Current and future treatment strategies

Dr. Mark Nelson
Chelsea & Westminster Hospital
Executive Committee of the British HIV Association (BHIVA)
“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the Medical Assistance & Medical Education (MAME) Programs
30 years of HIV drug development

- But...
- There is still room for improvement
  - No HIV vaccine
  - Morbidity is still an issue
  - Mortality could be further improved

1983: Identification of HIV
1985: HIV antibody testing developed
1987: First NRTI approved in US
1995: First HIV protease inhibitor approved
1996: First NNRTI approved
2003: First fusion inhibitor approved
2007: First CCR5 receptor antagonist approved
2007: First integrase inhibitor approved
2014: Over 30 approved antiretroviral drugs

Adapted from Palmisano L & Vella S. Ann Ist Super Sanita 2011;47:44–8.
1. FDA. Available at: http://www.fda.gov/ForConsumers/byAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118915.htm. Accessed 16 Sep 2013
### LES POTAGES, HORS D’OEUVRE ET OEUFS

- Consommé riche de volaille tremblant à l’estragon, et sa fondue de tomates aux poivrons

* Tian de légumes provençaux aux senteurs des sous-bois et à l’huile d’olive aux herbes *

- Délicates feuilles de gnocchi de pommes de terre servies tièdes, méli-mélo d’asperges à la truffe écrasée et son coulis d’artichauts

- Terrine de foie gras au blanc de volaille enrobé de pistaches, accompagnée de grains de raisins en ratafia

- Oeufs pochés en feuilleté aux pointes d’asperges, sauce mousseline

- Tartare de tomates au basilic, crémeux frais d’œufs brouillés et légumes du moment à la grecque

- Indulgence d’esturgeon, de saumon fumé et de caviar Sevruga sur blinis au froment et grains de maïs

### LES CRUSTACES ET COQUILLAGES

- Tourteau et queues de langoustines au naturel, servis sur une crème onctueuse à la pêche, croquants de concombre

- Tronçonnées de homard poêlées minute au Porto blanc

- Noix de Saint-Jacques poêlées sur coussin d’algues marines, salade de fines herbes confondues et de petits chipirons, vinaigrette safranée

### LES DESSERTS

- Crème brûlée à la pistache, glace vanille

- Farandole de glaces et sorbets de saison, quelques pétales candis de roses du jardin

- Dôme de rhubarbe en gelée de Bonnezeaux et sorbet aux framboises

- Crémeux de chocolat, coulant d’abricot et son sorbet à l’infusion de verveine

- Spoom à la fraise et son coulis, petites larmes de meringue, tutti frutti de fruits d’été mentholé
You Choose for Me
Escargots?
Cuisses de Grenouilles?
### Guideline recommendations for first-line treatment of adult treatment-naive patients

<table>
<thead>
<tr>
<th></th>
<th>IAS¹</th>
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<td>✓</td>
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</tbody>
</table>

- **✓** Recommended/preferred
- **Alternative**
- **Acceptable but less so than recommended/preferred or alternative; may be some cautions**
- **✗** Not recommended


*ABC/3TC only preferred for use with DTG in HLA B*5701-negative patients.
Mortality among persons 25–44 years old, USA, 1982–1995


Introduction of PIs

- Unintentional injury
- Cancer
- Heart disease
- Suicide
- HIV infection
- Homicide
- Chronic liver disease
- Stroke
- Diabetes

* Preliminary 1998 data

Centers for Disease Control HIV Mortality (through 2005). Available at:
Survival
Efficacy
Tolerability
Improved clinical outcomes: ACTG 320

Percentage of patients (%)

AIDS/death
Death
AIDS/death
Death
AIDS/death
Death

AZT (or d4T) + 3TC (n=579)
IDV + AZT (or d4T) + 3TC (n=577)

Adapted from Hammer SM et al. NEJM 1997;337:725–33
...a potent armamentarium

Up to 90% of treatment-naive patients can now achieve undetectable HIV-1 RNA

Large head to head study
Small head to head study

Continuum of care
Persons living with HIV in the UK 2011

- Total: 100%
  - Diagnosed: 76%
  - On treatment: 65%
  - Undetectable VL: 58%

n=96,000  n=72,950  n=62,400  n=55,650

HIV and AIDS Reporting System
HIV and STI Department, Health Protection Agency - Colindale
THE MARLOWE PLAYERS
present

Charles Dickens
A Tale of Two Cities
Adapted by
Mark Fitzgibbon

At Derby Playhouse, Studio Theatre
March 28th - April 1st 2000
Time 7.45pm
Tickets £6.00 (£5.00 concessions)
BOX OFFICE 01332 363275
an amateur production
# HAART teams

