Progress and Challenges of Antiretroviral Medications

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RVD Pharmacist, Hospital Sungai Buloh
After attending this presentation, participants will be able to:

1. Describe the evolution of antiretroviral therapy and current treatment guidelines

2. Describe current challenges with recommended treatment guidelines.
1. Evolution of antiretroviral therapy

Let’s start
Evolution of antiretroviral therapy
Challenges of early NRTI regimens:

• High pill burdens
• Treatment limiting toxicities
• Inconvenient dosing
• Emergence of resistance through mutations
Early Steps
mid-90’s
Human immunodeficiency virus (HIV) protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)

The ‘Cocktail’
1996
Triple-combination therapy, using dual-NRTI “backbones” in combination with a “third agent,” that was either a PI or an NNRTI - maximally suppressive regimens or highly active antiretroviral therapy.

1998-present:
The strategy of using two NRTIs plus a potent third agent still forms the cornerstone of current treatment principles, and is now referred to as combination antiretroviral therapy.

Sources: Centers for Disease Control and Prevention: Gay Men’s Health Crisis
adapted from New York Times, June 25, 2000

Jim McManus for the NY Times
The evolution of three decades of antiretroviral therapy: Development of >25 drugs across five different classes over the last 27 years.
HOW HAVE WE PROGRESSED SO FAR?
1. Simpler Treatment


- ddI Sachet buffered powder for oral solution
- ddI buffered powder for oral solution
- ddI buffered tablets
- ddI reduced-mass tablet
- ddI-EC 400 mg
# Dosing Evolutions: Fixed-Dose Combinations

<table>
<thead>
<tr>
<th>Individual Drugs</th>
<th>Fixed-Dose NRTIs</th>
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<tbody>
<tr>
<td>ABC/3TC</td>
<td>4 pills/day 1 tablet QD</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>2 pills/day 1 tablet QD</td>
</tr>
<tr>
<td>TDF/FTC/EFV</td>
<td>3 pills/day 1 tablet QD</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>4 pills/day 1 tablet BID (2/day)</td>
</tr>
<tr>
<td>ZDV/ABC/3TC</td>
<td>6 pills/day 1 tablet BID (2/day)</td>
</tr>
</tbody>
</table>

One pill once a day for HIV is a reality
Regimen Attributes With Impact on Adherence: Patient Perceptions

- Total pills per day: 14%
- Dosing frequency: 13%
- Adverse events: 12%
- Diet restrictions: 11%
- Pill size: 10%
- Number of refills: 9%
- Number of copays: 9%
- Number of prescriptions: 8%
- Number of bottles: 8%
- Bedtime dosing: 6%

Potential Advantages of Fixed-Dose Formulations

- Reduced pill burden
- Increased adherence
- Improved patient satisfaction
- Reduced risk of dosing errors
2. Phasing out of toxic and inconvenient ART

- Phasing out of stavudine (d4T) in 2010
- Metabolic toxicity and long-term complications.
- Increased regimen substitution & treatment interruption
- Price reductions in ARV drugs in recent years
Temporal evolution of ARV drug pipeline:
Moving towards smarter and better HIV treatment options

- Tenofovir
- Tenofovir alafenamide

withdrawn or no longer recommended ARVs
3. Towards Affordable HIV Drugs

Example price evolution of first line ARVs. Price reduction for the 2016 WHO Guidelines first-line recommended tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) fixed dose combination.
Prices are still falling, but second-line ART costs three times more than first-line ART

MALAYSIAN SCENARIO:
First Line ART : RM 40 per pt/month
Second Line ART : RM 600 per pt/month

Source: WHO Global Price Reporting Mechanism.
## Recommended Regimens: Malaysian Consensus Guidelines

