Top 10 stories in HIV Medicine

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Story 1: United States Epidemic: Spotlight on the Real News
- What is the big picture?
- Are new HIV infections going up or down?
- Who and where are the newly infected?
- Who is living with HIV?
- What is happening in San Francisco?

The “Big Picture” in the U.S.
- Number of new HIV diagnosis: 37,600
- Number of persons living with HIV: 1.2 million
- Percent of persons infected with HIV who do not know it: 13%
- Percent of people diagnosed with HIV who are virally suppressed: 65%

Disclosures
- Receive funding for research from NIH
- Gilead sciences provides antiretroviral therapy for NIH funded SEARCH research study
**Estimated annual HIV infections in the U.S. declined 18%**

Between 2008 - 2014 infections fell from 45,700 to 37,600

Gay and bisexual men remain most affected

<table>
<thead>
<tr>
<th>Region</th>
<th>New HIV Diagnoses</th>
<th>U.S. Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td>Southeast</td>
<td>26%</td>
<td>44%</td>
</tr>
<tr>
<td>South</td>
<td>63%</td>
<td>44%</td>
</tr>
<tr>
<td>Central</td>
<td></td>
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<tr>
<td>West</td>
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<tr>
<td>Islands/District</td>
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**AR1: >50% of new infections are in what region of the U.S.?**

- Northeast
- Southeast
- South
- Central
- West
- Islands/District

**Answer: the South**
States with the most cases and the highest rates of infection

<table>
<thead>
<tr>
<th>State</th>
<th>New HIV Diagnoses, Number (%)</th>
<th>State/Area</th>
<th>New HIV Diagnoses, per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florida</td>
<td>4,849 (12%)</td>
<td>District of Columbia</td>
<td>66.1</td>
</tr>
<tr>
<td>California</td>
<td>4,720 (11%)</td>
<td>Louisiana</td>
<td>29.2</td>
</tr>
<tr>
<td>Texas</td>
<td>4,417 (11%)</td>
<td>Georgia</td>
<td>28.3</td>
</tr>
<tr>
<td>New York</td>
<td>3,123 (8%)</td>
<td>Florida</td>
<td>27.9</td>
</tr>
<tr>
<td>Georgia</td>
<td>2,181 (6%)</td>
<td>Maryland</td>
<td>26.7</td>
</tr>
<tr>
<td>Illinois</td>
<td>1,472 (4%)</td>
<td>Mississippi</td>
<td>20.6</td>
</tr>
<tr>
<td>Maryland</td>
<td>1,347 (4%)</td>
<td>Texas</td>
<td>20.1</td>
</tr>
<tr>
<td>North Carolina</td>
<td>1,335 (4%)</td>
<td>Nevada</td>
<td>20.1</td>
</tr>
<tr>
<td>New Jersey</td>
<td>1,195 (3%)</td>
<td>New York</td>
<td>18.6</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>1,170 (3%)</td>
<td>Puerto Rico</td>
<td>17.1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>35,603 (100%)</td>
<td>US Total</td>
<td>14.7</td>
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More than twice as many new diagnoses of HIV were reported in states with a large number of cases. Source: CDC HIV Surveillance Report, 2015.

HIV: Spanning life stages

- **New Infections:** 17% of new HIV infections in the U.S. among persons 50 years and older
  - Among these 43% black, 36% white, and 17% latino
- **Presentation:** 40% are persons 55 and older and had AIDS at time of diagnosis
- **Living with HIV:** 45% living with HIV are aged 50 and older
  - San Francisco 63% over 50 years of age

New HIV diagnoses, deaths, prevalence in San Francisco 2006-2016

2013: Getting To Zero: Expand PREP, RAPID, LINCS

2010: Universal ART

16% decline in new infections in one year

Disparities in achieving viral suppression in San Francisco

<table>
<thead>
<tr>
<th>Lower rates of viral suppression among:</th>
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<tbody>
<tr>
<td>Females</td>
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<tr>
<td>African Americans</td>
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<tr>
<td>Youth</td>
</tr>
<tr>
<td>PWID</td>
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<tr>
<td>Homeless</td>
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Source: SFPDH HIV Epidemiology Annual Report 2016
Conclusions: Real News calls for Real Action