<table>
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<td>Doctors</td>
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<td>Nurses</td>
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<td>Pharmacists</td>
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### HAART teams

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<td>14</td>
<td>5+8</td>
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<tr>
<td>Pharmacists</td>
<td>4</td>
<td>1</td>
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<tr>
<td>Patients</td>
<td>4210</td>
<td>9122</td>
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<tr>
<td>On-treatment</td>
<td>3117</td>
<td>3045</td>
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## Available Antiretrovirals 2010

<table>
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<th>Protease Inhibitors</th>
<th>New Classes</th>
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<tbody>
<tr>
<td>Abacavir</td>
<td>Efavirenz</td>
<td>Atazanavir</td>
<td>Fusion Inhibitors</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Nevirapine</td>
<td>Darunavir</td>
<td>- Enfuvirtide</td>
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<tr>
<td>Emtricitabine</td>
<td>Etravirine</td>
<td>Fos-Amprenavir</td>
<td>- Maraviroc</td>
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<tr>
<td>Lamivudine</td>
<td></td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td></td>
<td>Lopinavir</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>Nelfinavir</td>
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<tr>
<td>Zidovudine</td>
<td></td>
<td>Ritonavir</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Saquinavir</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Tipranavir</td>
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</tr>
</tbody>
</table>

- R5 Inhibitors
  - Maraviroc

- Integrase Inhibitors
  - Raltegravir
Available Antiretrovirals - Ethiopia

NRTIs
• Didanosine
• Lamivudine
• Stavudine
• Zidovudine

NNRTIs
• Efavirenz
• Nevirapine

Protease Inhibitors
• Lopinavir
• Nelfinavir

New Classes

www.emea.europa.eu
Monitoring at Chelsea and Westminster
Monitoring in Ethiopia
Naïve patients undetectable viral load at 6 months
Naïve patients undetectable viral load at 6 months

- Chelsea and Westminster: 90%
- Ethiopia: 90%
Naïve patients undetectable viral load at 6 months

![Graph showing viral load percentages in Chelsea and Westminster, Ethiopia, and Uganda. The percentages are 100% for Chelsea and Westminster, 90% for Ethiopia, and 90% for Uganda.](image-url)
UK CHIC – Life expectancy

Life expectancy by CD4 count compared with UK population

LE at exact age 20 years:
- 1996-2008
  - UK women: 61.6 yrs
  - UK men: 57.8 yrs
  - HIV+ women: 50.2 yrs
  - HIV+ men: 39.5 yrs

- 1996–99 HIV+:
  - 30.0 yrs

- 2006–08 HIV+:
  - 45.8 yrs

Start triple ART post 2000
- CD4 200–350:
  - 53.4 yrs
- CD4 100–199:
  - 41.0 yrs
- CD4 <100:
  - 37.9 yrs

Impact on life expectancy of late diagnosis and treatment of HIV-1 infected individuals:
UK CHIC M May, M Gompels, C Sabin for UK CHIC. HIV10 Glasgow abstract 1629596
Living Well with HIV

For me, staying healthy with HIV is about a few basic things:

- A positive attitude. Partnering with my doctor. Taking medicine every day.
- Getting to know the people and organizations that can help me stay healthy. 
- For information about being well with HIV, call 1-800-342-AIDS or visit www.hivinfo.org.
PARTNER Study

Condomless Sex Acts and Rate of HIV Transmission by Sexual Behaviour

Suppressive ART resulted in zero linked transmissions to HIV-negative partners with condomless sex, despite a substantial number of sex acts. Unlinked transmissions did occur. Additional follow-up in MSM is forthcoming in the PARTNER2 study.

Rodger A, et al. CROI 2014; Boston. #153LB
Survival
Efficacy
Tolerability
To Tolerate
To Tolerate

• To endure
Toxicity of first generation PIs

- Nausea
- Diarrhoea
- Metabolic disturbances
- Body shape changes
- Paraesthesia
- Dysgeusia
And nucleosides were associated with......
Resulting in.....
## Toxicities: delayed recognition

