduced Community Viral Load (CVL) and New HIV Infections, San Francisco

Perinatal HIV Transmission

- Without ARV drugs during pregnancy, risk of transmission from mother to infant is 1 in 4.
- Pediatric AIDS Clinical Trials Group (PACTG) 076 found that by giving zidovudine (ZDV) to the pregnant woman during pregnancy, labor, and delivery, and to her newborn, transmission could be reduced to 8%.
- The risk of perinatal transmission can now be less than 2% (1 in 50) with:
  - Highly effective ARV therapy (HAART)
  - Elective Cesarean section as appropriate
  - Formula feeding
Estimated Number of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2006—United States and Dependent Areas

No. of cases

Year of diagnosis


Note: Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.
Births to HIV-Infected Women and Number of Perinatally Acquired HIV Infections*
by Year of Birth, 1990-2006

* HIV or AIDS at first diagnosis for a child exposed to HIV during mother’s pregnancy, at birth, and/or during breastfeeding.
KEY POINTS!

- Test everyone aged 15-65 at least once
- Test at least annually for those at risk
- Confirm that your patient is linked to care
“The top doesn’t come off. It’s preventative medicine.”
TREATMENT AS PREVENTION

- ART
  - IMPROVE HEALTH
  - HIV TRANSMISSION
  - PARTNER
  - POPULATION

TREATMENT
PREVENTION
Treatment as Prevention: HPTN 052–96% Reduction in HIV Transmission

- HIV serodiscordant couples randomized to receive either early or delayed ART
- Early ART was initiated in the HIV-infected partner at enrollment
- Delayed ART was initiated after 2 consecutive CD4 cell counts ≤250 cells/mm³ or the development of an AIDS-related illness

Kaplan-Meier estimate for cumulative probabilities of linked HIV-1 transmission between partners among those in the early-therapy and delayed-therapy groups

<table>
<thead>
<tr>
<th>Years Since Randomization</th>
<th>Early</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.99</td>
<td>0.97</td>
</tr>
<tr>
<td>2</td>
<td>0.98</td>
<td>0.95</td>
</tr>
<tr>
<td>3</td>
<td>0.97</td>
<td>0.94</td>
</tr>
<tr>
<td>4</td>
<td>0.96</td>
<td>0.93</td>
</tr>
<tr>
<td>5</td>
<td>0.95</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Number at Risk
- Delayed: 882, 655, 297, 80, 26, 22
HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

Total HIV-1 Transmission Events: 39
(4 in immediate arm and 35 in delayed arm; \( P < .0001 \))

Linked Transmissions: 28

Unlinked or TBD Transmissions: 11

Delayed Arm: 27
Immediate Arm: 1

\( P < .001 \)

Single transmission in patient in immediate ART arm believed to have occurred close to time therapy began and prior to suppression of VL

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral treatment for prevention</td>
<td>96% (73–99)</td>
</tr>
<tr>
<td>ART trials for prevention HPTN 052 Africa,</td>
<td></td>
</tr>
<tr>
<td>Asia, Americas</td>
<td></td>
</tr>
<tr>
<td>PrEP for discordant couples</td>
<td>73% (49–85)</td>
</tr>
<tr>
<td>Partners PrEP Uganda, Kenya</td>
<td></td>
</tr>
<tr>
<td>PrEP for heterosexual men and women</td>
<td>63% (23–84)</td>
</tr>
<tr>
<td>TDF2 Botswana</td>
<td></td>
</tr>
<tr>
<td>Medical male circumcision</td>
<td>54% (38–66)</td>
</tr>
<tr>
<td>Orange Farm, Rakar' Kusumy</td>
<td></td>
</tr>
<tr>
<td>PrEP for MSMs iPrEP Africa, Thailand</td>
<td>44% (15–63)</td>
</tr>
<tr>
<td>PrEP for MSMs</td>
<td></td>
</tr>
<tr>
<td>iPrEP Africa, Americas, South Africa</td>
<td>42% (23–58)</td>
</tr>
<tr>
<td>Sexually transmitted diseases treatment</td>
<td>39% (6–60)</td>
</tr>
<tr>
<td>Mwanza Tanzania</td>
<td></td>
</tr>
<tr>
<td>Microbicide</td>
<td></td>
</tr>
<tr>
<td>CAPRISA 004 South Africa</td>
<td>31% (1–51)</td>
</tr>
<tr>
<td>HIV vaccine</td>
<td></td>
</tr>
<tr>
<td>RV144 Thailand</td>
<td></td>
</tr>
</tbody>
</table>
Over 1 Million Adults in the United States Are at Risk for Sexually Acquired HIV\(^1\)

