Top Articles in HIV Published Last Year

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Conflicts of Interest

Chief Editor, *NEJM Journal Watch HIV/AIDS*

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Learning objectives

1. To review the most relevant literature for clinicians published during the past year.

2. To identify practice implications of significant articles in HIV published during the past year.
Methodology

- Selected 15 as most relevant for this presentation.
- Included also 4 presentations from CROI, IAC and R4P
EPIDEMIOLOGY
Jan 2015: 11 newly diagnosed cases of HIV noted in a small rural county in Indiana that had reported only 5 cases from 2004 through 2013.

CDC investigation identified 181 outbreak-related HIV-1 infections from November 2014 through August 2015.

Among HIV infected individuals: 96% reported IDU (88% injected oxymorphone) during the previous 12 months and 92% HCV co-infected.

157 of 159 tested individuals had sequences that were highly related to the HIV-1 pol gene.

Control measures included expansion of free HIV and HCV testing, the establishment of a local HIV clinic and an emergency syringe-exchange program.
The CDC estimates that the lifetime cost of treating the HIV and HCV infected patients in the Indiana outbreak could approach $100 million dollars.....

An ounce of prevention...
Acute HCV infection used as the best proxy to unsterile IDU.

Six variables significantly associated with acute HCV:
- Drug-overdose deaths per 100,000 population
- Prescription opioid sales per 10,000 population
- Median per capita income
- Percent of population of white non-Hispanic race/ethnicity
- Percent of population ≥16 years unemployed
- Buprenorphine prescribing potential by waiver per 10,000 population.

220 counties in 26 states as vulnerable.
- Mostly rural; > 50% clustered around Appalachia
- Tennessee, Kentucky, and West Virginia having close to 50% of their counties considered “vulnerable”.
Practice Implications:

- The opioid epidemic is a public health emergency.
- Every day:
  - More than 650,000 opioid prescriptions dispensed
  - 3,900 people initiate nonmedical use of prescription opioids
  - 580 people initiate heroin use
  - 78 people die from an opioid-related overdose
- Practitioners need to be aware of this problem, learn how to diagnose and manage opioid addiction and be vigilant to the risks of overdose and infectious diseases complications.
- The number of organ donors has dramatically increased as a result (2,924% increase since 1994)
In the US the number of perinatal HIV transmissions has fallen from 216 in 2002 to 69 in 2013 (from 5.4 to 1.8 per 100,000 live births).

Among infected mothers who transmitted HIV to their infants 63% were African-American and 18.3% Hispanic/Latino and many had no perinatal care.

70% of cases occurred in 10 states and 40% in 5 Southern States.

During the most recent 4-year period (2010 – 2013), 36.2% of cases occurred in 3 States (Florida = 48; Texas = 44 and Georgia = 42).
Practice Implications:

- We can end perinatal HIV in the US
- We need to make sure every pregnant woman is tested for HIV and that HIV-infected women who are pregnant are in ART and suppressed
- Every case of perinatal HIV should be investigated as a sentinel event to understand what caused the case to occur
Prevention
The interim analyses from HPTN 052 study showed that among HIV-serodiscordant couples, antiretroviral therapy (ART) for the infected partner reduced the risk for HIV transmission to the uninfected partner by 96%, at a median follow-up of 1.7 years.

- *N Engl J Med* 2011; 365:493. We now have more than 5 years of follow-up data.

- Final results published in 2016 with more than 5 years of follow-up confirm these findings.

- The risk for linked partner infection was 93% lower with early ART than with delayed ART.
1,166 serodifferent couples enrolled:
- 269 heterosexual (male partner infected); 279 heterosexual (female partner infected) and 340 MSM.

Adherence >93%, and virtually all HIV-infected participants had a viral load <50 copies/mL.

Median number of condomless sex acts within the partnership was 42 per year for MSM and 35 and 36, respectively, for HIV-negative heterosexual men and women.