<table>
<thead>
<tr>
<th>Year</th>
<th>Preferred First Line</th>
<th>Alternative</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>TDF + FTC + EFV</td>
<td>AZT + 3TC + EFV (or NVP)</td>
<td>ATV/r plus TDF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABC + 3TC + EFV (or NVP)</td>
<td>LPV/r plus TDF/FTCa</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC + Raltegravir (if intolerant of nNRTI)</td>
<td>TDF + FTC + NVP</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>TDF + FTC + Raltegravir</td>
<td>AZT + 3TC + EFV (or NVP)</td>
<td>TDF + FTC + ATV/r</td>
</tr>
<tr>
<td></td>
<td>TDF + FTC + Dolutegravir (if intolerant to NNRTI)</td>
<td>ABC + 3TC + EFV (or NVP)</td>
<td>TDF + FTC + LPV/r</td>
</tr>
</tbody>
</table>
First Line Treatment Evolution: Malaysian Scenario

Zidovudine + Lamivudine + Efavirenz
- 3 pills a day
- RM 42

Tenofovir + Emtricitabine + Efavirenz
- 2 pills a day
- RM 40

Tenofovir + Emtricitabine/3TC + Efavirenz
- 1 pill a day
- ~ RM 140
Antiretroviral Therapy Challenges in the Last Decade

- Adherence
- Management of toxicities
- Long-term complications
- Drug interactions
Adherence

Scenario 1
CC is about to start on ARV therapy. He has been very ill and is taking other medications—cotrimoxazole for PCP prophylaxis and fluconazole for oral candidiasis. He already has nausea and mild diarrhea.

He is worried that the ARVs will make him feel sicker. He thinks he will have problems organizing and remembering his medications.
Adherence

Scenario 2
Mrs RH is about to start on ARV therapy. She has many competing priorities. She works as a housekeeper from early morning until the late evening. She has 3 children and an extended family to care for.

She has not told her employer about her HIV status, and her husband is the only family member who knows.
### How Much Adherence Is Required for Optimal Results of ART?

<table>
<thead>
<tr>
<th>% Adherence to PI Therapy</th>
<th>% of Clients/Patients with Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;95</td>
<td>21.7</td>
</tr>
<tr>
<td>90–94.9</td>
<td>54.6</td>
</tr>
<tr>
<td>80–89.9</td>
<td>66.7</td>
</tr>
<tr>
<td>70–79.9</td>
<td>71.4</td>
</tr>
<tr>
<td>&lt;70</td>
<td>82.1</td>
</tr>
</tbody>
</table>

**Virologic failure** is defined as an HIV RNA level greater than 400 copies/ml at the last clinic visit.

Adherence and AIDS-Free Survival

10% Adherence difference = 21% reduction in risk of AIDS

Bangsberg D, et al. AIDS. 2001:15:1181
Sub-Optimal Adherence Predisposes to Resistance

Toxicity Was a Major Reason for Discontinuation of First-Line ARV

ICONA study group

Median follow-up: 45 weeks
Study population: 862 ARV-naive patients
Discontinuations: n = 312 (36%)

Learning Point: Anticipate, monitor and manage side effects

Medication-Related Factors and Adherence

Adverse effects (AEs) have been reported with virtually all ARV medications and are among the most common reasons for switching or discontinuation of therapy and for medication nonadherence.

“Minor” common side effects may be as important to the patient as major grade 3/4 events.

- Nausea, vomiting, dizziness, rashes, and diarrhea are common reasons why patients stop their medications.

Most patients are asymptomatic when treatment is started.

- Development of even minor symptoms can therefore be distressing.
Strategies to Promote Medication Adherence

- Peer support groups
- Education and counselling
- Identify barriers to adherence and provide individualized interventions
- Modified directly observed therapy either in the home
- Alarm Reminders

“Treatment buddy” – a person to whom they have disclosed their HIV status who can help them to keep appointments, provide reminders, assist with refills, offer support, and let the clinic know if there is a problem.
Antiretroviral Therapy Challenges in the Last Decade

- Adherence
- Management of toxicities
- Long-term complications
- Drug interactions
Drug Toxicity

Case 1
JS arrives to clinic after lost to follow up for 1 year.

She is HIV treatment naive, CD4+ cell count is 310 cells/mm$^3$, HIV viral load 75,000 copies/mL.

She is a widow and has 2 young children. She reports difficulty remembering to take medications everyday.

She was then started with Tenofovir 300mg /Emtricitabine 200mg 1 tablet and Efavirenz 600mg once daily.