<table>
<thead>
<tr>
<th>Drug / class</th>
<th>FDA approval</th>
<th>Toxicity</th>
<th>Strong signal</th>
<th>Delay (years)</th>
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<tr>
<td>Zidovudine</td>
<td>1987</td>
<td>lipoatrophy</td>
<td>1999</td>
<td>12</td>
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<tr>
<td>Stavudine</td>
<td>1994</td>
<td>lipoatrophy</td>
<td>1999</td>
<td>5</td>
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<tr>
<td>Nevirapine</td>
<td>1996</td>
<td>hepatitis / rash at higher CD4</td>
<td>2005</td>
<td>9</td>
</tr>
<tr>
<td>PIs</td>
<td>1996-</td>
<td>heart attack</td>
<td>2003</td>
<td>7</td>
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<tr>
<td>Efavirenz</td>
<td>1998</td>
<td>suicidality</td>
<td>2013</td>
<td>15</td>
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<tr>
<td>Abacavir</td>
<td>1998</td>
<td>heart attack</td>
<td>2008</td>
<td>10</td>
</tr>
<tr>
<td>Tenofovir</td>
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<td>kidney disease</td>
<td>2006</td>
<td>5</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2001</td>
<td>fracture</td>
<td>2013</td>
<td>12</td>
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<tr>
<td>Raltegravir</td>
<td>2007</td>
<td>myopathy</td>
<td>2012</td>
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</table>

NICOLAS SARKOZY

L'ÉTÉ AMÉRICAIN
Tolerability drives adherence, which drives efficacy
Tolerability drives adherence, which drives efficacy
Tolerability drives adherence, which drives efficacy
Toxicity drives non-adherence, which drives failure
Toxicity drives non-adherence, which drives failure
Toxicity drives non-adherence, which drives failure
Adherence
Efficacy
Tolerability
“Drugs don’t work if people don’t take them”

Former US Surgeon
General C. Everett Koop
• “Drugs do work if people do take them”

Mark R. Nelson
UK Surgeon General
Complexity of Regimens

Adherence Issues: ZDV + ddl + IDV

- Wake up, take IDV (2 pills), drink 12 oz. water, no food
- Breakfast + ZDV (1 pill)
- Take ddl (2 tablets), no food
- Drink 12 oz. water
- Lunch
- Take IDV (2 pills), drink 12 oz. water, no food
- Dinner + ZDV (1 pill)
- Take IDV (2 pills), drink 12 oz. water, no food
- Just before bed, take ddl (2 tablets), no food

The Complexity of Adherence

- Dietary Restrictions
- Dosing Frequency
- Host Variables
- Adverse Events
- Aging
- Mental States
- Injection Drug/Alcohol Use
- Lifestyle
- Toxicity

Regimen
## Pooled adherence ART-naïve patients

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once-daily</th>
<th></th>
<th>Twice-daily</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
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<tr>
<td>Eron 2004 [48]</td>
<td>94</td>
<td>18.3</td>
<td>19</td>
<td>92</td>
<td>17.2</td>
<td>19</td>
<td>3.5%</td>
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<tr>
<td>Gallant 2006 [49]</td>
<td>90</td>
<td>11.7</td>
<td>244</td>
<td>87</td>
<td>14</td>
<td>243</td>
<td>18.9%</td>
<td></td>
<td></td>
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<tr>
<td>Gonzalez-Garcia 2010 [15]</td>
<td>99</td>
<td>9.9</td>
<td>333</td>
<td>93</td>
<td>25.5</td>
<td>331</td>
<td>16.8%</td>
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<tr>
<td>Kubota 2006 [50]</td>
<td>94.3</td>
<td>15.8</td>
<td>411</td>
<td>92.9</td>
<td>15.7</td>
<td>195</td>
<td>17.7%</td>
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<td>Molina 2007 [54]</td>
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<td>11</td>
<td>115</td>
<td>92.6</td>
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<td>75</td>
<td>16.9%</td>
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<td>Molina 2008 [53]</td>
<td>82</td>
<td>38.4</td>
<td>401</td>
<td>84</td>
<td>36.7</td>
<td>378</td>
<td>10.5%</td>
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<td>Podsadecki 2008 [56]</td>
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<td>20.7</td>
<td>310</td>
<td>83.8</td>
<td>20.7</td>
<td>296</td>
<td>15.7%</td>
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<tr>
<td>Total (95% CI)</td>
<td>1833</td>
<td></td>
<td>1537</td>
<td>100.0%</td>
<td>4.00</td>
<td>[1.70, 6.31]</td>
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Heterogeneity: Tau²=5.96; Chi²=18.93, df=6 (p=0.004); I²=68%
Test for overall effect: Z=3.40 (p=0.0007)

Nachega J et al. EACS 2013. Abstr PS4/5
## Pooled virologic suppression in ART-naïve patients