- Nationally, there was a very modest decline in rates of HIV over the last 6 years (18%)
- Overall viral suppression rates are suboptimal (55%)
- Disparities must be addressed for prevention and treatment approaches
  - Youth, women, PWID, homeless, foreign born, others
- We need to find persons early in disease—Late presentations can be lethal
- We need resources and investment for our aging population

Story 2: ART – a new framework for initial therapy in DHSS Guidelines

- Recommended for “most people with HIV”
- Recommended for “certain clinical situations”

AR2: First line therapy— which is Not recommended for “most people with HIV”? 

- DTG + ABC/3TC
- DTG+ TDF*/FTC
- EVG+ TDF*/FTC
- RAL+ TDF*/FTC
- DRV/C + TDF/FTC

* Or TAF

Answer: DRV/c + TDF/FTC is Not recommended for most people

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI + 2 NRTIs:
- DTG/ABC/3TC (AI) if HLA-B*5701 negative
- DTG + tenofovir*/FTC (AI for both TAF/FTC and TDF/FTC)
- EVG + tenofovir*/FTC (AI for both TAF/FTC and TDF/FTC)
- RAL + tenofovir*/FTC (AI for TDF/FTC, All for TAF/FTC)

DHSS guidelines, October 2017
Recommended “in certain situations” – what kind of situations?

- Patient virus or genetics – drug resistance, HLAB5701+
- Patient preference
  - Fewer pills
  - Taking pills with food
  - Smaller pills
- Co-morbidities
  - Renal disease
  - Cardiovascular disease
  - Hepatitis B
  - TB

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

**Boosted PI + 2 NRTIs**: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) + tenofovir/FTC (All for DRV/r and All for DRV/c)
- (ATV/c or ATV/r) + tenofovir/FTC (Both)

**NNRTI + 2 NRTIs**

- EFV or etravirine (EFV or etravirine)
- RPV/tenofovir/FTC (RPV/tenofovir/FTC)
- RPV/tenofovir/FTC (RPV/tenofovir/FTC) – if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm²

**INSTI + 2 NRTIs**

- RAL + ABC/3TC (RAL + ABC/3TC) – if HLA-B*5701–negative and HIV RNA <100,000 copies/mL

Regimens to Consider when ABC, TAF, and TDF Cannot be Used

- DRV/2PC (DRV/2PC)
- Efavirenz (EFV)
- RPV/tenofovir/FTC (RPV/tenofovir/FTC)
- RPV/tenofovir/FTC (RPV/tenofovir/FTC) – if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm²

Recommended “in certain clinical situations” (e.g. DRV/c+ TDF/FTC), we will discuss these during the conference

Story 3: INSTIs: The “First Line”

... but never alone

2 studies with DTG monotherapy:
High virologic failure and resistance

**Dolumono Study N=104**

- Adults, suppressed on ART x 6 months
- DTG 50 mg qd vs continue ART
- All switch to DTG at 24 weeks
- RESULTS: 8 Virologic failures by week 72

**Retrospective review DTG monotherapy N=122**

- RESULTS: 11 Virologic failures
- 9/11 INSTI resistance
- 9/11 INSTI resistance

*VT with GMA*  VS *VT without GMA*
Summary

- Old thinking– Dolutegravir has a very high genetic barrier and resistance unlikely to happen in patients with no prior INSTI
- New thinking- Dolutegravir resistance can happen:
  - Never use DTG monotherapy
  - Make sure combination therapy has potency to protect DTG
- Under study/new data
  - DTG+ 3TC for treatment naïve and for switch
  - DTC+ rilpivirine for switch

Story 4: Switch Mania

Switching ART in patients with viral load suppression

- Why? – toxicity, potency, simplicity, drug interactions, pregnancy
- Why not? Patients like current regimen, unknown drug resistant mutations, lack of data on such a switch for patient with a complicated history
- Why is this such an issue now? New data, new co-formulated drugs, new drug combinations suited for specific situations

SWITCH: Boosted PI/TDF/FTC to Single tablet Darunavir/cobi/FTC/TAF

- Orkin, Lancet HIV, 2017

EMERALD STUDY

- N=1141
- Endpoint: Virologic Failure
- 48 weeks
- Findings: Single tablet PI combination effective and safe
Virologic outcomes

<table>
<thead>
<tr>
<th>Percentage-point difference</th>
<th>DTG + RPV is non-inferior to CAR with respect to snapshot in the ITT-E population (&lt;50 c/mL) at Week 48</th>
</tr>
</thead>
</table>

*Adjusted for age and baseline 3rd agent.