Four weeks into HAART, she reported persistent dizziness and anxiety. Claims have lost hope.

Patient feels that symptoms are due to Efavirenz, hence skipped a few doses of EFV.
Efavirenz Disadvantages

- Low genetic barrier to resistance
- Higher incidence of adverse effects
  - Neurotoxicities: abnormal dreams, depression, dizziness, headaches
- Involved in Cytochrome P450 3A4 (CYP3A4) and 2D6
Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial

ENCORE1 Study Group†

Findings
The modified intention-to-treat analysis consisted of 630 patients (efavirenz 400=321; efavirenz 600=309). 32% were women; 37% were African, 33% were Asian, and 30% were white. The mean baseline CD4 cell count was 273 cells per μL (SD 99) and median plasma HIV-RNA was 4.75 log_{10} copies per mL (IQR 0.88). The proportion of participants with a viral load below 200 copies per mL at week 48 was 94.1% for efavirenz 400 mg and 92.2% for 600 mg (difference 1.85%, 95% CI -2.1 to 5.79). CD4 T-cell counts at week 48 were significantly higher for the 400 mg group than for the 600 mg group (mean difference 25 cells per μL, 95% CI 6-44; p=0.01). We recorded no difference in grade or number of patients reporting adverse events (efavirenz 400=89.1%, efavirenz 600=88.4%; difference 0.75%, 95% CI -4.19 to 5.69; p=0.77). Study drug-related adverse events were significantly more frequent in the 600 mg group than in the 400 mg group (146% [47] vs 118 [37]), difference -10.5%, 95% CI -18.2 to -2.8; p=0.01) and significantly fewer patients with these events stopped treatment (400 mg=6 [2%], 600 mg=18 [6%], difference -3.96%, 95% CI -6.96 to -0.95; p=0.01).

Interpretation
Our findings suggest that a reduced dose of 400 mg efavirenz is non-inferior to the standard dose of 600 mg, when combined with tenofovir and emtricitabine during 48 weeks in ART-naive adults with HIV-1 infection. Adverse events related to the study drug were more frequent with 600 mg efavirenz than with 400 mg. Lower dose efavirenz should be recommended as part of routine care.
### Adverse events – related to study drug

<table>
<thead>
<tr>
<th></th>
<th>EFV400 N=321</th>
<th>EFV600 N=309</th>
<th>Difference (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) patients reporting AE</td>
<td>286 (89.1)</td>
<td>273 (88.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) patients with study drug related AE</td>
<td>118 (36.8)</td>
<td>146 (47.2)</td>
<td>-10.5% (-18.2, -2.8)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Number (%) patients stopping drug due to related AE</td>
<td>6 (1.9)</td>
<td>18 (5.8)</td>
<td>-3.96 (-6.96, -0.95)</td>
<td>0.010*</td>
</tr>
</tbody>
</table>

Reference: ENCORE1 study: Efficacy of 400mg Efavirenz versus standard 600mg dose in HIV-infected, antiretroviral-naive adults: a randomised, double-blinded, placebo-controlled, non-inferiority trial
Efavirenz Adverse Events

Reference: ENCORE1 study: Efficacy of 400mg Efavirenz versus standard 600mg dose in HIV-infected, antiretroviral-naive adults: a randomised, double-blinded, placebo-controlled, non-inferiority trial
JS was prescribed with T. Efavirenz 400mg ON and continued with TenvirEM.

2 weeks into the regimen, claims very minimal drowsiness.