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once-daily</th>
<th>Twice-daily</th>
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<th>Risk ratio</th>
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<td>Total</td>
<td>Events</td>
<td>Total</td>
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<td>19</td>
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<tr>
<td>Gallant 2006 [49]</td>
<td>194</td>
<td>244</td>
<td>171</td>
<td>243</td>
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<tr>
<td>Gathe 2008 [60]</td>
<td>145</td>
<td>310</td>
<td>128</td>
<td>296</td>
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<tr>
<td>Molina 2007 [54]</td>
<td>66</td>
<td>115</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>Molina 2008 [53]</td>
<td>343</td>
<td>440</td>
<td>338</td>
<td>443</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1128</td>
<td>1076</td>
<td>100.0%</td>
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</table>

Total events: 762, 692

Heterogeneity: Tau²=0.00; Chi²=3.04, df=4 (p=0.55); I²=0%
Test for overall effect: Z=1.97 (p=0.05)

Nachega J et al. EACS 2013. Abstr PS4/5
Single Tablet Regimens (STRs)

Current
- **ATRIPLA (1550 mg)**
- **EVIPLERA (1150 mg)**
- **STRIBILD (1350 mg)**

Future
- **DRV-STR (1550 mg)**
  - DRV/COBI/FTC/TAF
- **STRIBILD 2.0 (1050mg)**
- **DOLUTEGRAVIR/ABACAVIR/LAMIVUDINE**

2. Mathias AA, et al. IAC 2010; Vienna. THLBPE17
Rationale for STRs

STRs can have a positive impact on treatment outcomes of interest

• Adherence\(^1\)–\(^2\)
  – Improved quality of life
  – No refill misalignment
  – Simultaneous dosing of all ARVs

• Health outcomes & healthcare costs\(^3\)–\(^7\)
  – Improved virologic outcomes
  – Few discontinuations
  – Remain undetectable longer, potentially reducing transmission
  – Longer duration of therapy
  – Lower risk of hospitalisation
  – Lower healthcare costs
  – Lower pharmacy costs

• Patient convenience
  – Simple\(^1\)
  – Single co-pay

Patient reported outcomes STR enhances patients’ acceptability of HAART and self-reported adherence

230 patients on stable HAART completed questionnaires on their attitude towards HAART, adherence level and the acceptability of their regimen\(^1,2\)

**Patient reported acceptability of current HAART regimen\(^1\)**

<table>
<thead>
<tr>
<th>% Patients</th>
<th>(\text{STR})</th>
<th>QD&gt;1 Pill</th>
<th>BID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>84</td>
<td>25</td>
</tr>
</tbody>
</table>

- Extremely / very
- Little + not at all

**Self-reported non-adherence\(^2\)**

<table>
<thead>
<tr>
<th>% Patients</th>
<th>(\text{STR})</th>
<th>QD&gt;1 Pill</th>
<th>BID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>25</td>
<td>45</td>
</tr>
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</table>

Suboptimal adherence defined as self-reporting having missed at least one dose during the past week

Patients receiving a STR reported a higher acceptability of their regimen and better adherence compared with those receiving more complex regimens

Real world adherence and association between adherence and viral outcomes

Evaluation of published associations among use of STR vs. MTR, ART adherence and treatment efficacy/effectiveness

Meta-analysis: odds of achieving ≥95% real-world adherence with STR vs. MTR

Association between adherence and viral outcomes

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>Viral Failure Rate*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High Adherence</td>
<td>Low Adherence</td>
</tr>
<tr>
<td>Cohen et al., 2013*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rilpivirine+2NRTIs</td>
<td>639</td>
<td>19%</td>
<td>44%</td>
</tr>
<tr>
<td>Efavirenz+2NRTIs</td>
<td>599</td>
<td>16%</td>
<td>35%</td>
</tr>
<tr>
<td>Martin et al., 2008†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI-based regimen</td>
<td>662</td>
<td>1.4%</td>
<td>6.2% (a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31.4% (b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51.7% (c)</td>
</tr>
</tbody>
</table>

*High adherence, >95%; low adherence, ≤95%
†High adherence, ≥90%; low adherence, (a) 80-89%, (b) 70-79%, (c) <70%
¥ The drug efficacy/effectiveness was measured as viral load (RNA level), viral suppression rate, viral failure rate, or undetectable RNA level

- In comparative real-world studies, patients receiving STRs vs. MTRs had a 70% greater odds of achieving ≥95% adherence
- Available evidence supports a positive and clinically significant association between higher adherence and viral suppression

Sweet D, et al. IAC 2014. Melbourne, Australia. #THPE421
"I AM A SPECIAL ONE"
"I wouldn't say I was the best manager in the business. But I was definitely in the top one."

— Brian Clough
quaestio quaestio $q_0 < ? ? ?$
How low can you go?