33% of HIV-neg MSM and 4% of HIV-neg heterosexuals has condomless sex with other partners.

During 1.3 years of follow up 11 HIV-neg individuals became infected — 10 MSM and 1 heterosexual, of whom 8 reported sex with other partners.
- No phylogenetically linked transmissions occurred.

Risk of transmission was ZERO (upper 95% CI for within-couple transmission was 0.30 per 100 couple-years of follow-up.)
Figure 1. Rate of HIV Transmission According to Sexual Behavior Reported by the HIV-Negative Partner

<table>
<thead>
<tr>
<th>HIV-Negative Members of Eligible Couples Reporting</th>
<th>Upper 95% Confidence Limit</th>
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<tbody>
<tr>
<td>Specific Sex Act, No./Total (%)</td>
<td>Rate of Within-Couple Transmission, per 100 Couple-Years of Follow-up</td>
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### All
- **Any sex**: 863/866 (99.7) 1238 0.30
- **Vaginal sex**: 532/878 (60.6) 629 0.59
- **Anal sex**: 449/849 (52.9) 522 0.71
- **Insertive anal sex**: 363/862 (42.1) 417 0.88
- **Receptive anal sex with ejaculation**: 185/864 (21.4) 166 2.23

### Heterosexual women
- **Any sex**: 261/262 (99.6) 381 0.97
- **Vaginal sex with ejaculation**: 193/259 (74.5) 246 1.50
- **Vaginal sex without ejaculation**: 207/257 (80.5) 238 1.55
- **Anal sex**: 61/236 (23.8) 60 6.16
- **Receptive anal sex with ejaculation**: 37/255 (14.5) 29 12.71
- **Receptive anal sex without ejaculation**: 55/253 (21.7) 45 8.14

### Heterosexual men
- **Any sex**: 272/274 (99.3) 418 0.88
- **Vaginal sex**: 271/275 (98.5) 383 0.96
- **Anal sex**: 60/264 (22.7) 47 7.85
- **Insertive anal sex**: 60/264 (22.7) 47 7.85

### Men who have sex with men
- **Any sex**: 330/330 (100) 439 0.84
- **Anal sex**: 328/329 (99.7) 415 0.89
- **Insertive anal sex**: 303/329 (92.1) 370 1.00
- **Receptive anal sex with ejaculation**: 148/329 (45.0) 137 2.70
- **Receptive anal sex without ejaculation**: 217/324 (67.0) 220 1.68
Practice Implications:

- Treatment IS Prevention
- But we need to be sure HIV-infected persons are on treatment and suppressed
- Improving the care continuum is critical if we are to achieve the public health benefits of TasP
Young black and Latino MSM have the highest risk for HIV infection in the U.S.

PrEP is approved only for people aged >18 years

ATN-funded 48-week open-label PrEP demonstration and safety study that enrolled young MSM in 12 U.S. urban centers

Of 2186 men screened, 200 (median age, 20 years; 55% black, 27% Latino) were eligible and willing to participate; 81% reported condomless sex in the past month.

Participants received a standard PrEP regimen, with monthly check-ins through week 12 and quarterly through week 48.

22 participants discontinued study medication

Adherence was 56% by week 4 but dropped to 34% by week 48.4

4 seroconversions occurred during the study (HIV incidence, 3.29 per 100 person-years)

Incidence of other sexually transmitted infections was high.
Practice Implications:

- We need PrEP approved for < 18 years-old
- Adherence for adolescents and young adults is extremely challenging
- New strategies are needed (HPTN 083)
On demand PEP with Doxycycline for MSM enrolled in a PrEP Trial

Molina JM et al. CROI 2017 (Abst #91LB)

- High risk MSM in IPERGAY enrolled in a prospective randomized 1:1 to take either two pills of doxycycline (100mg per pill) within 72h after condomless sexual intercourse (without exceeding 6 pills per week) or no PEP.