However complain of fever and generalized rashes.
Incidence of Efavirenz-induced rash:

Learning Point:
- Treat through mild to moderate rash with closer monitoring
- Discontinue efavirenz if severe rash or with systemic illness
What would you do?
A. Continue TenvirEM + Efavirenz
B. Continue TenvirEM + Efavirenz + Antihistamine
C. TenvirEM + Raltegravir 400mg BD
D. TenvirEM + Dolutegravir 50mg OD

Regimen of choice

TenvirEM + Dolutegravir

Due to inavailability, JS was started on T. Raltegravir
New kids on the block

**Integrase STIs (INSTIs)**

- **Raltegravir** 2007
- **Elvitegravir** 2012
- **Dolutegravir** 2013

All are very well tolerated.
Integrase Inhibitors

Chance to develop drug resistance

RAL
EGV/ cobi

Low

DTG*

*may consider for patients with adherence concern
Tenofovir disoproxil fumarate

Part of recommended first line regimens

Associated kidney disease is characterized either by a decrease in eGFR or by proximal tubule dysfunction, such as Fanconi syndrome

Also plays major role in PrEP and PEP

May be observed even a few months after TDF initiation
Tenofovir-induced nephrotoxicity

Risk factors

- Underlying renal disease
- Old age
- BMI <18.5 (or body weight < 50 kg)
- Untreated Diabetes Mellitus
- Untreated Hypertension
- Concomitant nephrotoxic drugs or a boosted Protease Inhibitor
- Prolonged NSAIDS use


FUTURE DIRECTION

TAF has improved renal profile with:

- Fewer discontinuations due to significant renal events
- Can be used with CrCl below 30mL/min

• 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV

* T_{1/2} based on in vitro plasma data.
Drug Toxicity

Case 2
Drug toxicity: Scenario 2

AJ is a 45 y/o male with CrCl 40 ml/min, CD4+ cell count 380 cells/mm3 and HIV viral load 100,000 copies/mL.

He has no other comorbidities.

He has strong desire for a once daily regimen.
What recommended or alternative regimens are available for AJ?
## Renal Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard Dosage</th>
<th>Dosing in renal impairment ClCr (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir</strong></td>
<td>300 mg BD OR 600 mg OD</td>
<td>Dosage adjustment is not necessary</td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td>150 mg BD OR 300 mg OD</td>
<td>30-49 150 mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-29 150 mg first dose, then 100 mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-14 150 mg first dose, then 50 mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;5 50 mg first dose, then 25 mg OD</td>
</tr>
<tr>
<td><strong>Tenofovir</strong></td>
<td>300 mg OD</td>
<td>30-49 300 mg Q 48 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-29 300 mg Q 72 H</td>
</tr>
<tr>
<td><strong>Zidovudine</strong></td>
<td>300 mg BD</td>
<td>&lt;15 100 mg Q 6-8 H</td>
</tr>
</tbody>
</table>
Major Symptoms Associated With Abacavir Hypersensitivity

- Fever 80%
- Rash 70%
- Gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain) >50%
- Generalized malaise and fatigue >40%
- Other symptoms e.g. respiratory (may mimic influenza illness), musculoskeletal

Antiretroviral Therapy Challenges in the Last Decade

Adherence

Management of toxicities

Long-term complications

Drug interactions
Long term Complications

Case 1
Mr. SS, 41 year old HIV-infected man on PI-based ART presents for routine follow-up. He complains of recent weight gain, especially in the abdomen. His fasting lipid profile was also found to be raised significantly.

PMH: HIV infection x 5 years
Well controlled on ART (VL <20)
Most recent CD4 = 360
No OIs

Current Medications:
AZT+3TC + lopinavir/ritonavir (Kaletra) x 2 years
What intervention(s) would you recommend to improve his lipid profile?
A. Discontinue lopinavir/ritonavir, substitute atazanavir/RTV
B. Ask him to replace his donuts with granola
C. Start Pravastatin
D. Nothing needs to be done; dyslipidemia associated with HIV/ART is not associated with an increase in CAD

Answer: A, B, C
Most protease inhibitors have been associated with marked elevations in triglycerides and LDL but little effect on HDL levels.

NNRTIs also associated with dyslipidemic effects.

Substantial evidence that PI-based ART increases risk of coronary artery disease (CAD)\(^2-4\).

