HIV treatment revision: As simple as old versus new?

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What is an “old regimen”?

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>AZT (1987)</td>
<td>Initially 4-hourly, day + night</td>
</tr>
<tr>
<td>1995</td>
<td>AZT + 3TC (1997)</td>
<td>Twice-daily co-formulated regimens</td>
</tr>
</tbody>
</table>

Switching for dosing simplification?

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

‘Early’ HAART era
Twice-daily co-formulated regimens
AZT + 3TC (1997)

‘Late’ HAART era
Once-daily co-formulated regimens
ABC + 3TC (2004)
TDF + FTC (2004)
TDF + FTC + EFV = Atripla (2006)

Contemporary HAART: once-daily one-pill regimens

- Baseline VL <10,000 copies/mL
- Take with food
- Drug Interaction: PPIs
- TDF + FTC + Rilpivirine (Eviplera)
- TDF + FTC + Elvitegravir + Cobicistat* (Stribild)
- ABC + 3TC + Dolutegravir (Triumeq)
- Any viral load (HLA-B*5701–ve)
- No food requirement
- Drug Interaction: Metformin

*Not yet approved in Australia

Switching from old regimens

Pre-HAART era
- HIV uncontrolled, poorly controlled, poor long-term prognosis
- High-dose monotherapy NRTI therapy, limited treatment options
- Issues of drug toxicity outweighed need for survival benefit
- Advocacy focused on access to therapy

‘Early’ HAART era
- HIV well controlled, long-term prognosis improved
- Multiple ART regimens, selected for therapeutic efficacy
- Drug toxicity assumes more importance, but efficacy paramount
- Advocacy focused on access + improved therapy tolerability + long-term outcomes

‘Late’ HAART era
- Multiple ART regimens: greater choice of equally highly effective HAART
- Improved drug safety + tolerability, better understanding and monitoring of drug toxicity
- Advocacy focused on drug tolerability, long-term outcomes and specific management of complications


NRTIs
- Zidovudine, Lamivudine (1987)
- Zidovudine, Lamivudine, ddl (1996)
- Zidovudine, Lamivudine, ddI (1996)

Ritonavir-boosted PIs
- Darunavir, Atazanavir (2007)
- Darunavir, Atazanavir, Ritonavir (2007)

NNRTIs
- Nevirapine (1995)
- Nevirapine, Efavirenz (2000)

INIs, CCR5 inhibitor
- Indinavir (1997)
- Indinavir, saquinavir (2000)

Dual NRTIs
- Zidovudine, lamivudine (1996)
- Zidovudine, lamivudine, ddI (1996)

Single tablet regimens
- 1996
- 2000
- 2004

Drug interaction: CYP3A4*
Switching for toxicity?

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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

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?

Applying the Rumsfeldian sieve

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 (MES), 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')
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?

Genital tract ART penetration

Central nervous system penetration scores

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

A Randomized Open-Label Study of Three-versus Five-Drug Combination Antiretroviral Therapy in Newly HIV-1-Infected Individuals

Matthew B. Brenchley, M.D.,* Taylor M. Everly, M.D., M.S.,* Donald Gwemer, M.P.H.,* Martha Conley, M.D.,* Melissa La Mer, Ph.D.,* Kristina Rodriguez, M.P.H.,* Vincent Saha, M.D.,* Sarah Falmer, Ph.D.,* Nicole Prado, Ph.D.,* Loree M. Weiner, M.D., Ph.D.,*


Methods—Twenty HIV-1-infected patients were randomized 1:1 to receive 3-drug (N=10) or 5-drug (N=10) therapy. The primary endpoint was the percent of patients with undetectable plasma viremia using standard RT-PCR and the single copy assay (N=5) after 48 weeks. Secondary endpoints included levels of cellular-associated HIV-1 DNA and RNA, and levels of infectious virus in coculturing CD+ 3 cells or at week 96 and quantitative and qualitative immunological responses.

Results—At 48 weeks, 3 subjects remained on study and were included in the re-analyzed analysis. Three of 18 (16.7%) in the 5-drug arm and 9 of 22 (40.9%) in the 3-drug arm had plasma HIV-1 RNA levels below detection by both traditional RT-PCR and N=5 (N=0.46). Fisher exact test). No significant differences in absolute levels of viral DNA or changes in viral RNA content were seen among 60-weeks of therapy. Mean levels of infectious HIV-1 in coculturing CD+ 3 cells at week 96 of 3 subjects treated with 3-drugs and 13 with 5-drugs were 4.67 and 7.73 respectively (P=0.81). No differences were seen in quantitative or qualitative immunological determinants, including markers of immune activation.


Genital tract ART penetration

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

Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV

Genciva M Elbimama,*, Raya Nakazawa,† Bruce Sirimanne,‡ Chin-Huei Ling,‡ Victor DeCristofaro,‡ Karen Bennett,‡ Robert Paul,‡ Kabane Kallekepa,‡ Dongmin Chou,‡ Christina Georgopoulou,‡ Sallieyn J Harwood,‡ Raymond P Schiffman,‡ and Victor G Velcourt‡
Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>CPE score (2008)</th>
<th>CPE score (2010)</th>
<th>ME score</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEV</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dalcarb</td>
<td>20</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Indinavir</td>
<td>8</td>
<td>12.5</td>
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</tr>
<tr>
<td>Lopinavir</td>
<td>20</td>
<td>50</td>
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</tr>
<tr>
<td>Norvir</td>
<td>240</td>
<td>4</td>
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<tr>
<td>Transferase</td>
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<td>50</td>
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<tr>
<td>Zalcitabine</td>
<td>3</td>
<td>333</td>
<td>1</td>
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<tr>
<td>Zidovudine</td>
<td>20</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>NNRTI</td>
<td>10</td>
<td>108</td>
<td>3</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>10</td>
<td>108</td>
<td>3</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>20</td>
<td>20</td>
<td>4</td>
</tr>
</tbody>
</table>

Also noted in D:A:D study: *J Acquir Immune Defic Syndr. 2015;68:568-77

Cancer risk and ART

Lipids and integrase inhibitors vs EFV vs DRV

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"No one, however smart, however well educated, however experienced, is the suppository of all wisdom."

...But for the moment, knowing what you know is most likely enough.
HIV treatment revision: Into the future?

I would not say that the future is less predictable than the past.
I think the past was not predictable when it started.