- Tested every 8 weeks for HIV and syphilis as well as CT and NG in urine samples, oral and anal swabs.

- 232 pts were randomized. Median follow-up was 8.7 months (IQR: 7.8-9.7).

- 73 acquired an STIs during the study period, 28 pts in the PEP arm (24%, 37.7 events per 100 pt-years) vs. 45 pts in the no PEP arm (38.8%, 69.7 events per 100 pt-years). HR = 0.53 (95% CI: 0.33-0.85, P=0.008).
  - GC = 0.83 (95% CI: 0.47-1.47, p=0.52)
  - CT = 0.30 (95% CI: 0.13-0.70, p=0.006)
  - Syphilis = 0.27 (95% CI: 0.07-0.98, p<0.05)

- On demand PEP with doxycycline reduced the incidence of chlamydia infection and syphilis in high risk MSM and has an acceptable safety profile. The long-term efficacy of this strategy and its impact on antibiotic resistance needs to be assessed.
Practice Implications:

- Interesting study but not ready for “prime time”
Antiretroviral Therapy
TDF-based regimens recommended for treatment of HIV/HBV coinfection by all major guidelines

- TAF now available and has high efficacy and improved renal and bone safety
  - Co-formulated E/C/F/TAF) has been studied in multiple phase 3 studies

- Open-label switch study among 72 HIV/HBV co-infected patients

- At 48 weeks 91.7% maintained or achieved virologic suppression

- Seroconversion occurred in 2.9% of HBsAg + and 3.3% of HBeAg+ participants

- E/C/F/TAF was associated with improved renal function and reduced bone turnover
Practice Implications:

- This study supports the use of E/C/F/TAF for treatment of HIV/HBV coinfected patients
Bictegravir vs. Dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomized, double-blind, phase 2 trial

P. Sax et al. Lancet HIV April 2017

- Bictegravir is a new HIV integrase inhibitor
- Both bictegravir and dolutegravir do not require boosting
- In this randomized, phase II trial at week 24, 97% in the bictegravir group and 94% of the dolutegravir group had HIV RNA levels of <50 copies/mL and at week 48 viral suppression was still high (97% and 91%, respectively).
- No participant in the bictegravir group developed resistance.
- Both integrase inhibitors were well tolerated; only one person discontinued bictegravir because of an adverse event (urticaria in a patient with preexisting atopic dermatitis).
- Phase III trials are underway using bictegravir/TAF/TFC as a single-pill coformulation.
PADDLE - Dolutegravir-Lamivudine as initial therapy in HIV-Infected, ARV naïve patients.

P. Cahn et al. AIDS 2016 (Abst # FRAB0104LB)

- To evaluate the antiviral efficacy, safety and tolerability of a 2-drug regimen with 3TC and DTG in HIV-1 infected, treatment-naïve individuals.

- 20 ARV naïve patients (mostly men) with CD4 = 507 (296 – 517) cells/uL and VL = 24,128 (11,686 – 36,794) copies/ml
  - (VL < 100,000 copies/ml was an entry criteria)

- At week 24 all had a VL < 50 copies/ml and at week 48 18/20 (90%) were < 50 copies/ml

- In this pilot, proof of concept study, dual therapy with DTG plus lamivudine induced rapid virologic suppression with a favorable safety/tolerability profile in HIV-1 infected, treatment-naïve individuals.

- Larger trials now being conducted by ACTG (NCT02582684) and ViiV Healthcare (NCT02831673)
SWORD 1&2: Switch to dolutegravir + Rilpivirine maintains virologic suppression
Llibre JM, et al. CROI 2017 (Abst 44LB)

- Two identical open-label, multicenter, global, phase III, non-inferiority studies evaluated the efficacy and safety of switching from a 3 or 4-drug current antiretroviral regimen (CAR) to DTG+RPV once daily in HIV-1-infected adults, with HIV-1 RNA<50c/mL (VL<50c/mL) for at least 12 months and no history of virologic failure.