Estimated Number of Adults at Risk for HIV Infection, by Gender and Transmission Risk Group—United States, 2015\(^a,1\)

<table>
<thead>
<tr>
<th>Transmission Risk Group</th>
<th>Estimated Number</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>813,970</td>
<td>75.9%</td>
</tr>
<tr>
<td>Heterosexually active adults:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Men</td>
<td>81,410</td>
<td>7.6%</td>
</tr>
<tr>
<td>• Women</td>
<td>176,670</td>
<td>16.5%</td>
</tr>
<tr>
<td>Total</td>
<td>1,072,040</td>
<td>100%</td>
</tr>
</tbody>
</table>

a. Does not include data on people who inject drugs.

1. Adapted from Smith DK, et al. CROI 2018; Boston, MA. Abstract #86.
• There is now evidence-based confirmation that the risk of HIV transmission from a person living with HIV (PLHIV), who is on Antiretroviral Therapy (ART) and has achieved an undetectable viral load in their blood for at least 6 months is negligible to non-existent.

• While HIV is not always transmitted even with a detectable viral load, when the partner with HIV has an undetectable viral load this both protects their own health and prevents new HIV infections.

https://www.preventionaccess.org/consensus
People living with HIV on ART with an undetectable viral load in their blood have a negligible risk of sexual transmission of HIV.

Depending on the drugs employed it may take as long as six months for the viral load to become undetectable.

Continued and reliable HIV suppression requires selection of appropriate agents and excellent adherence to treatment.

HIV viral suppression should be monitored to assure both personal health and public health benefits.

https://www.preventionaccess.org/consensus
U=U is a simple but hugely important campaign based on a solid foundation of scientific evidence.

It has already been successful in influencing public opinion, causing more people with HIV (and their friends and families) to comprehend that they can live long, healthy lives, have children, and never have to worry about passing on their infection to others.

The CDC officially backing the science behind the campaign is another key step towards U=U being the most important message of 2017 in the fight against HIV.

The Lancet, November, 2017
▪ One has captured the imagination of people living with HIV (PLWH around the world while the other seems to have disappeared.

▪ **U = U** was created by community to empower PLwH to have an undetectable viral load so they can’t transmit HIV

▪ **TasP** was created by scientists to explain how HIV treatment is also HIV prevention
**U = U vs. Treatment As Prevention (TasP)**

- **U = U** - Needs private health insurance, the Affordable Care Act, Medicaid, expanded Medicaid, or Ryan White services to be effective.
- Without continuous and sustained access to healthcare and meds, none of our efforts to end the epidemic will work.
- HRSA’s HIV/AIDS Bureau (HAB) will play a critical role.
- Ending the epidemic means retaining PLWH and people on PrEP in healthcare

  - So far, PrEP is not reaching communities of color.
  - 400,000 PLWH have fallen out of care or are unaware of their HIV status.
- FTC/TDF is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk
- This indication is based on clinical trials in MSM at high risk for HIV-1 infection and in heterosexual serodiscordant couples

FTC/TDF (TRUVADA) FOR PrEP INDICATION

- Emtricitabine (FTC) 200 mg
- Tenofovir disoproxil fumarate (TDF) 300 mg
Consultation with an expert can help determine if the exposure poses a “negligible risk” to explore whether alternative approaches, including a modified regimen, are appropriate.

When Is HIV oPEP Indicated

Is the Exposure from blood, bloody fluid, or other potentially infectious material or device?

- No
  - No oPEP indicated
- Yes
  - oPEP indicated
HIV oPEP: What to Give

Three-drug oPEP regimens are now the recommended regimens for all exposures.