The aim is to keep your viral load under 50, what we call undetectable.
Drug resistance
Efavirenz
Efavirenz
Potency: STARTMRK
RAL vs EFV in naive patients to 240 weeks

Bid, twice-daily; qhs, every night before bedtime.
A new era in HIV treatment

Efficacy: newer treatments outperform EFV

Newer ARVs have demonstrated higher rates of virologic suppression compared to EFV-based regimens in HIV-1 infected ART-naive patients

EFV: Cross-study comparison of the overall incidence of neuropsychiatric adverse events

Post-approval, EFV-associated CNS toxicity has been consistently reported in both randomized clinical trials and cohort studies.
The majority of cases of CNS toxicity leading to treatment modification occurred after having been established on EFV/FTC/TDF STR for more than 3 months.
Time to suicidality, primary analysis

Hazard ratio (95% CI)
2.28 (1.27 to 4.10), \( p = 0.006 \)

47 events/5817 PY*
(8.08/1000 PY)

15 events/4099 PY*
(3.66/1000 PY)

*Person Years, sum of at-risk follow-up

As-treated HR
2.16 (1.16–4.00)

Tolerability: Newer ARVs outperform EFV

Incidence of specific AEs of interest (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>EFV Pts, n</th>
<th>Dizziness</th>
<th>Insomnia</th>
<th>Abnormal Dreams</th>
<th>Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EFV</td>
<td>Comp</td>
<td>EFV</td>
<td>Comp</td>
<td>EFV</td>
</tr>
<tr>
<td>GS-102¹</td>
<td>EVG/COBI</td>
<td>352</td>
<td>24</td>
<td>7</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>STaR²</td>
<td>RPV</td>
<td>392</td>
<td>22</td>
<td>7</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>STARTMRK³</td>
<td>RAL</td>
<td>284</td>
<td>35</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>SINGLE⁴</td>
<td>DTG</td>
<td>419</td>
<td>35</td>
<td>9</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>ECHO/THRIVE⁵,⁶</td>
<td>RPV</td>
<td>682</td>
<td>28</td>
<td>10</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Randomized, controlled trials in ART-naïve patients have shown newer ARVs to be associated with a lower incidence of neuropsychiatric symptoms and rash compared with EFV.
<table>
<thead>
<tr>
<th>Resistance Category</th>
<th>Clinical Study Number</th>
<th>903</th>
<th>934</th>
<th>104 &amp; 111 Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Year</td>
<td></td>
<td>2000</td>
<td>2003</td>
<td>2013</td>
</tr>
<tr>
<td>NNRTI-R</td>
<td></td>
<td>0.5%</td>
<td>4.2%</td>
<td>8.7% *</td>
</tr>
<tr>
<td>K103N</td>
<td></td>
<td>0.3%</td>
<td>3.2%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Y181C</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1.1%</td>
</tr>
<tr>
<td>NRTI-R</td>
<td></td>
<td>3.2%</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>TAMs</td>
<td></td>
<td>2.8%</td>
<td>2.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td>M184V/I</td>
<td></td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>K65R</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0.1%</td>
</tr>
<tr>
<td>PI-R</td>
<td></td>
<td>1.2%</td>
<td>2.4%</td>
<td>2.9% *</td>
</tr>
<tr>
<td>INSTI-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T66I</td>
<td></td>
<td>1%</td>
<td>0</td>
<td>1.4%</td>
</tr>
<tr>
<td>T97A polymorphism</td>
<td></td>
<td></td>
<td></td>
<td>0.07%</td>
</tr>
</tbody>
</table>

Note: Increases in NNRTI-R from 2000 to 2003, 2000 to 2013, and 2003 to 2013 were statistically significant (p-value < 0.0001, < 0.0001, and 0.0008, respectively). Increase in PI-R from 2000 to 2013 was statistically significant (p-value: 0.03). All other comparisons were not statistically significant. Fisher's exact and Chi-square tests.
Drug-drug interactions

DRV/r

Diarrhoea
Drug-drug interactions

LOP/r

Diarrhoea
A5257 Study Design*

HIV-infected patients, ≥18 yr, with no previous ART, VL ≥ 1000 c/mL at US Sites

Randomized 1:1:1 to Open Label Therapy
Stratified by screening HIV-1 RNA level (≥ vs < 100,000 c/mL), A5260s metabolic substudy participation, cardiovascular risk

ATV 300 mg QD + RTV 100mg QD + FTC/TDF 200/300 mg QD
RAL 400 mg BID + FTC/TDF 200/300 mg QD
DRV 800 mg QD + RTV 100 mg QD + FTC/TDF 200/300 mg QD