2. 11\(^{th}\) CROI, 2004, Abstract 739.
Dyslipidemia in Adults on ART
Effects of PIs on Lipids

- CV subcommittee of ACTG summarized effects of PIs on ‘lipids’ by degree of abnormality:¹

<table>
<thead>
<tr>
<th>ATV</th>
<th>SQV</th>
<th>IDV</th>
<th>NFV</th>
<th>APV</th>
<th>LPV/r</th>
<th>RTV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>Little, if any</td>
<td>Fewest</td>
<td>Intermediate</td>
<td>Most marked</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Includes cross-study comparisons; direct comparisons for all PIs are not available
At therapeutic doses²

Further data now available:
ATV/r has less effect than LPV/r on TC and fasting TG (p≤0.005)³

ATV = atazanavir; SQV = saquinavir;
IDV = indinavir; NFV = nefinavir;
APV = amprenavir; LPV/r = lopinavir/ritonavir;
RTV = ritonavir; fosamprenavir/ritonavir;
ATV/r = atazanavir/ritonavir

4. DeJesus E et al. 10th CROI, Boston 2003, #178;
5. Walmsley S et al. 11th CROI, 2004; Poster 90
Half of Deaths in HIV-Infected Patients Now Due to Non-AIDS-Related Causes

Etiology of non-AIDS-related events

Non-AIDS-related events are more common in HIV disease, even after adjustment for age, cART exposure and traditional risk factors.

Current Approach

Manage known traditional risk factors of serious non-AIDS events

- Smoking
- Hypertension
- Obesity, excess visceral fat
- Diabetes
Antiretroviral Therapy Challenges in the Last Decade

- Adherence
- Management of toxicities
- Long-term complications
- Drug interactions
Drug Interactions
Drug Interactions: Case 1

A 57 y.o. male patient has a T cell count = 358 and an undetectable viral load on AZT/3TC/Kaletra. A significant increase from his baseline cholesterol levels was noted.

Patient is a non-smoker but has a positive family history of heart disease.

His provider plans to start him on a STATIN.

Which agent would you recommend?
Most of the statins undergo metabolism via CYP3A4 in the liver.

Lovastatin > Simvastatin > Atorvastatin = Rosuvastatin > Pravastatin

Extensively met Less met

<table>
<thead>
<tr>
<th>HAART</th>
<th>ACTION</th>
<th>EFFECTS</th>
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</table>

Lovastatin and Simvastatin are contraindicated with protease inhibitors.

Choice of statin: Pravastatin > Atorvastatin = Rosuvastatin
Mr. SS comes in after 3 months 7 kg weight loss, 3 weeks of cough and intermittent fever.

On examination, T 38.8 C, BP 100/70, HR 104, RR 20. He has prominent cervical adenopathy, and course breath sounds over his R upper and mid lung zones. Sputum AFB 3+ Diagnosed as smear positive PTB.
Which anti tuberculosis agent would you recommend?
## Rifampicin Decreases Blood Levels of NNRTI and Protease Inhibitors

<table>
<thead>
<tr>
<th>NNRTI/ PI</th>
<th>Effect of rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine (NVP)</td>
<td>↓ 37-58%</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>↓ 13-26%</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↓ by 35%</td>
</tr>
<tr>
<td>Darunavir</td>
<td>↓ by 81%</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>↓ by 82%</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>↓ by 75%</td>
</tr>
</tbody>
</table>
Preferred ART

- T. Tenofovir/Emtricitabine
- T. Efavirenz 600mg ON

What if EFV cannot be used??

- T. Dolutegravir 50mg BD
- T. Raltegravir 800mg BD

What if integrase inhibitor is not available?

- Nevirapine 200mg BD (with no once-daily lead-in phase) may be an alternative.

Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis, CDC 2013
Rifampicin is contraindicated

Substitute with RIFABUTIN 150mg OD

A two week “wash out” period is recommended between the last dose of RIF and the first dose PIs

The potent effect of RIF as a CYP450 inducer continues up to at least 2 weeks
Management of drug interactions

Are there therapeutically acceptable alternatives?
- e.g. rifabutin instead of rifampin

Are there recommended dose adjustments?

Monitoring for toxicities or subtherapeutic responses.
Overall Conclusions

Virologic suppression and immune restoration remain the most important goals of HIV disease management.

With increasing longevity of HIV-infected patients, focus is shifting toward whole health patient care.

- Management of age-related comorbidities is critical in order to optimize long-term outcomes.
Thank you!