HIV treatment revision: As simple as old versus new?

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What is an “old regimen”?

Switching for dosing simplification?

Switching from old regimens

Pre-HAART era
1990s
AZT (1987)
High-level, multiple-doses per day regimens
 Initially 4-hourly, day + night

‘Early’ HAART era
2000s
AZT + 3TC (2004)
Twice-daily co-formulated regimens

‘Late’ HAART era
2000–2002 onwards
ABC + 3TC + Dolutegravir (Triumeq)
Once-daily co-formulated regimens

Contemporary HAART: once-daily one-pill regimens
2000–2002 onwards
TDF + FTC + Rilpivirine (Eviplera)
Any viral load
No food requirement
Drug interaction: PPIs

TDF + FTC + Elvitegravir + Cobicistat* (Stribild)
Any viral load
No food requirement
Drug interaction: CYP3A4*

ABC + 3TC + Dolutegravir (Triumeq)
Any viral load (HLA-B*57–ve)
No food requirement
Drug interaction: Metformin
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“No one, however smart, however well educated, however experienced, is the suppository of all wisdom.”

What do you do when you’re asked to do nothing?

“I don’t want to change my therapy”
Applying the Rumsfeldian sieve

1. What do we know that we know?
Plasma viral load <40 copies/mL on ART regimen X
CD4 T cell count 350 cells/µL (from nadir <100 cells/µL)
Cardiovascular risk calculation: 12% 5-yr risk (63 yrs old)
Renal function and protein/creatinine ratio: eGFR >90, urine PCR 16 mg/mmol
FRAX score and BMD (+/- metabolic bone study): osteopenia

2. What do we know that we do not know?
Plasma VL below 40 copies/mL, CSF or seminal fluid VL
Immune activation markers, esp innate (eg monocyte) markers
Cognitive function and risk of cognitive decline in future
Cancer risk?
Transmissibility risk?

3. What don’t we know that we do not know?
Do new drugs achieve better outcomes due to things that we can’t measure?
• Do they penetrate different sites?
  ... Brain (CPE), Monocytes (IMES), genital tract?
• Do they do things beyond reduce viral load?
  ... Reduce innate immune activation?
• Do they have additional benefits?
  ... Reduce malignancy risk, or frailty ('inflammaging')

TOXICITY?
Applying the Rumsfeldian sieve

2. What do we know that we do not know?

- Plasma VL below 40 copies/mL, CSF or seminal fluid VL
- Immune activation markers, esp innate (eg monocyte) markers
- Cognitive function and risk of cognitive decline in future
- Cancer risk?
- Transmissibility risk?

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### Genital tract ART penetration

**Men**

- TDF/FTC/EFV = 7
- TDF/FTC/ATZ = 6
- ABC/3TC/LPV = 2.5
- ABC/3TC/NVP = 2.5

**Women**

- TDF/FTC/EFV = 6
- TDF/FTC/ATZ = 5
- ABC/3TC/LPV = 2.5
- ABC/3TC/NVP = 2.5

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**Central nervous system penetration scores**

- **2008**
  - TDF/FTC/EFV = 4
  - TDF/FTC/ATZ = 4
  - ABC/3TC/LPV = 2
  - ABC/3TC/NVP = 2

- **2010**
  - TDF/FTC/EFV = 4
  - TDF/FTC/ATZ = 4
  - ABC/3TC/LPV = 2.5
  - ABC/3TC/NVP = 2.5

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### Treatment intensification, residual viremia and the latent reservoir... a long tale

**Raltegravir Concentrations in the Genital Tract of HIV-1-Infected Women Treated with a Raltegravir-Containing Regimen (TIVA 01 Study)**

- Opti Chanes, Gillian Puttock, Hafter Tsimbila, Carina Hofmeyr, Carina Coetzee, Larry Gold, Patrick Nunn, Antoinette Hart, Michelle Lin, Gisela de la Hoz, Delphine Radley, Bou Florence, C. O'Brian, Rosseter, S. Wladimirov, E. Khamulis, A. Van Der Merwe, P. van der West, L. H. van der Merwe, T. J. van der Merwe

- Anti-Reverse Transcriptase Agents and Cervical Tissue Levels of Raltegravir in Women on a Raltegravir Versus a Boosted Atazanavir Regimen. AIDS Res Hum Retroviruses. 2015 May 21

**Study of TDF/FTC + Raltegravir (n=14) or Atazanavir (n=19) in HIV+ women**

- Raltegravir CVL level 519% higher than Atazanavir (p<0.001)
- Genital tract VL <40 copies/mL in 90% of subjects, no difference by group
- No changes in cervical CD4+ or CD8+ cell activation markers by group

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**Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV**

- Enitalize M Mluku, 1, 3, 4, 6, 8, 9, 10, 11, 12, 13, 14
  - Bruce Blower, 1, 3, 4, 6, 8, 9, 10, 11, 12, 13, 14
  - Bruce Blower, 1, 3, 4, 6, 8, 9, 10, 11, 12, 13, 14
CPE score (2010)

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>Acute infection in macrophages (EC50, nM)</th>
<th>CPE score</th>
</tr>
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<tbody>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
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<tr>
<td>Nevirapine</td>
<td>50</td>
<td>2</td>
</tr>
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<td>Delavirdine</td>
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<td>3</td>
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<tr>
<td>Efavirenz</td>
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<td>2</td>
</tr>
<tr>
<td>NVP</td>
<td>300</td>
<td>3</td>
</tr>
</tbody>
</table>

Immune activation and integrase inhibitors

Differential Reduction in Monocyte Activation and Vascular Inflammation With Integrase Inhibitor-Based Initial Antiretroviral Therapy Among HIV-Infected Individuals

Cancer risk and ART

Exposure to Antiretroviral Therapy and Risk of Cancer in HIV-infected Persons

Lipids and integrase inhibitors vs EFV vs DRV

Comparative Changes of Lipid Levels in Treatment-Naïve, HIV-1-Infected Adults Treated With Didanosine vs. Efavirenz, Raltegravir, and Ritonavir-Boosted Durvalume-Based Regimens Over 48 Weeks

Cancer risk and ART

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...But for the moment, knowing what you know is most likely enough

*Also noted in D:A:D study: J Acquir Immune Defic Syndr. 2015;68:568-77
I would not say that the future is less predictable than the past. I think the past was not predictable when it started.