Study Conclusion 96 weeks after final participant enrolled
Follow-up continued for 96 weeks after randomization of last subject (range 2-4 years) regardless of status on randomized ART

*With the exception of RTV, all ART drugs were provided by the study
Cumulative Incidence of Virologic Failure

ATV/r vs RAL
3.4% (-0.7%, 7.4%)

DRV/r vs RAL
5.6% (1.3%, 9.9%)

ATV/r vs DRV/r
-2.2% (-6.7%, 2.3%)
Cumulative Incidence of Tolerability Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- **ATV/r vs RAL**
  - 13% (9.4%, 16%)

- **DRV/r vs RAL**
  - 3.6% (1.4%, 5.8%)

- **ATV/r vs DRV/r**
  - 9.2% (5.5%, 13%)
Cumulative Incidence of Virologic or Tolerability Failure

*Consistent results seen with TLOVR at a 200 copies/ml threshold*
Proportion VL ≤50 copies/mL

**ITT, regardless of ART change**

![Graph showing proportion VL ≤50 copies/mL for ATV/r, RAL, and DRV/r at different study weeks.]

**ITT, off-ART=failure (SNAPSHOT)**

![Graph showing proportion VL ≤50 copies/mL for ATV/r, RAL, and DRV/r at different study weeks.]

<table>
<thead>
<tr>
<th></th>
<th>24</th>
<th>48</th>
<th>96</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>83%</td>
<td>90%</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td>RAL</td>
<td>90%</td>
<td>92%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>83%</td>
<td>88%</td>
<td>89%</td>
<td>90%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>24</th>
<th>48</th>
<th>96</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>70%</td>
<td>73%</td>
<td>63%</td>
<td>62%</td>
</tr>
<tr>
<td>RAL</td>
<td>84%</td>
<td>83%</td>
<td>80%</td>
<td>76%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>77%</td>
<td>77%</td>
<td>73%</td>
<td>71%</td>
</tr>
</tbody>
</table>
Potency: Study 102

EVG vs EFV in naive patients to 144 weeks

- EVG/COBI/FTC/TDF showed durable, high rates of virologic success through to Week 144 in Study 102 (80% vs 75% for EFV/FTC/TDF)
  - Treatment difference at W144: 4.9% (95% CI: -1.3% to 11.1%)

Proportion <50 c/mL (95% CI) and CD4 Change from Baseline

Adjusted treatment difference between groups:
+8.3% (95% CI +2.0% to +14.6%) p=0.010
Potency: Study 103
ATV vs EVG in naive patients to 144 weeks

- In study 103, EVG/COBI/FTC/TDF maintained high rates of virologic success (78% vs 75%) through to W144 (78% vs 75% with ATV/r/FTC/TDF)
  - Treatment difference at W144 3.1% (95% CI: -3.2% to 9.4%)

Proportion (95% CI) of Individuals With HIV-1 RNA <50 c/mL Over Time – Snapshot

- DTG: 80%
- DRV/r: 68%

Week: 0 4 8 12 16 24 36 48 96
Proportion (%): 0 10 20 30 40 50 60 70 80 90 100

Test for superiority: $P=0.002$

Molina et al. HIV Drug Therapy Glasgow 2014; Glasgow, UK. Slides 0155.
Multicenter, international, randomised, open-label, Phase 3b, 96-week study

ARV-naïve
HIV-1 RNA ≥2500 c/mL
Sensitivity to EFV, FTC, RPV, TDF (N=786)

Primary endpoint:
• Efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 48 (Snapshot analysis); non-inferiority margin of 12%

Secondary endpoints:
• Safety and efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 96 (Snapshot analysis)
• Change in CD4 cell count at Weeks 48 and 96
• Genotype/phenotype resistance at time of virologic failure
STaR Study: 96 Week Safety Analysis

Virologic Outcomes by Snapshot Analysis and CD4 Changes

- Mean CD4 count change (cells/mm$^3$):
  - Week 48: CPA +200 vs. ATR +191 (p=0.37)
  - Week 96: CPA +278 vs. ATR +259 (p=0.17)

Cohen C, et al. IAC 2014. Melbourne, Australia. #WEPE064
STaR – Virologic failure at Weeks 48 & 96
stratified by baseline HIV-1 RNA – snapshot analysis

Virologic failure definition:
• Week 48 or 96 HIV-1 RNA > 50 c/mL,
or discontinued study drug due to lack
of efficacy or other reasons and last available
HIV-1 RNA >50 c/mL

* Post hoc analyses; analyses for non-inferiority only
pre-specified for ≤100,000 c/mL and >100,000 c/mL