Guidelines no longer require assessing the degree of risk for the purpose of choosing a “basic” two-drug regimen vs. an “expanded” three-drug regimen.

There are some special circumstances, however, in which a two-drug regimen can be considered/used, especially when recommended antiretroviral medications are unavailable or there is concern about potential toxicity or adherence difficulties. In addition,
Preferred HIV 3-Drug Occupational PEP Regimen:

Truvada™ 1 tablet by mouth once daily
[co-formulated Tenofovir DF (Viread®; TDF) 300mg + emtricitabine (Emtriva™; FTC) 200mg]

PLUS

dolutegravir (Tivicay™) 50mg PO once daily
Duration: 28 days
or
raltegravir (Isentress®; RAL) 400mg by mouth twice daily

https://nccc.ucsf.edu/clinical-resources/pep-resources/pep-quick-guide/
## Alternative HIV Occupational PEP Regimens:

May combine one drug or drug pair from Column One with one pair of nucleoside/nucleotide reverse transcriptase inhibitors from Column Two

<table>
<thead>
<tr>
<th>Column One</th>
<th>Column Two</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir (Isentress® ; RAL)</td>
<td>Tenofovir DF (Viread® ; TDF) + lamivudine (Epivir® ; 3TC)</td>
</tr>
<tr>
<td>Dolutegravir (Tivicay™; DTG)</td>
<td>Zidovudine (Retrovir™ ; ZDV; AZT) + lamivudine (Epivir® ; 3TC); available co-formulated as Combivir®</td>
</tr>
<tr>
<td>Darunavir (Prezista® ; DRV) + ritonavir (Norvir® ; RTV)</td>
<td>Zidovudine (Retrovir™ ; ZDV ; AZT) + emtrictabine (Emtriva™ ; FTC)</td>
</tr>
<tr>
<td>Atazanavir (Reyataz® ; ATV) + ritonavir (Norvir® ; RTV)</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra® ; LPV/RTV)</td>
<td></td>
</tr>
<tr>
<td>Etravirine (Intelence® ; ETR)</td>
<td></td>
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<tr>
<td>Rilpivirine (Edurant™ ; RPV)</td>
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</tbody>
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https://nccer.ucsf.edu/clinical-resources/pep-resources/pep-quick-guide/
“Doc, how long do I have...?”

...”Many decades”
Many Decades...
IF they get the right care!
Licensure of Antiretroviral Agents by Year

1987: zidovudine (Retrovir)
1987: zidovudine (Retrovir)
1991: didanosine (Videx)
1992: zalcitabine (Hivid)
1994: stavudine (Zerit)
1995: lamivudine (Epivir)
     saquinavir (Invirase)
1996: ritonavir (Norvir)
     nevirapine (Viramune)
1997: nelfinavir (Viracept)
     delavirdine (Rescriptor)
1998: efavirenz (Sustiva)
     abacavir (Ziagen)
1999: amprenavir (Agenerase)
2000: lopinavir/ritonavir (Kaletra)
2001: tenofovir (Viread)
2003: enfuvirtide (Fuzeon)
     6/03: atazanavir (Reyataz)
     7/03: emtricitabine (Emtriva)
     8/04: lamivudine/abacavir sulfate (Epzicom)
     6/05: tipranavir (Aptivus)
     6/06: darunavir (Prezista)
     7/06: efavirenz/emtricitabine, tenofovir DF (Atripla)
     8/07: maraviroc (Selzentry)
     10/07: raltegravir (Isentress)
     1/08: etravirine (Intelence)
     5/20/11: rilpivirine (Edurant)
     8/11: rilpivirine/tenofovir/emtricitabine (Complera)
     8/12: abacavir/dolutegravir/lamivudine (Triumeq)
     1/29/15: atazanavir 300 mg and cobicistat 150 mg (Evotaz)
     11/5/15: elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya)
     3/1/16: rilpivirine/emtricitabine/tenofovir alafenamide (Odefsey)
     4/6/16: emtricitabine/tenofovir alafenamide (Descovy)
     11/21/17: dolutegravir sodium / rilpivirine hydrochloride (Juluca)
     2/7/18: bictegravir 50 mg /emtricitabine 200 mg/tenofovir alafenamide 25mg (Biktavar)
     3/6/18: ibalizumab-uiyk IV 2,000mg/800mg (Trogarzo)
     2/5/2018: efavirenz, lamivudine, and tenofovir disoproxil fumarate (Symfi)
     2/5/18: efavirenz, lamivudine, and tenofovir disoproxil fumarate (Symfi Lo)
     2/28/18: lamivudine and tenofovir disoproxil fumarate (Temixys, 3TC/TDF)
     2/28/18: lamivudine/tenofovir disoproxil (Cimduo)
     7/17/18: doravirine 800 mg/cobicistat 150mg/emtricitabine 200mg/tenofovir alafenamide 10 mg (Symtuza)
     8/30/18: doravirine (Pifeltro)
     8/30/18: doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo)
     11/28/18: lamivudine and tenofovir disoproxil fumarate; (Temixys; Celltrion)
     4/8/2019: dolutegravir and lamivudine (Dovato)

