Polypharmacy in people with HIV: Effects on the brain

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Multimorbidity and Polypharmacy in PWH

• Advances in the HIV field have vastly altered the prognosis of people with HIV (PWH)
  – Antiretroviral therapy has become more potent & less toxic
  – Newer drugs are coformulated and dosed less frequently
  – With the advent of “treatment as prevention”, efforts to engage PWH in healthcare have further expanded
• As a result, survival of PWH is approaching that of the general population
  – PWH are developing aging-related medical comorbidities more frequently than the general population
  – PWH generally take more medications than people without HIV
Survival of PWH is Improving but Aging-Related Diseases are More Frequent

Adults with HIV are at Greater Risk for Multimorbidity than the General Population

Schouten et al, Clin Infect Dis 2014; 59(12):1787–97

Courlet et al, Open Forum Infect Dis 2019; 6(12):ofz531

Challenges in Clinical Management of PWH

• Multimorbidity extends beyond medical disorders
  – PWH have a substantial burden of drug addiction, sexual violence, and mental illness
  – They are at risk for poverty and housing and food insecurity
  – Less likely to have self-efficacy, including healthcare efficacy

• Drug-drug interactions are common in PWH
  – Many antiretroviral drugs are metabolized by cytochrome P450 or glucuronidation pathways
  – ART drugs may be both victims and perpetrators of interactions
  – Polypharmacy may be excluded from clinical trials of new drugs
Risk for Polypharmacy is Worsening in PWH


Courlet et al, Open Forum Infect Dis 2019; 6(12):ofz531

Justice et al, AIDS 2018, 32:739–749

McNicholl et al, Pharmacotherapy 2017; 37(12):1498–1506
Drug-Drug Interactions are More Common in PWH Than in People Without HIV

Courlet et al, Open Forum Infect Dis 2019; 6(12):ofz531

Halloran et al, Antiviral Therapy 2019, 24: 193-201

Back & Marzolini, J Intl AIDS Soc 2020, 23:e25449

PDDI = Potential Drug-Drug Interaction
Added Risk in PWH: Non-Adherence to ART

Proportion with > 95% Adherence to ART Drugs
or > 90% Adherence to non-ART Drugs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection drug use</td>
<td>0.56 (0.35-0.90)</td>
</tr>
<tr>
<td>ART naïve&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.80 (4.18-27.89)</td>
</tr>
<tr>
<td>ART changes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.42 (3.26-21.78)</td>
</tr>
<tr>
<td>Low Predictor Index&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.60 (1.58-4.29)</td>
</tr>
<tr>
<td>Polypharmacy&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.36 (0.21-0.61)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Only variables with > 90% adherence are included.
<sup>b</sup>ART naïve: no ART change since starting ART.
<sup>c</sup>Patients with ART changes since starting ART.
<sup>d</sup>Takes into account need for dose adjustment in renal or liver impairment and number of associated non-HIV medications. This tool allows placing patients into high-risk or low-risk categories for developing drug-related problems.
<sup>e</sup>Patients with 5 or more prescription medications in a medication regimen. ART = antiretroviral therapy; CI = confidence interval.


Another Risk of Polypharmacy is Greater Vulnerability to Neurotoxic Adverse Effects