Changing Preferences
NEAT 001/ANRS 143 study design

- Phase III, randomised, open-label, multicenter, parallel-group, non-inferiority, strategic trial
- 78 sites, 15 countries (Austria, Belgium, Denmark, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden)

HIV-1 ART-naïve
≥ 18 years
HIV-1 RNA > 1000 c/ml
CD4 ≤ 500/mm³
HBs Ag negative
No major IAS-USA resistance mutations

Randomisation 1:1
stratified by country and participation in virology/immunology substudy

- Composite virological and clinical primary endpoint (6 components)

DRV+r 800+100 mg QD + RAL 400 mg BID
DRV+r 800+100 mg QD + TDF/FTC FDC QD

Minimum
Week 96

Raffi F et al. CROI 2014 oral 84LB
Primary analysis:

time from randomisation to primary endpoint

Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>401</td>
<td>404</td>
</tr>
<tr>
<td>N with primary endpoint</td>
<td>76 (19%)</td>
<td>61 (15%)</td>
</tr>
<tr>
<td>V1. Regimen change for insufficient response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 log_{10} c/ml HIV RNA reduction W18*</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HIV RNA ≥ 400 c/ml W24*</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>V2. HIV RNA ≥ 50 c/ml at W32*</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>V3. HIV RNA ≥ 50 c/ml after W32*</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>C1. Death</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>C2. AIDS event</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>C3. SNAIDS event</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

* confirmed by a subsequent measurement

Estimated proportion reaching primary endpoint at W96
RAL: 17.4% vs TDF/FTC: 13.7%
Adjusted difference: 3.7% (95% CI: -1.1, 8.6%)

Probability of reaching primary endpoint

log rank p=0.12
Primary endpoint at W96 by baseline characteristics

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r

<table>
<thead>
<tr>
<th></th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 805</td>
<td>-1.1</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>17.4 %</td>
<td>13.7 %</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100,000 c/ml</td>
<td>-3.9</td>
<td>13.5</td>
</tr>
<tr>
<td>n = 530</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100,000 c/ml</td>
<td>-0.05</td>
<td>19.3</td>
</tr>
<tr>
<td>n = 275</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 %</td>
<td>27 %</td>
</tr>
<tr>
<td></td>
<td>p = 0.09*</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200/mm³</td>
<td>-3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>n = 123</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.0 %</td>
<td>21.3 %</td>
</tr>
<tr>
<td>Baseline CD4+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200/mm³</td>
<td>-3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>n = 682</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.6 %</td>
<td>12.2 %</td>
</tr>
<tr>
<td></td>
<td>p = 0.02*</td>
<td></td>
</tr>
</tbody>
</table>

Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

* Test for homogeneity
Design

**Primary Endpoint:** Loss of future drug options, defined as: new intermediate/high level resistance to $\geq 1$ drug to which the patient’s virus was considered to be sensitive at trial entry.

- * Return to triple therapy *permanently* for confirmed VL rebound >50 copies/ml ($\times 3$), toxicity, or patient wish.
- ** Return to triple therapy *temporarily* for pregnancy/breastfeeding, or requirement for short-term medication with PI interactions.
### Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OTT (n=291)</th>
<th>Plm (n=296)</th>
<th>Difference Plm–OTT (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL rebound ≥ 50 copies/ml, confirmed - n (%)</td>
<td>8 (3.2%)</td>
<td>95 (35.0%)</td>
<td>31.8% (24.6 to 39.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loss of future drug options [by 36 months] - n (%)</td>
<td>2 (0.7%)</td>
<td>6 (2.1%)</td>
<td>1.4% (-0.4 to 3.4%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Loss of future drug options [by end of trial] - n (%)</td>
<td>4 (1.8%)</td>
<td>6 (2.1%)</td>
<td>0.2% (-2.5 to 2.6%)</td>
<td>0.85</td>
</tr>
<tr>
<td>By drug class – n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NNRTI</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PI</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 change, cells/mm³ mean (SE)</td>
<td>+91 (9)</td>
<td>+108 (9)</td>
<td>+17 (-10 to +43)</td>
<td>0.21</td>
</tr>
<tr>
<td>Serious disease complication n (%)</td>
<td>8 (2.8%)</td>
<td>15 (5.1%)</td>
<td>2.3% (-0.8% to 5.4%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Grade 3/4 adverse event n (%)</td>
<td>159 (55%)</td>
<td>137 (46%)</td>
<td>-8.4% (-16.4% to 0.3%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Neurocognitive function [NPZ-5] change -mean (SE)</td>
<td>+0.51 (0.04)</td>
<td>+0.50 (0.04)</td>
<td>-0.01 (-0.11 to +0.09)</td>
<td>0.86</td>
</tr>
<tr>
<td>Cost of ART drugs, £ mean (SE)</td>
<td>30,230 (860)</td>
<td>21,260 (700)</td>
<td>-8970 (-6,790 to -11,160)</td>
<td>-</td>
</tr>
</tbody>
</table>

