People Aging with HIV in the US: A Simulation Modeling Approach

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Funded by: NIA R01AG069575, the Jerome and Celia Reich HIV Scholar Award, HU CFAR
Disclosures

• Co-author at UpToDate.com
Outline

• **Background**
• Simulation modeling
• Model projections
  • MSM aging with HIV
  • Age-associated dementia
• Costs
• Conclusions
Age distribution of PWH in the US, 2018

Total Number of PWH
Age 50-69 = 475,000
Age 70+ = 44,000

Declining HIV-related mortality, 2010-2018

Multimorbidity, polypharmacy, and frailty

• Multimorbidity is common and is rising among PWH
  – Traditional and HIV-related risk factors contribute to multimorbidity

• Polypharmacy includes risks of adverse events and drug-drug interactions

• Among PWH >50y, frailty is common (10.9%) and pre-frailty very common (47.2%)
  – Similar in frequency to community-dwelling adults >65y
People aging with HIV in the US

- Life expectancy of PWH who are engaged in care and virologically suppressed is near normal, but age-associated co-morbidities are rising

- Given trends in multimorbidity, additional clinical complexity and costs are anticipated in the future

- Simulation modeling can be used to project the future burden of co-morbidities among people aging with HIV

Marcus et al. JAMA Netw Open. 2020, Wong et al. CID 2017
People aging with HIV in the US

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Marcus et al. *JAMA Netw Open*. 2020, Wong et al. *CID 2017*
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What can we do in simulation modeling?

• Use existing data to project longer-term clinical and economic outcomes

• Investigate the impact of uncertainty in data on outcomes of interest

• Examine which parameters have the greatest influence on outcomes

• Estimate the value of specific interventions
“All models are wrong, but some are useful.”

– George Box
Cost-effectiveness of preventing AIDS complications (CEPAC) model*

- CEPAC is a simulation model of HIV disease and treatment that incorporates CD4, HIV RNA, ART, opportunistic infections, and age-associated comorbidities

*Funded by NIAID, NIMH, NICHD, NIA
Cost-effectiveness of preventing AIDS complications (CEPAC) model*

• CEPAC is a simulation model of HIV disease and treatment that incorporates CD4, HIV RNA, ART, opportunistic infections, and age-associated comorbidities

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• Data are from public use datasets, observational cohorts, and clinical trials

• Model outcomes are reported in projected life expectancy, detailed clinical outcomes, and costs

*Funded by NIAID, NIMH, NICHD, NIA
The CEPAC microsimulation model

- Acute HIV Infection
- Chronic HIV Infection
- Death
- Acute Clinical Event
The CEPAC microsimulation model

- Acute HIV Infection
- Chronic HIV Infection
- Death
- Acute Clinical Event

- Opportunistic infections
- Age-associated co-morbidities
The CEPAC microsimulation model

- Acute HIV Infection
- Chronic HIV Infection
- Death
- Acute Clinical Event

- Age
- Gender
- CD4+
- HIV RNA
The CEPAC microsimulation model

- Acute HIV Infection
- Chronic HIV Infection
- Acute Clinical Event
- Death
The CEPAC microsimulation model

- Acute HIV Infection
- Chronic HIV Infection
- Acute Clinical Event
- Death
The CEPAC microsimulation model
The CEPAC microsimulation model

Acute HIV Infection → Chronic HIV Infection → Death → Acute Clinical Event → Acute HIV Infection
CEPAC model outcomes

- Clinical events
- Life years
- Transmissions
- Costs
# CEPAC investigators

<table>
<thead>
<tr>
<th>Category</th>
<th>Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEPAC Adult (US and International)</td>
<td>Ken Freedberg</td>
</tr>
<tr>
<td>• South Africa, Cote d’Ivoire, India, Brazil</td>
<td></td>
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<tr>
<td>• Zimbabwe, Botswana, Mozambique</td>
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<tr>
<td>Aging and co-morbidities</td>
<td>Emily Hyle</td>
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<tr>
<td>Smoking &amp; TB</td>
<td>Krishna Reddy</td>
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<tr>
<td>CEPAC Pediatrics &amp; Perinatal Transmission</td>
<td>Andrea Ciaranello &amp; Caitlin Dugdale</td>
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<tr>
<td>CEPAC Adolescents &amp; Young Adults</td>
<td>Anne Neilan</td>
</tr>
<tr>
<td>HBV natural history and treatment</td>
<td>Amir Mohareb &amp; Emily Hyle</td>
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</tbody>
</table>
CDC HIV testing recommendations (1993, 1996, 2001)

- Routine HIV screening in settings prevalence ≥1%
- Targeted testing based on risk assessment
- Prevention counseling required
Expanded Screening for HIV in the United States — An Analysis of Cost-Effectiveness

A. David Paltiel, Ph.D., Milton C. Weinstein, Ph.D., April D. Kimmel, M.Sc., George R. Seage III, Sc.D., M.P.H., Elena Losina, Ph.D., Hong Zhang, S.M., Kenneth A. Freedberg, M.D., and Rochelle P. Walensky, M.D., M.P.H.