**Highlighted yellow:** generic available in U.S.
**Highlighted grey:** generic available, but rarely/never used
**Blue:** Fixed dose combinations of existing drugs

Updated: 4/2/2019
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<tbody>
<tr>
<td>&gt; 500</td>
<td>Offer if VL &gt; 20,000</td>
<td>Offer if VL &gt; 55,000</td>
<td>Consider if VL ≥ 100,000</td>
<td>Consider in certain groups</td>
<td>Consider</td>
<td>Treat</td>
</tr>
<tr>
<td>350-500</td>
<td>Offer if VL &gt; 20,000</td>
<td>Consider if VL &gt; 55,000</td>
<td>Consider if VL ≥ 100,000</td>
<td>Consider in certain groups</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>200-350</td>
<td>Offer if VL &gt; 20,000</td>
<td>Offer, but controversy exists</td>
<td>Offer after discussion with patient</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>&lt; 200 or symptomatic disease</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
</tbody>
</table>
DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART in Most Patients With HIV Infection

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status or intent
- No currently recommended first-line regimens contain a pharmacologic-boosting agent
- With FDA approval of 1200-mg RAL,[3] all options now available QD (except in pregnancy)[4]

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**Class** | **DHHS[1]** | **IAS-USA[2]**
--- | --- | ---
INSTI | - BIC/FTC/TAF*  
- DTG/ABC/3TC*  
- DTG + FTC/(TAF or TDF)  
- RAL + FTC/(TAF or TDF) | - BIC/FTC/TAF*  
- DTG/ABC/3TC*  
- DTG + FTC/TAF

*Single-tablet regimens.

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Slide credit: clinicaloptions.com
Improved Clinical Outcomes With Rapid ART Initiation

- Systematic review of ART initiation within 14 days of eligibility determination across 4 randomized clinical trials

- Compared with standard care, **same-day ART increased** likelihood of ART initiation in first 90 days, patient retention, and viral suppression at 12 mos

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART start within 90 days</td>
<td>1.35 (1.13-1.62)</td>
</tr>
<tr>
<td>Retained in care at 12 mos</td>
<td>1.11 (0.99-1.26)</td>
</tr>
<tr>
<td>Viral suppression at 12 mos</td>
<td>1.17 (1.07-1.27)</td>
</tr>
<tr>
<td>LTFU at 12 mos</td>
<td>0.66 (0.42-1.04)</td>
</tr>
<tr>
<td>Died by 12 mos</td>
<td>0.53 (0.28-1.00)</td>
</tr>
</tbody>
</table>

- dolutegravir sodium/rilpivirine hydrochloride (Juluca)
- bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25mg (Biktarvy)
- ibalizumab-uiyk IV 2,000mg/800mg (Trogarzo)
- darunavir 800 mg/cobicistat 150mg/emtricitabine 200mg/ tenofovir alafenamide 10 mg (Symtuza)
- doravirine (Pifeltro)
- doravirine/lamivudine/ tenofovir disoproxil fumarate (Delstrigo)
- dolutegravir and lamivudine (Dovato)
dolutegravir sodium/rilpivirine hydrochloride (Juluca)

- The first complete treatment regimen
  - containing only two drugs.