- 1024 participants randomized 1:1 to switch to DTG+RPV or continue CAR through week 48.

- Switching to DTG+RPV was non-inferior to continuing CAR at Wk48 for VL<50c/mL in pooled analysis of both the ITTe population [95% vs. 95%; difference: -0.4% (95% CI: -3.1%, 2.3%)] and the per-protocol population [96% vs. 96%; difference: 0.7% (95% CI: -3.3%, 1.8%)].

- One pt on DTG+RPV with protocol defined VF had an NNRTI RAM (K101K/E); no pts had any INI RAMs.

- More adverse events (AEs) were reported and led to discontinuation in the DTG+RPV arm.
Practice Implications:

- These three studies recently presented or published give us an insight into what the future might bring in ART:
  - A new ITI-based single pill therapy (Bictegravir),
  - Dual therapy (PADDLE)
  - An NRTI-free regimen (SWORD)
Pilot program for newly diagnosed HIV+ patients with acute or recent infection (<6 months) or CD4 count < 200 cells/uL.

86 patients were referred of whom 39 (45%) were managed with the rapid ART protocol ((usually dolutegravir and FTC/tenofovir with observed first dose and telephone follow-up) and 47 received the clinic standard of care.

Most (97%) were men and nonwhite (66%), and had frequent homelessness (28%), and many had mental health disorders (42%) or illicit substance use (42%).

In the rapid ART group, 37 (95%) took their first ART dose within 24 hours of first visit, usually observed during the initial visit.

The median time from diagnosis to viral suppression (HIV <200 copies/mL) was significantly lower in the rapid ART group than in the concomitant nonintervention participants or in historical controls in the universal-ART era (65 vs. 170 and 190 days, respectively).
Time to VL suppression by ART initiation strategy: SFGH 2006-2014

N = 39

RAPID vs. universal ART p<0.001

C. M. Pilcher, et al. JAIDS 2016; Jul 16; [e-pub].
Other same day ART studies that have been published or presented....
Practice Implications:

- Initiation of ART immediately after HIV diagnosis is feasible and effective.
- We need to reduce the time between diagnosis and initiation of therapy.
- This will not only be good practice but may improve retention in care.
Complications & Co-infections
After ART initiation patients experience substantial declines in bone mineral density (BMD). The largest losses occur in patients who initiate a TDF-containing regimen.

Can giving a bisphosphonate, which inhibits bone resorption, prevent ART-induced BMD loss?

RCT double-blind, phase IIb trial involving 63 HIV-infected patients initiating ART treatment with TDF/FTC plus ritonavir-boosted atazanavir. Most were black (84%) and male (79%), and 67% were current smokers.

On the day ART was started, patients received either a single intravenous infusion of zoledronic acid or placebo.

From baseline to week 48, lumbar-spine BMD, assessed by DXA scans, declined 4.4% in patients receiving placebo, but remained unchanged in those receiving zoledronic acid.

Zoledronic acid led to an 11% increase in lumbar spine BMD at week 48 relative to placebo. Similar findings were seen at the hip and femoral neck.
C-terminal telopeptide of collagen (CTx) – marker of bone reabsorption:

- CTx became significantly lower in the ZOL arm at week 12, 24 and 48.
- ZOL led to a 73% reduction in bone resorption relative to placebo at 12 weeks.