Cost-Effectiveness of Screening for HIV in the Era of Highly Active Antiretroviral Therapy

**Screening for HIV Infection**

- In all health-care settings, screening for HIV infection should be performed routinely for all patients aged 13–64 years. Health-care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be <0.1%. In the absence of existing data for HIV prevalence, health-care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is <1 per 1,000 patients screened, at which point such screening is no longer warranted.
Should We Be Testing for Baseline Integrase Resistance in Patients Newly Diagnosed With Human Immunodeficiency Virus?

Yiannis Koulias,1,2 Paul E. Sax,2,3 Naomi F. Fields,4 Rochelle P. Walensky,2,3,4,5 and Emily P. Hyle2,4,5

1Department of Medicine, Brigham and Women’s Hospital, 2Harvard Medical School, 3Division of Infectious Diseases, Brigham and Women’s Hospital, and 4Medical Practice Evaluation Center, Department of Medicine and 5Division of Infectious Diseases, Massachusetts General Hospital, Boston
• Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes.

• If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should ensure that genotypic resistance testing also includes the integrase gene.
Cost-Effectiveness of Long-Acting Injectable HIV Preexposure Prophylaxis in the United States

A Cost-Effectiveness Analysis

Anne M. Neilan, MD, MPH; Raphael J. Landovitz, MD, MSc; Mylinh H. Le, BA; Beatriz Grinsztejn, MD, PhD;
Kenneth A. Freedberg, MD, MSc; Marybeth McCauley, MPH; Nattanicha Wattananimitgil, BA; Myron S. Cohen, MD;
Andrea L. Ciaranello, MD, MPH; Meredith E. Clement, MD; Krishna P. Reddy, MD, MS; Emily P. Hyle, MD, MSc;
A. David Paltiel, PhD; and Rochelle P. Walensky, MD, MPH
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MSM aging with HIV in the US

• To project the burden of age-associated comorbidities among people with HIV in the US, we first must examine the face validity of model-projected numbers and age distribution of people aging with HIV

• We focused initially on MSM with HIV as the largest group of people with HIV engaged in care in the US
Objective

• To use CEPAC to project the numbers and age distribution of MSM on ART from 2021 to 2031
Simulating the HIV care continuum

- Incident
- Undiagnosed
- Prevalent
  - On ART
  - Out of Care

PWH who have been diagnosed
Progression along the HIV care continuum

All PWH

- Incident
- Undiagnosed

PWH who have been diagnosed

On ART

Out of Care

Hyle et al. CROI 2021
## Cohort characteristics at model start

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<th>Cohort</th>
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</tr>
<tr>
<td>Off ART (out of care)</td>
<td>325 (53)</td>
<td>45.7 (11.8)</td>
<td>124,000</td>
</tr>
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</table>

CEPAC-US: Projected numbers of MSM on ART
Results: CEPAC-PEARL Collaboration

Age Groups of MSM on ART:
- CEPAC-US Age Groups
  - <30y
  - 30-49y
  - 50-64y
  - 65+y
- PEARL Age Groups
  - <30y
  - 30-49y
  - 50-64y
  - 65+y

CEPAC-US: Projected Numbers of MSM on ART

PEARL: Projected Numbers of MSM on ART

*PEARL is led by Drs. Keri Althoff and Parastu Kasaie (R01AG053100)
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PWH and Dementia

HAND  VCID  Alzheimer’s
We focused on the anticipated burden of age-associated dementias among people aging with HIV in the US.
Objective

- To compare the cumulative incidence of age-associated dementias (AAD) among 3 populations:
  - General US population
  - People at high risk for HIV acquisition
  - People with diagnosed HIV (PWDH)
Comparison of simulated cohorts

<table>
<thead>
<tr>
<th>General</th>
<th>People at high-risk of HIV acquisition</th>
<th>PWDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>Age</td>
</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>AAD natural history</td>
<td>AAD natural history</td>
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</tr>
<tr>
<td>Non-HIV-related mortality</td>
<td>Non-HIV-related mortality*</td>
<td>Non-HIV-related mortality*</td>
</tr>
<tr>
<td>No HIV-specific parameters</td>
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*Higher relative mortality risk from major HIV transmission categories were incorporated for the populations at high risk of and with HIV
Model input parameters