SWITCH: ART to 2 Drug
Dolutegravir + Rilpivirine

- N=1024
- Endpoint: Virologic suppression
- 48 weeks
- Findings: DTG/RPV effective and safe

SWITCH: ART to 2 Drug
Dolutegravir + 3TC

- N=104 entered phase II
- Endpoint: Virologic suppression at 48 weeks
- Findings: 97% viral suppression at week 48, no INSTI resistance; 1 NRTI resistance

SWITCH: ART to 2 drug injection
Cabotegravir + Rilpivirine

- N=309
- Oral cabotegravir + ABC/3TC
- Randomize to injection (Q4 or Q8 weeks) cabotegravir + rilpivirine vs continue oral
- Endpoint: Virologic suppression
- Findings: injection (Q4 or 8 weeks) effective and safe

Summary: Switch for patients with viral load suppression

- "Switch" ART is major and complicated element of HIV medicine – but it can help our patients!
- New options with robust data (examples)
  - Single pill protease inhibitor combination: Darunavir, cobicistat, FTC, TAF (Prezobix)
  - 2 drug: Dolutegravir + Rilpivirine
- 2 drug options under study in Phase III trials (examples)
  - INSTI: Dolutegravir + 3TC
  - Injection: Cabotegravir + Rilpivirine
Story 5: 2 New antiretroviral Agents*

Doravirine

- NNRTI, once-daily dosing (100 mg), active in vitro against common NNRTI resistance mutations (including K103N, Y181C, E138K)
- No food or PPI restrictions
- Phase 2: Doravirine + TDF/FTC: HIV RNA suppression matches efavirenz, fewer adverse events

Bictegravir

- INSTI, once daily 50 mg, unboosted
- Active against many INSTI resistance mutations (in vitro)
- Phase 2: performed comparably to dolutegravir
- CYP3A4 metabolized

Pipeline and innovation

*among many
**Bictegravir/TAF/FTC (single pill) combination vs Dolutegravir + TAF/FTC**

- **GS-1490 study**
- **N=657, ART naïve**
- **Endpoint: Virologic suppression**
- **48 weeks**
- **Findings: Viral suppression Bictegravir similar to dolutegravir regimen**
- **No INSTI resistance**

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**Story 6: Intermittent PrEP – is it time?**

- **Answer: MSM**

- **IPERGAY extension study**
  - 361 participants
  - On demand PrEP
  - Median 18 pills/month
  - Compare HIV incidence to prior control arm of IPERGAY

- **Results:**
  - 97% reduction in new HIV infections with intermittent PrEP
  - Condomless sex increased 77% to 86% – high, but no increase in STIs

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**AR3: New data suggest intermittent (vs daily) PrEP is promising option for**

- MSM
- Women
- Both
- Neither
Where are we in PrEP?

• CDC recommends daily PrEP for MSM
  • Recommendation based on IPrEx and Partners PrEP
  • IPERGAY study not considered sufficient to change recommendation
• CDC recommends daily PrEP for women
  • Pharmacokinetic data support this recommendation

What is happening in communities?

• Persons are already using intermittent PrEP
• Communities are in discussion on policy
• Providers are faced with a variety of new situations regarding PrEP, PEP and seroconversion

Story 7: Steroids—any role in TB IRIS for prevention?

AR4: In what situation does addition of steroids have positive effect on outcomes?

• Cryptococcal meningitis (reduce mortality)
• TB (reduce IRIS)
• Both Cryptococcal meningitis and TB

AR4: In what situation does addition of steroids have positive effect on outcomes?