Hinckley et al, CROI 2016, Abstract 395
Robertson et al, J Neurovirol 2012, 18: 388-299
Polypharmacy is Associated with Worse Neurocognitive Performance in PWH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Polypharmacy (n=677, 70.8%)</th>
<th>Polypharmacy (n=279, 29.2%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years), mean (SD)</td>
<td>42.2 (10.2)</td>
<td>48.9 (10.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex (Male), n (%)</td>
<td>584 (86.4)</td>
<td>242 (86.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Asian</td>
<td>12 (2)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>121 (18)</td>
<td>38 (14)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>199 (29)</td>
<td>44 (16)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>322 (48)</td>
<td>186 (66)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>23 (3)</td>
<td>9 (3)</td>
<td></td>
</tr>
<tr>
<td>CD4+ T-cell Count, mean (SD), ml−1</td>
<td>520 (285)</td>
<td>539 (355)</td>
<td>0.44</td>
</tr>
<tr>
<td>Plasma HIV RNA, log mean (SD) copies/mL</td>
<td>2.363 (0.928)</td>
<td>2.107 (0.844)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ART, n (%)</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>INSTI</td>
<td>109 (16)</td>
<td>71 (25)</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>238 (35)</td>
<td>88 (32)</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>275 (41)</td>
<td>135 (48)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lifetime Substance Use</td>
<td>349/473 (73.8)</td>
<td>185/252 (73.4)</td>
<td>0.91</td>
</tr>
<tr>
<td>Lifetime Psychiatric Diagnosis</td>
<td>42/312 (13.5)</td>
<td>36/185 (19.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27/677 (4.0)</td>
<td>39/279 (14.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>113/663 (17.0)</td>
<td>115/279 (41.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Ma, et al CROI 2019, Abstract 437
Women with HIV are More Likely to Use Drugs with Neuropsychiatric Adverse Effects

NP-AE Drug Use and ART

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cART use</td>
<td>1.46 (1.35-1.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>cART adherence</td>
<td>1.03 (0.95-1.12)</td>
<td>0.45</td>
</tr>
<tr>
<td>Undetectable viral load</td>
<td>1.12 (1.05-1.19)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Radtke, et al. CROI 2018, Abstract 401
# Effects of Anticholinergic Burden in Aging Adults with HIV

Kamkwalala, et al CROI 2020, Abstract 414

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β estimate</td>
<td>p value</td>
</tr>
<tr>
<td>Anticholinergic Burden</td>
<td>1.08</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Current Psychiatric Diagnosis</td>
<td>7.37</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lifetime Psychiatric Diagnosis</td>
<td>4.44</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lifetime Substance Use Diagnosis</td>
<td>2.02</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Current Substance Use Diagnosis</td>
<td>2.35</td>
<td>0.0004</td>
</tr>
<tr>
<td>Number of Prescribed Drugs</td>
<td>0.29</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum Triglycerides</td>
<td>0.006</td>
<td>0.009</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum High Density Lipoprotein</td>
<td>-0.06</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Kamkwalala, et al CROI 2020, Abstract 414
Challenges in clinical trials

- Polypharmacy is excluded from many clinical trials of new ART drugs (or unaccounted for adequately)
  - Bias and effects on generalization
- Few clinical trials of deprescribing or switching to safer alternative drugs in PWH have been performed
- Inadequate representation of the diversity of the population of PWH
  - Women
  - Underrepresented Minorities (racial/ethnic, sexual)
CNS Adverse Effects of Dolutegravir

N=565
DTG Only

de Boer et al, AIDS 2016, 30:2831–2834

N=1,950
InSTIs Only

Hoffmann et al, HIV Medicine 2017, 18, 56--63

N=4,041
DTG vs. RAL

Elzi et al, AIDS 2017, 31:1853–1858

N=6,347
DTG or 3 Others

Fettiplace et al, J AIDS 2017;74:423–431

Toxicity:
RAL 4.3%
DTG 3.6%

Psychiatric event

Depression
Approach to Polypharmacy in the Clinic

• **Intensification vs. Simplification/Deprescribing**
  – PWH can have low-level HIV replication and inflammation so clinical trials are investigating ART intensification to 4 or more drugs to better suppress HIV replication
  – Other trials are reducing the number of ART drugs from 3 to 2
  – Few trials are investigating deprescribing of non-ART drugs

• **Need for Personalized Medicine and Involvement of Geriatricians and Pharmacists in Clinical Management of PWH**
The Problems of Polypharmacy in PWH Are Similar but the Scale May be Greater

Ware, et al. AIDS Patient Care STDs 2019, 33(8):354-365


PIMS = Potentially Inappropriate Medications
Deprescribing of ART and Non-ART Drugs