- People aged 55 without AAD at model start

- Developed age- and sex-stratified AAD incidence and mortality rates from general population in the US

- Estimated the HIV care continuum and virologic suppression among PWDH from CDC sources
CEPAC-projected AAD outcomes (males)

Survival

AAD Cumulative Incidence

- General population
- People at high risk for HIV acquisition
- PWDH

Hyle et al. CROI 2020
Sensitivity analyses

• HIV-focused parameters
  • No loss to follow-up (LTFU)

• AAD-focused parameters
  • 2x AAD incidence
  • Premature aging
    • 2x AAD incidence
    • Mortality shifted 5y earlier
CEPAC-projected AAD outcomes: sensitivity analysis (males)

Survival

![Survival graph showing proportion alive, males (%)]

Calendar Year: 2015 to 2050

AAD Cumulative Incidence

![AAD cumulative incidence graph](males)

Calendar Year: 2015 to 2050

- General population
- People at high risk for HIV acquisition
- PWDH, no LTFU
- PWDH

Hyle et al. CROI 2020
CEPAC-projected AAD outcomes: sensitivity analysis (males)

Survival

AAD Cumulative Incidence

Hyle et al. CROI 2020
CEPAC-projected AAD outcomes: sensitivity analysis (males)

Survival

AAD Cumulative Incidence

Proportion alive, males (%)

Calendar Year

2015 2025 2035 2045

0 10 20 30 40 50 60 70 80 90 100

General population

People at high risk for HIV acquisition

PWDH, no LTFU

PWDH, 2x AAD incidence

Calendar Year

2015 2020 2025 2030 2035 2040 2045 2050

0 5 10 15 20 25 30 35 40 45

AAD cumulative incidence among males (%)

Calendar Year

2015 2025 2035 2045

Hyle et al. CROI 2020

CEPAC - projected AAD outcomes: sensitivity analysis (males)
Next steps

• Account for HIV-specific causes of dementia

• Incorporate multimorbidity with a focus on comorbidities that can be synergistic with dementia and HIV:
  • Cardiovascular disease
  • Depression

• Include dementia screening, treatment, and costs
Future work

• To examine the future impact of co-morbidities and geriatric syndromes among people with HIV, including costs, to anticipate future health systems needs

• To investigate the clinical implications and cost-effectiveness of different interventions to prevent or treat age-associated co-morbidities
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ART costs in the US

- Among all well-resourced countries, the US has the highest ART costs and the lowest rate of HIV viral suppression.

$3-4,000 out-of-pocket per year

Only 66% virally suppressed

DHHS ART guidelines

<table>
<thead>
<tr>
<th>Recommended Initial Regimens for Most People with HIV</th>
<th>Recommended Initial Regimens in Certain Clinical Situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Have demonstrated durable virologic efficacy</td>
<td>• Effective and tolerable, but have some disadvantages or have less supporting data from randomized clinical trials</td>
</tr>
<tr>
<td>• Favorable tolerability and toxicity profiles</td>
<td>• In certain clinical situations, one of these regimens may be preferred</td>
</tr>
<tr>
<td>• Ease of use</td>
<td></td>
</tr>
</tbody>
</table>
Rising ART costs in the US

• To characterize changes in initial ART regimen costs over time, focusing on recommended regimens for:
  • Most people with HIV
  • Certain clinical situations

• Obtained the annual, average wholesale price of ART regimens recommended by the DHHS guidelines (2012-18)
Annual ART average wholesale prices (AWP)
Annual ART average wholesale prices (AWP)

McCann JAMA Intern Med. 2020
Annual ART average wholesale prices (AWP)
Who pays for ART among aging PWH?
Medicare Part D

• Approximately 25% of PWH in clinical care are enrolled in Medicare
  • Most are also enrolled in Medicare Part D for prescriptions

• Complicated cost-sharing structure in Medicare Part D obscures who bears the burden of high ART costs
Part D cost-sharing between patients, insurance plans, manufacturers, and Medicare for ART
Inequities in Medicare Part D cost-sharing

• With standard coverage, annual out-of-pocket costs are substantial ($3,300-$4,400/year)
Inequities in Medicare Part D cost-sharing

- With standard coverage, annual out-of-pocket costs are substantial ($3,300-$4,400/year)