Patton et al. CROI 2014 poster 550
Primary virologic and safety endpoints (high viral load stratum at DSMB action)

N=797; median (25th, 75th) follow-up = 60 weeks (28, 84)

Time to virologic failure

- TDF/FTC (26 events)
- ABC/3TC (57 events)

Time to safety endpoint

- TDF/FTC (78 events)
- ABC/3TC (130 events)

Log rank test p-value = 0.0003
HR (95% CI) 2.33 (1.46, 3.72)

Log rank test p-value < 0.0001
HR (95% CI) 1.89 (1.43, 2.50)

**Tenofovir Alafenamide (TAF)**

*Next Generation Prodrug of Tenofovir-increased liver, lymph concentration*

---

**Gut**
- TFV
- TDF
- TAF

**Plasma**
- TDF/TFV
- TAF

**Lymphoid Cells**
- TAF
- TFV
- TFV-MP
- TFV-DP

---

TAF 10mg in E/C/F/TAF has PK comparable to TAF 25mg alone^2:
- COBI ↑ TAF levels ~2.2-fold

Relative to TDF 300 mg, TAF 25 mg has^3:
- Increased anti-HIV-1 activity in Phase 1
- Increased intracellular TFV-DP levels by ~7-fold
- Decreased circulating plasma TFV levels by ~90%
- Lower levels of TFV in kidney and bone tissue expected

---

^1 P Ruane, et al. CROI 2012; Paper # 103
^2 S Ramanathan, et al. IWCPHT 2012; Abstract O_13
Virologic response (M=F, ITT)
GS-US-292-0102 – Week 24 Analysis

Resistance
3 subjects met protocol-specified criteria for resistance analysis

Confirmed >400 copies/mL of HIV-1 RNA at Week 24 or the discontinuation visit

E/C/F/TAF arm (n=1)
• 1 subject with Week 24 rebound
No resistance detected

STB arm (n=2)
• 1 subject with persistent viremia
  – NRTI resistance (M184V + K70E)
  – No EVG resistance
• 1 subject with late rebound
  – No resistance detected

• Mean change from baseline CD4+ cell count:
  – E/C/F/TAF, +163 cells/μL
  – STB, +177 cells/μL (p = 0.76)

A Zolopa et al., CROI 2013; Paper #99LB. Randomized, placebo-controlled, double-blind study. N=150.
Median estimated GFR (Cockcroft-Gault)
GS-US-292-0102 – Week 24 Analysis

• Change in eGFR at Week 24
  – E/C/F/TAF: -4.8 mL/min
  – STB: -11.8 mL/min (p=0.04)

A Zolopa et al., CROI 2013; Paper # 99LB. Randomized, placebo-controlled, double-blind study. N=150.
Moving forward with cART – what’s the target?

- Potent viral suppression
- Improved tolerability
- Regimen simplicity
- Durability of response

Optimal immune restoration
Minimal inflammation/activation

Trust Me, I'm a Doctor
ARV therapy – Do doctors and patients think alike?

<table>
<thead>
<tr>
<th>Rank</th>
<th>Patient (N=114)</th>
<th>HCP (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (most important)</td>
<td>Efficacy</td>
<td>Efficacy</td>
</tr>
<tr>
<td>2</td>
<td>CD4 rise</td>
<td>Low toxicity</td>
</tr>
<tr>
<td>3</td>
<td>Protecting others</td>
<td>CD4 rise</td>
</tr>
<tr>
<td>4</td>
<td>Low toxicity</td>
<td>Once daily dosing</td>
</tr>
<tr>
<td>5</td>
<td>Resistance if fails</td>
<td>STR</td>
</tr>
<tr>
<td>6</td>
<td>Drug interactions</td>
<td>Low tablet load</td>
</tr>
<tr>
<td>7</td>
<td>Once daily dosing</td>
<td>Protecting others</td>
</tr>
<tr>
<td>8</td>
<td>Low tablet load</td>
<td>Drug interactions</td>
</tr>
<tr>
<td>9</td>
<td>STR</td>
<td>Resistance if fails</td>
</tr>
<tr>
<td>10 (least important)</td>
<td>Cost</td>
<td>Cost</td>
</tr>
</tbody>
</table>

Redlin, S. 'Personal' communication. 2014. ARV therapy – Do doctors and patients think alike?
Thank you

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