Algorithm for deprescribing ARV in PLWH

- Patients’ multidimensional evaluation
- Drug reconciliation
- ID evaluation
- WHO?
- ARV complexity (in particular PLWH with polypharmacy)
- WHEN?
- ART-experienced PLWH with optimal profile of resistance testing
- HOW?
- Reduction of ARV pill burden \(\rightarrow\) STR
- Long acting ARV therapy
- Reduction of ARV active components \(\rightarrow\) ZDR
- WHY?
- Quality of life

Recommendations for deprescribing benzodiazepines in HIV-infected patients (adapted from ref. 94)

- **ANALYZE THE USE OF THESE DRUGS IN THE CONTEXT OF MANAGING ASSOCIATED COMORBID CONDITIONS**
  - Other sleep disorders (e.g., restless leg syndrome)
  - Uncontrolled anxiety, depression, mental or physical status that may cause or aggravate insomnia
  - Effective benzodiazepine, especially for anxiety
  - Cessation of alcohol consumption

- **INVOLVE THE PATIENT** (discuss potential risks, benefits, withdrawal plan, symptoms, and duration)

- **DEPREScribing RECOMMENDED**
  - Minimize the use of drugs that aggravate insomnia (e.g., caffeine, alcohol)
  - Treat underlying conditions
  - Consider consulting a psychologist, psychiatrist, or sleep specialist

- **GRADUAL WITHDRAWAL OF DRUGS** (Gradual withdrawal in collaboration with the patient. It is recommended to reduce consumption by 25% every 2 weeks and, if possible, by 12.5% towards the end)

- **Fortnightly monitoring during withdrawal**
  - Expected benefits:
    - Improvement in alertness, cognition, daytime sleepiness, and reduction in falls
    - Withdrawal symptoms:
      - Insomnia, anxiety, irritability, sweating, gastrointestinal symptoms (with a mean duration of days to weeks)
  - Do not administer drugs to control insomnia
  - Focus on behavior

## Prioritization of Key Components of Care (6Ms)

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Components</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| Mind       | Cognition, depression, mood | • Evaluate and treat mood disorders  
• Evaluate and treat comorbidities  
• Ensure safety |
| Mobility   | Gait, balance, falls | • Fall intervention programs  
• Physical/occupational therapy  
• Home safety assessments |
| Medications| Polypharmacy and DDIs | • Deprescribe  
• Identify medication adverse effects |
| Multicomplexity | Consideration of comorbidities in the context of complex social circumstances and limitations | • Identify highest priority screening and treatment guidelines  
• Assess living conditions and competing priorities |
| Matters Most to Me | Health goals and care preferences | • Coordinate advance care planning  
• Manage goals of care  
• Risk/benefit discussions when considering priorities and goals of care |

Summary and Conclusions

• Potent ART has vastly improved the survival of PWH but they are developing aging-related medical disorders more frequently than people without HIV

• This has led to more frequent polypharmacy along with its complications, including effects on…
  – Cognition and mood
  – ART adherence

• These effects are not adequately addressed in clinical trials or in clinical management

• Attention is growing but more must be done
Acknowledgements

Study Volunteers

UC San Diego
- Igor Grant
- Ronald J. Ellis
- Robert Heaton
- J. Allen McCutchan
- David Moore
- Brookie Best
- Brook Henry
- Cris Achim

- Sara Gianella
- Davey Smith
- Ajay Bharti
- Sanjay Mehta
- Chris Fennema
- Connie Benson
- Chip Schooley
- Doug Richman

CHARTER/NNTC
- Todd Hulgan
- Asha Kallianpur
- David Clifford
- Justin McArthur
- Ned Sacktor
- Ann Collier

- Ann Collier
- Christina Marra
- Susan Morgello
- David Simpson
- Ben Gelman
- Howard Fox

Trainees
- Qing Ma (Buffalo)
- Bert Anderson (Emory)
- Jenny Iudicello
- Kemi Okwuegbuna
- Josue Perez Santiago
- Micol Ferrara
- Ameet Dravid