Osteocalcin – marker of bone formation:

- Placebo arm had significantly higher serum osteocalcin levels than ZOL arm at each time point.
Practice Implications:

- Bone loss is important problem with ART
- A single low dose of a long-acting bisphosphonate can completely block ART induced bone resorption and protect against further loss of bone mineral density during the initial 48 week period when bone loss is running high
- Further studies are needed
Immediate Antiretroviral Therapy Reduces Risk of Infection-Related Cancer During Early HIV Infection


- START study analysis to determine factors associated with cancer development.
- Infection-related cancers defined as those driven by EBV (non-Hodgkin lymphoma), and HPV (anal cancer, cervical cancer)
- There were 14 cancers among persons randomized to immediate ART (6 infection-related and 8 infection-unrelated) and 39 cancers in the deferred arm (23 infection-related and 16 infection-unrelated)
- Immediate ART significantly reduces the risk of infection-related cancer by 74% (p = 0.003) and infection-unrelated cancers by 51% (p = 0.103)
- Predictors of infection-related cancer were older age, higher BMI, low to middle income region, baseline HIV RNA and baseline CD8 count.
Practice Implications:

- Immediate ART is good....do we need more data to convince us of this?
Prospective, open-label trial in which 64 HIV-infected patients with early syphilis were randomized to receive either a single dose or three weekly doses of intramuscular benzathine penicillin G.

After 12 months of follow-up, serologic response rates, defined as a ≥4-fold decline in RPR titer were not significantly different between the single- and three-dose regimens by intention-to-treat analysis (80% and 93%, respectively) or by per-protocol analysis (93% and 100%).

There were also no clinical-treatment failures or differences in response rates between the single- and three-dose regimens when patients were stratified by baseline CD4 cell count (<350 or >350 cells/µL), HIV RNA, use of antiretroviral therapy, baseline RPR titer (<32 or >32), or stage of syphilis (primary, secondary, or early latent).
Practice Implications:

- This study supports the CDC's current treatment recommendation of administration of a single dose of benzathine penicillin for early syphilis, regardless of a patient's HIV serostatus.
ART Scale-up
Progress towards 90-90-90 goals

Botswana’s progress toward achieving the 2020 UNAIDS 90-90-90 antiretroviral therapy and virological suppression goals: a population-based survey

A. 83.3% of those infected knew their status
B. 87.4% of those who knew their status were on ART
C. 96.5% of those on ART were virally suppressed

Thus, 70.2% of HIV-infected people were suppressed!

Sweden, the first country to achieve the Joint United Nations Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO) 90-90-90 continuum of HIV care targets

ANRS 12249 TASP - ESTIMATED CASCADE OF CARE

UNAIDS target

- Diagnosed: 90.0%
- On treatment: 90.0%
- Virally suppressed: 90.0%

\[ \text{Total} = 90.0\% \times 90.0\% \times 90.0\% = 72.9\% \]

TasP trial (1\textsuperscript{st} January 2016)

- Control:
  - Diagnosed: 93.4%
  - On treatment: 46.0%
  - Virally suppressed: 93.6%
  \[ \text{Total} = 93.4\% \times 46.0\% \times 93.6\% = 40.2\% \]

- Intervention:
  - Diagnosed: 92.3%
  - On treatment: 49.2%
  - Virally suppressed: 93.4%
  \[ \text{Total} = 92.3\% \times 49.2\% \times 93.4\% = 42.4\% \]

D. Pillay, HIVR4P 2016;
Abstract PL01.01
HIV Workforce
Qualifications, Demographics, Satisfaction, and Future Capacity of the HIV Care Provider Workforce in the United States, 2013–2014

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In 2013 ~ 8,257 (95% CI, 6902 – 9601) HIV care providers in the US

- 41.9% in private practice (32% women) and 47.5% in RWHAP facilities (55% women)
- 63% white, 11% black, 11% Hispanic
- 58% met criteria of HIV specialist
- 83% provided primary care
HIV Provider Satisfaction at HIV Clinics
% Very Satisfied or Satisfied with...
(2013-2014 MMP Provider Survey)

Meeting Future Demand
Predictions from the MMP Provider Study

Estimate Modest but Insufficient Increase in HIV Care Providers:
- Assumes stable ID and primary care positions

Estimate 190 net new providers = capacity to provide care to 65,000 additional patients over 5 years

Prevalence estimated to increase by 30,000 annually so need for care of ~ 100,000 patients by 2019.
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