- Low-income subsidies (LIS) are available but vary depending on person’s income
  - At $135%-150% of federal poverty level, Medicare beneficiaries would pay 15% of ART costs
Inequities in Medicare Part D cost-sharing

• With standard coverage, annual out-of-pocket costs are substantial ($3,300-$4,400/year)

• Low-income subsidies (LIS) are available but vary depending on person’s income
  • At $135%-150% of federal poverty level, Medicare beneficiaries would pay 15% of ART costs

• Higher ART prices result in greater costs assumed by Medicare beneficiaries or government payers (Ryan White; Medicare)
Anticipated growth in Medicare beneficiaries with HIV by 2033

Almost 500,000 Medicare beneficiaries by 2033

Association of HIV with health care spending among Medicare beneficiaries

• Utilizing 2016 Medicare claims data, we compared Medicare spending among:
  
  • People without HIV (n=4.5 million)
  • People with HIV (n=21,564)
Overall Medicare spending for people with and without HIV

Mean risk-adjusted spending (per person)

- Total spending
- Total drug spending
- Other medical conditions
- Direct medical treatment of HIV (excluding ART)
- HIV-associated conditions and infections
- Mental health disorders

People with HIV
People without HIV

Figueroa *Health Affairs*, 2022
Overall Medicare spending for people with and without HIV

Mean risk-adjusted spending (per person)

- People with HIV
- People without HIV

- Total spending: $60,000 (Δ 209%)
- Total drug spending: $50,000 (Δ 785%)
- Other medical conditions: $20,000 (Δ 17%)
- Direct medical treatment of HIV (excluding ART)
- HIV-associated conditions and infections: $6,000 (Δ 66%)
- Mental health disorders: $4,000 (Δ 44%)

Figueroa Health Affairs, 2022
Not all Medicare beneficiaries with diagnosed HIV are prescribed ART

- Never Prescribed ART
- Prescribed less than 12m ART
- Prescribed 12m ART
More comorbidities among Medicare beneficiaries not prescribed ART

Figueroa *Health Affairs*, 2022
Medicare spending by HIV status and months since ART initiation

People prescribed ART had less Medicare spending on mental health and other medical comorbidities.
Incorporating costs in CEPAC

- Estimated costs of care can be used to populate the model
- Each clinical event is associated with a cost that includes any relevant visits, labs, medications
How will we use model-projected costs?

• Project the total direct medical costs incurred by PWH over a specific time-frame for HIV and non-HIV-related clinical care

• Compare the costs of different sub-populations of PWH

• Compare the clinical outcomes and costs of different interventions to examine the “cost-effectiveness” of one intervention compared with others
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Conclusions

• People aging with HIV will grow in number given the effectiveness of ART

• Multimorbidity is a major issue and will increase as people age
  • Screening and treatment strategies are essential
  • Costs will grow with a direct impact on PWH due to out-of-pocket costs, as well as on taxpayers

• Simulation modeling is a method to examine and investigate interventions that are clinically effective and cost-effective
# US CEPAC Team

<table>
<thead>
<tr>
<th>Christopher Alba, BS</th>
<th>Kenneth Freedberg, MD, MSc</th>
<th>Pamela Pei, PhD</th>
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<tr>
<td>Alyssa Amick, MPH</td>
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Thank you

Contact information: Emily Hyle

Email: ehyle@mgh.harvard.edu
Twitter: @EmilyHyle

Funding sources: The Jerome and Celia Reich HIV Scholar Award and R01 AG069575
Additional slides
Increasing multimorbidity among PWH in care

Wong et al. *CID* 2017
“Traditional” risk factors are important

• Compared with HIV-related risk factors for non-communicable diseases, traditional risk factors contribute markedly to risk:
  • smoking, dyslipidemia, hypertension, and chronic hepatitis C infection

• A substantial proportion of these comorbidities could be prevented with increased targeted interventions and screening
“Traditional” risk factors are important

Risk Factors for Cardiovascular Disease among PWH

- Ever Smoking (vs. never) 37%
- Elevated total cholesterol (vs. lower) 44%
- Hypertension (vs. none) 42%
- Diabetes (vs. none) 1%
- Stage 4 CKD (vs. none) 1%
- CD4 <200 (vs. ≥200) cells per µL 6%
- HIV RNA >400 (vs. ≤400) copies per mL 5%
- Clinical AIDS diagnosis (vs. none) -3%
- HCV+ (vs. HCV-) 6%

Althoff et al. Lancet HIV 2019
CEPAC-US: Age distribution among MSM on ART

Hyle et al. CROI 2021