• Cryptococcal meningitis (reduce mortality)
• TB (reduce IRIS)
• Both Cryptococcal meningitis and TB
Answer: TB IRIS prevention: “PredART” Study

- Double blind, placebo controlled RCT
- TB/HIV N=240
- CD4<100
- Start ART, prednisone vs no prednisone

- 30% more IRIS in placebo group
- Faster time to IRIS

Meintjes, CROI, 2017

Summary: Change of practice: Use prednisone to prevent TB IRIS in high risk patients

Add prednisone (40 mg for 2 weeks, 20 mg for 2 weeks) in HIV/TB cases with CD4<100 to prevent IRIS because this intervention:

- Reduced TB-IRIS by 30%
- Reduced treatment TB-IRIS by 53%
- No excess infection/malignancy

Reminder from last year: Steroids had no benefit on IRIS/outcomes for HIV+ persons treated for cryptococcal meningitis

Beardsley, NEJM, 2016

Story 8: Heart Health: Time for Pitavastatin?

INTREPID Study

STUDY

- What is optimal lipid lowering agent?
- Double blind RCT, N=252
- HIV+, ART>6 months, HIV RNA<200, dyslipidemia

INTERVENTION

- Pitavastatin 4 mg vs pravastatin 40 mg

RESULTS

- Pitavastatin better: 31% vs 20% LDL reduction
- No difference AE, glucose metabolism

Aberg, Lancet, HIV 2017
INTREPID Conclusions - change of practice?

- Aging HIV population
- Persons with HIV are at greater risk for cardiovascular disease
- Consider pitavastatin 4 mg daily as front line agent for persons with cardiovascular risk factors

Ongoing primary prevention clinical outcome study:

REPRIEVE N= 6500: Pitavastatin vs therapeutic lifestyle changes, 6 year study

Story 9: Global aspirations

- Move to INSTI first line
- Same day ART start
- Self testing

19.5 million persons on ART: Moving to INSTI first line

New WHO Recommendation: Rapid ART Initiation

WHO 2017 ART Guidelines update:

- “Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.”
  - “Rapid” defined as within 7 days
- “ART initiation should be offered on the same day to people who are ready to start.”

DHSS 2017 ART Guidelines update: “Same day ART initiation is investigational”
South Africa: Rapid patients started sooner

- N=463
- 97% of patients in rapid start on ART by 90 days
- 75% started on the same day
- Rapid patients spent 2.5 hours on average in their ART start visit
- Viral suppression higher with rapid: 64% vs 55%

Rosen, PLOS Medicine, 2016

HIV Self Testing

Addresses Barriers:
- Awareness
- Stigma

HIV Self Testing: 2 fold higher than standard care:

UNITAIDS Self Testing Africa (STAR)

- Approach: Door to door, lay-workers, sex workers, peers, workplace, VAMC
- Outcomes:
  - Distributed 380,000 HIV self test kits in first year
  - 12-26% first time testers
  - Increased uptake in youth and men

“A hora e agora” Brazil

- “The time is now”
- Secure web based platform
- Free HIV oral ST
- Online tutorials, 24 hour hotline
- Confirmatory testing at clinic

HIVST
Story 10: Global 90-90-90 report card

73% “population level” suppression

Fast-Track Targets

by 2020

90-90-90
Treatment

500,000
New infections among adults

ZERO
Discrimination

by 2030

95-95-95
Treatment

200,000
New infections among adults

ZERO
Discrimination

Which countries have adapted “Treat all”?

COUNTRIES ADOPTING THE TREAT ALL GLOBAL STANDARD

AR5: What percent of persons with HIV globally are aware of their status?

- 30%
- 50%
- 70%
- 90%
A major milestone was reached in 2016: for the first time, more than half of all people living with HIV (53% [39–65%]) were accessing antiretroviral therapy. More than four in five people on treatment had suppressed viral loads, reflecting high rates of retention across all regions. Data reported by 72 countries show that retention on antiretroviral therapy after 12 months ranged from 72% in western and central Africa to 89% in the Middle East and North Africa (Figure 3.15).

When the gaps across the HIV testing and treatment cascade are combined, however, they translate to 44% [32–53%] of all people living with HIV being virally suppressed in 2016—substantially lower than the 73% required for full achievement of the 90–90–90 targets (Figure 3.4).