- Can be used to replace ART in those who:
  - Are virologically suppressed (HIV-1 RNA less than 50 copies per mL)
  - Are on a stable antiretroviral regimen for at least 6 months
  - Have no history of treatment failure and
  - Have no known substitutions associated with resistance to the individual components of Juluca.

The recommended dosage of JULUCA is one tablet taken orally once daily with a meal.

bictegavir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (BIKTARVY®)

- A single-tablet regimen (STR)
- Combines the FTC/TAF backbone with bictegavir, a novel and unboosted integrase strand transfer inhibitor.
- Bictegavir is an integrase inhibitor with a 50 mg dose that does not need to be boosted or taken with food.
- It is co-formulated with 200 mg emtricitabine and a 25 mg dose of TAF.

http://www.biktarvyhcp.com/
bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (BIKTARVY®)

• Bictegravir has a plasma half-life of 18 hours, which suggests some flexibility for adherence and
• a resistance profile that might retain sensitivity to resistance mutations associated with raltegravir and elvitegravir but that is similar to dolutegravir.

http://www.biktarvyhcp.com/
ibalizumab-uiyk (TROGARZO)

- Treatment of human immunodeficiency virus type 1 (HIV-1) infection
- Injection for intravenous use in heavily treatment-experienced adults with multidrug resistant (MDR) HIV-1 infection failing their current antiretroviral regimen.
- A recombinant humanized monoclonal antibody, blocks HIV-1 from infecting CD4+ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.

TROGARZO (ibalizumab-uiyk)

- TROGARZO is administered intravenously once every 14 days and used in combination with other antiretroviral medications.
- Patients should receive a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks.
- The most common adverse reactions to TROGARZO were
  - diarrhea,
  - dizziness,
  - nausea and
  - rash.
- Severe side effects included rash and changes in the immune system (immune reconstitution syndrome).

• One pill daily with food
• A complete regimen (1 pill daily) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults:
  – who have no prior antiretroviral treatment history or
  – who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.
• Prior to Initiation:
  – Prior to or when initiating, test patients for HBV infection
  – Prior to or when initiating, and during treatment on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients.
  • In patients with chronic kidney disease, also assess serum phosphorus

doravirine (Pifeltro)

- New non-nucleoside reverse transcriptase inhibitor (NNRTI) to be administered in combination with other antiretroviral medicines.

- **doravirine 100 mg/3TC 300 mg/TDF 300 mg (Delstrigo)**
- Once-daily fixed-dose combination tablet as a complete regimen.
- Tx of HIV-1 with no antiretroviral treatment history.

dolutegravir and lamivudine (Dovato)

- This is the first FDA-approved two-drug, fixed-dose, complete regimen for HIV-infected adults who have never received treatment for HIV.
- The efficacy and safety of Dovato, one tablet taken daily, were demonstrated in two identical, randomized, double-blind, controlled clinical trials in 1,433 HIV-infected adults with no prior antiretroviral treatment history.
  - The trials showed that a drug regimen containing dolutegravir and lamivudine had a similar effect of reducing the amount of HIV in the blood compared to another drug regimen, which included dolutegravir, emtricitabine, and tenofovir.
  - The treatment was considered successful if the patient maintained low-levels (less than 50 copies/mL) of HIV RNA in their blood for at least 48 weeks.

Approved Therapy for HIV
ATLAS and FLAIR: Background

- Once-daily oral regimens containing 2 or 3 antiretrovirals
- Despite the success of daily oral therapy, considerable interest exists in LA treatment options
- Cabotegravir (CAB) is an HIV-1 integrase strand transfer inhibitor
  - Oral 30 mg tablet: $t_{1/2} \sim 40$ days
  - Long-acting IM injection, 20mg/mL: $t_{1/2} \sim 40$ days
- Rilpivirine (RPV) is an HIV-1 non-nucleoside reverse transcriptase inhibitor
  - Oral 25mg tablet: $t_{1/2} \sim 50$ hours
  - Long-acting IM injection, 300 mg/mL: $t_{1/2} \sim 90$ days
  - Two pivotal phase 3 studies (Atlas$^3$ and Flair$^2$) have reached their primary endpoints at 48 weeks
- Latte-2: CAB LA+RPV LA given every 4 or 8 weeks maintained HIV-1 RNA <50 c/mL for > 3 years$^1$

CAB Cabotegravir; IM intramuscular; LA, long-acting; RPV rilpivirine; $t_{1/2}$, half-life
**Study Design: ATLAS AND FLAIR**

### ATLAS: Switch to Long-Acting CAB + RPV vs Continued 3-Drug ART in Virologically Suppressed Adults

- Multicenter, randomized, open-label phase III noninferiority trial

- Adults on stable ART* (either first or second regimen) with HIV-1 RNA < 50 copies/mL for ≥ 6 mos with no previous VF
  (N = 616)

- CAB 30 mg + RPV 25 mg PO QD
  (n = 308)

- LA CAB 400 mg IM + LA RPV 600 mg IM Q4W
  (n = 303)

- Continue Baseline ART
  (n = 308)

- Comparator arm eligible to receive LA CAB + LA RPV in extension phase after Wk 52

### FLAIR: Long-Acting CAB + RPV Maintenance After DTG/ABC/3TC Induction

- Multicenter, randomized, open-label phase III noninferiority trial

- ART-naive patients with HIV-1 RNA ≥ 1000 copies/mL, HBsAg negative, no NNRTI RAMs*
  (N = 629)

- Induction Phase

- Maintenance Phase

- Continued DTG/ABC/3TC PO QD
  (n = 283)

- LA CAB 400 mg IM + LA RPV 600 mg IM Q4W
  (n = 278)
Long-Acting Cabotegravir + Rilpivirine for Maintenance: ATLAS Week 48 Results

ATLAS Conclusions:

• Monthly CAB LA + RPV LA was noninferior to 3-drug oral CAB at week 48 per Snapshot
  • Low rate of HIV-1 RNA ≥50 c/mL: 1.6% vs 1.0%
  • HIV-1 RNA <50 c/mL: 92.5% vs 95.5%

• Low confirmed virologic failure rate (1%) across both treatment arms
  • Two of 3 participants on CAB L+ RPV LA had NNRTI RAMS in baseline PBMCs

• Injection site reactions were mostly grade 1 or 2 and short-lived with few associated discontinuations

• Grade ¾ and serious Aes were infrequent in both treatment arms

• Significantly greater increase in treatment satisfaction reported with LA regimen over time vs CAR

• Overall, these results support the therapeutic potential of monthly CAB LA+RPVLA

Source: Conference on Retroviruses and Opportunistic Infections, March 4-7, 2019; Seattle, WA. http://www.natap.org/2019/CROI/croi_112.htm
FLAIR Conclusions:

• Monthly CAB LA + RPV LA was noninferior to continued oral DTG/ABC/3TC at week 48 for maintaining suppression of HIV-1

• Low confirmed virologic failure rate across both treatment arms: 1.4% vs. 1.1%
  • Three participants on CAB LA + RPV LA had treatment-emergent resistance for NNRTI and INSTI at CVF. All harbored HIV-1 subtype A1, warranting further investigation

• Injection site reactions in the LA arm were common but mainly grade 1 or 2 with few associated discontinuations

• Highly positive treatment satisfaction and preference outcomes with LA regimen

• Overall, these results support the therapeutic potential of monthly CAB LA + RPV LA for maintenance after oral induction in previously ART0Naive individuals

Source: Conference on Retroviruses and Opportunistic Infections, March 4-7, 2019; Seattle, WA. http://www.natap.org/2019/CROI/croi_112.htm
New Issues: Two VS. Three Drugs
GEMINI-1 and -2: DTG + 3TC Noninferior to DTG + TDF/FTC in Treatment-Naive Patients at Wk 48

- Parallel, international, randomized, double-blind phase III studies (N = 1433)
  - Baseline: 20% to 21% HIV-1 RNA > 100,000 copies/mL