Latin America
Middle East and North Africa
Western and central Africa
Asia and the Pacific
Eastern and southern Africa
Eastern Europe and central Asia
Caribbean
72%
86%
89%

Achieving “90-90-90” is possible: SEARCH: 84% population suppression

Summary
- We need to re-double our efforts in the U.S -- including PrEP and care for aging
- INSTI inhibitors are invaluable -- our first line agents around the world, and we need to use them wisely
- HIV patients have new and upcoming choices for simplifying therapy -- clinicians need to guide
- ART response in global epidemic encouraging -- but we need to put millions more on ART and reduce disparities
- Treatment, vaccine and cure will all be needed to end the epidemic

Acknowledgments
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- Vivek Jain
- Moses Kamya
- Maya Petersen
- Meg Newman
- Colleagues at WHO
- UNAIDS and the Global Fund
- SF Getting to zero consortium

Begin, be bold and venture to be wise
Horace
REACHING THE 90–90–90 TARGETS IN REGIONS, COUNTRIES AND COMMUNITIES

As the world approaches the midway point between the 2014 launch of the 90–90–90 targets and their December 2020 deadline, UNAIDS has reviewed the progress made. This has been done with the support of national AIDS programmes, which report data annually to the United Nations and the guidance of national programme managers, researchers and other experts within the UNAIDS Scientific and Technical Advisory Committee (STAC) on 90–90–90.

The latest epidemiological estimates and programme data from 168 countries in all regions reveal progress and gaps across the HIV testing and treatment cascade. Changes in HIV policy since 2014 were also reported by countries, as were the development and roll-out of innovations in technology and service delivery. Consistent with the commitment to leave no one behind in Transforming our world: the 2030 agenda for sustainable development, UNAIDS and its partners reviewed and synthesized country data and studies that revealed the particular challenges and strategies for securing the full preventive and therapeutic benefits of antiretroviral therapy among children, young people, women, men and key populations at higher risk of HIV acquisition.

The data show that substantial progress has been made towards the 90–90–90 targets. More than two thirds of all people living with HIV globally knew their HIV status in 2016. Among those who knew their HIV status, 77% [57– >89%] were accessing antiretroviral therapy, and 82% [60– >89%] of people on treatment had suppressed viral loads. Amid this progress, a major milestone was reached in 2016: for the first time, more than half of all people living with HIV (53% [39–65%]) were accessing antiretroviral therapy. This acceleration of HIV testing and treatment—within a comprehensive approach that includes condoms, voluntary medical male circumcision, pre-exposure prophylaxis (PrEP), and efforts to protect human rights and establish an enabling environment for service delivery—has contributed to a 32% global decline in AIDS-related deaths and a 16% global decline in new HIV infections between 2010 and 2016.

In eastern and southern Africa, the region most affected by the epidemic, gains across the three 90s have been particularly striking, bringing the region to a level of progress comparable to Latin America. If progress is sustained, these two regions will likely achieve the 90–90–90 targets alongside western and central Europe and North America. The Caribbean was near the global average for the second 90, but lagged behind on the first and third 90s. Asia and the Pacific, by contrast, was near the global average for the first and third 90s, but lagged behind on the second 90. Other regions are in danger of missing the 2020 deadline.

IMPACT OF VIRAL SUPPRESSION

The steady scale-up of antiretroviral therapy among people living with HIV is predominantly responsible for the global decline in AIDS-related deaths (see Chapter 2). In countries with high HIV burdens, the population-level impact of the virus and the roll-out of treatment can be seen clearly over time. In the 1990s and early 2000s, as AIDS-related deaths mounted in the 10 hardest-hit countries of eastern and southern Africa, life expectancy declined from 55.0 years in 1990 to 48.9 years in 2006. This population-level impact reversed after antiretroviral therapy became widely available, and life expectancy steadily rose, reaching 58.4 years in 2015 (Figure 3.21).

LIFE EXPECTANCY REBOUND FOLLOWING TREATMENT SCALE-UP


Figure 3.21. Life expectancy for 10 countries in eastern and southern Africa, 1960–2016