Virologic Success
- ITT-E: 91% DTG + 3TC, 93% DTG + TDF/FTC

Virologic Nonresponse
- DTG + 3TC: 3, DTG + TDF/FTC: 2

No Virologic Data
- DTG + 3TC: 6, DTG + TDF/FTC: 5

Treatment Difference*
- ITT-E: -1.7% (95% CI: -4.4% to 1.1%)
- PP: -1.3% (95% CI: -3.9% to 1.2%)

- No treatment-emergent INSTI or NRTI mutations in patients with VF in either arm

*Adjusted for HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count (≤ vs > 200 cells/mm³), and study (GEMINI-1 vs GEMINI-2).

†PP = the ITT-E population excluding significant protocol violations.


Slide credit: clinicaloptions.com
New Generics for HIV Treatment

The first two generic combination HIV treatment medications in the United States were introduced in March of 2018.

For some, who may be required to make this change by their insurance company or face higher costs, may have to change from their current one pill a day regimen back to two pills a day.
• lamivudine, tenofovir disoproxil fumarate (Cimduo, Temixys),
• efavirenz, lamivudine, and tenofovir disoproxil fumarate (Symfi)
• efavirenz, lamivudine, and tenofovir disoproxil fumarate (Symfi Lo)
New Generics for HIV Treatment

- Lamivudine and tenofovir disoproxil fumarate (Cimduo, Temixys) 300 mg/300 mg tablets is a once-daily combination of two nucleoside reverse transcriptase inhibitors.

- Indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 35 kg.

New Generics for HIV Treatment

- efavirenz, lamivudine and tenofovir disoproxil fumarate) 600 mg /300 mg/300 mg tablets (Symfi™), a once-daily, single-tablet regimen (STR).

- efavirenz, lamivudine and tenofovir disoproxil fumarate 400 mg /300 mg/300 mg tablets (Symfi Lo™), a once-daily, single-tablet regimen (STR).

- Both are indicated as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients weighing at least 40 kg (Symfi) and 35 kg (Symfi Lo).

In the Pipeline: What’s Coming Soon…

Attachment Inhibitors:
- Fostemsavir (GSK3684934)

Maturation Inhibitors:
- Bevirimat (formerly PA-457)
- Vivecon (MPC-9055)
- PA-1050040
- UK-201844
- GSK2838232
HIV clinicians are becoming geriatricians.
ATHENA: Older Pts Becoming More Prevalent in the HIV-Infected Population

- Observational cohort of 10,278 HIV-infected pts in the Netherlands
- Modeling study projections:
  - Proportion of HIV-positive pts ≥ 50 yrs of age to increase from 28% in 2010 to 73% in 2030
  - Median age of HIV-positive pts on combination ART to increase from 43.9 yrs in 2010 to 56.6 yrs in 2030

AGEhIV: Older HIV-Infected Pts at Increased Risk for Multiple Comorbidities

- Cross-sectional analysis of comorbidity prevalence in prospective cohort study of HIV-infected pts (n = 540) vs controls (n = 524) ≥ 45 yrs of age


Slide credit: clinicaloptions.com
Factors Related to Non-AIDS Comorbidities in HIV-Infected Pts

Factors
- AGING
- Chronic HIV infection
- ART toxicity
- HCV and other coinfections
- Genetics
- Obesity, exercise, diet, smoking
- Stress
- Depression

Conditions
- Inflammation and fibrosis
- Dyslipidemia
- Insulin resistance
- Decreased physical functioning

End Organ Disease
- Cardiovascular
- Renal
- Metabolic
- Functional
- Neuropsychiatric


Slide credit: clinicaloptions.com
The Concept of Frailty

- Multisystem clinical syndrome that reflects biological rather than chronological age; regarded as an end-stage state\[^1\]

- Associated with loss of functional homeostasis, inability to recover fully after stressors, and morbidity and excess mortality\[^1\]

**Fried Frailty Phenotype\[^2\]**

<table>
<thead>
<tr>
<th>Frailty Characteristic</th>
<th>Clinical Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrinking</td>
<td>Unintentional weight loss (&gt; 10 lbs) in prior year, sarcopenia</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Poor grip strength (lowest quintile by sex, BMI)</td>
</tr>
<tr>
<td>Poor endurance/exhaustion</td>
<td>Self-reported exhaustion</td>
</tr>
<tr>
<td>Slowness</td>
<td>Walking time per 15 ft (slowest quintile by sex, height)</td>
</tr>
<tr>
<td>Low activity</td>
<td>Low kcal/week expenditure (lowest quintile by sex)</td>
</tr>
</tbody>
</table>

*Frailty defined as presence of ≥ 3 criteria; prefrailty as presence of 1-2 criteria.

- Other tools: FRAIL Scale, Study of Osteoporotic Fractures (SOF) index, Clinical Frailty Scale\[^3-5\]

References in slidenotes.
Frailty Risk Factors in Aging HIV-Positive Pts

Risk Factors (OR: Frail vs Nonfrail)

- Diabetes: HR: 5.1, P = .007
- Neurologic Disease: HR: 3.9, P < .001
- Psychiatric Disease: HR: 3.9, P = .002
- CVD: HR: 3.8, P = .067
- Unhealthy Weight: HR: 3.7, P = .004
- Arthritis: HR: 3.6, P = .001
- Osteoporosis: HR: 3.5, P = .022
- Viral Hepatitis: HR: 3.3, P = .004
The Risk of Advanced Renal Disease in People Living with HIV

Incidence of Advanced Renal Disease Among 38,354 HIV-Positive Patients vs the General Population

Data from a large North American study cohort showed that the incidence of advanced renal disease is declining in people living with HIV.

However, the overall incidence of advanced renal disease in people living with HIV is higher than the general population.

Hypertension Is Increasing and More Prevalent Among HIV-Infected Pts

- Analysis of HTN in HIV-infected pts in UNC CFAR HIV Clinical Cohort, 1996-2013 (N = 3141)\(^1\)
- Hypertension incidence
  - 1996: 1.68 cases/100 PY
  - 2013: 5.35 cases/100 PY
- Key risk factors
  - Age
  - Obesity
  - Diabetes
  - Renal insufficiency
  - Nadir CD4+ cell count < 500 cells/mm\(^3\)

- Analysis of HTN in HIV-infected (n = 527) and HIV-uninfected (n = 517) persons in AGEhIV cohort\(^2\)
- HTN rate higher among HIV-infected vs HIV-uninfected persons
  - 48% vs 36%; aOR: 1.65; 95% CI: 1.25-2.19


Slide credit: clinicaloptions.com
Increased CVD Risk in People Living with HIV is Multifactorial

**HIV-INDUCED RISK FACTORS**
- Inflammation
- Use of ART
- Immune Activation
- CD4 Count
- Viral Load

**TRADITIONAL RISK FACTORS**
- Diabetes
- Smoking
- Hypertension
- Dyslipidemia
- Family History

## HIV and Cancer

- Assessment of malignancy in HIV-infected pts in EuroSIDA (N = 15,648)

<table>
<thead>
<tr>
<th>Malignancy Type</th>
<th>Malignancy</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection-related malignancies</td>
<td>Hodgkin/non-Hodgkin lymphoma (EBV)</td>
<td>Age</td>
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<tr>
<td></td>
<td>Hepatocellular carcinoma (HBV/HCV)</td>
<td>Lower CD4+ cell count</td>
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<tr>
<td></td>
<td>Kaposi sarcoma (HHV-8)</td>
<td>HBV coinfection</td>
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<tr>
<td></td>
<td>Anal, cervical, vulvar, vaginal, penile, stomach, and oral cancers (HPV)</td>
<td>Detectable HIV-1 RNA</td>
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<td>Prior ADM</td>
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<td>Infection-unrelated malignancies</td>
<td>Lung cancer</td>
<td>Age</td>
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<td>Prostate cancer</td>
<td>Lower CD4+ cell count</td>
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<td>Colorectal cancer</td>
<td>HBV coinfection</td>
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<tr>
<td></td>
<td>Breast cancer</td>
<td>Current smoking</td>
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Slide credit: clinicaloptions.com