Switching Therapy and other considerations for Successful Antiretroviral Therapy (ART)

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Imperial College Healthcare NHS Trust
HIV: a success story

- Suppression of viral load >90% of treated patients
- Immune restoration
- Better ART drugs
- Simplified treatment
- Improved survival
- Transmission reduced
Emerging co-morbidities in HIV

**Renal dysfunction**
30% of HIV+ patients have abnormal kidney function

**Reduced bone mineral density**
Increased prevalence of osteoporosis or osteopenia in spine, hip or forearm: 63% of HIV+ patients

**Neurocognitive dysfunction**
Neurological impairment present in ≥50% HIV+ patients

**Cardiovascular disease**
75% increase in risk of acute MI

**Cancer**
Increased risk of non-AIDS-defining cancers e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal and renal

**Frailty**
Increased frailty phenotype if HIV infected 3-14x; Associated with CD4 count

References:
# Toxicities today

<table>
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<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>INIs</th>
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<td>Mitochondrial toxicity</td>
<td>Rash and hepatotoxicity</td>
<td>GI/metabolic disturbance/ hyperlipidaemia</td>
<td>Myalgia</td>
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<tr>
<td>Abacavir: hypersensitivity and cardiovascular risk</td>
<td>Efavirenz: CNS disturbance</td>
<td>Atazanavir: jaundice/ hyperbilirubinaemia</td>
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<tr>
<td>Tenofovir: renal and bone</td>
<td></td>
<td>Darunavir: rash</td>
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Outline

- Why do patients/clinicians modify therapy?
- How do we monitor patients?
- How do we (safely) switch therapy?
Swiss cohort: reasons for discontinuation of HAART

Patients starting HAART: N=1318

Patients modifying HAART within 1 year: n=391 (29.7%)

Switched: n=297 (76.0%)
Discontinued for ≥4 weeks: n=94 (24.0%)

Most frequent toxicities:
- Gastrointestinal intolerance (28.9%)
- Hypersensitivity (18.3%)
- CNS adverse events (17.3%)
- Hepatic events (11.5%)

HAART, Highly active antiretroviral therapy; CNS, central nervous system
Why do patients switch therapy?

- Virological failure
Why do patients switch therapy?

- Virological failure
- Toxicity/tolerability
  - REACTIVE (‘real’ toxicity): after occurrence of an adverse event or a drug-drug interaction
  - PROACTIVE (‘potential’ toxicity): to avoid an adverse event/drug interaction
- Simplification: to improve adherence
- ‘Potentially better’ regimens
- Cost?
Do you consider proactive switching ART in stable patients for possible benefit in terms of potential co-morbidity (e.g. cardiovascular disease?), and when?
What are we asking the patient about?
What are we looking for?
What triggers a switch in ART?
Don’t always blame the drugs!
British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011

D Asboe, C Aitken, M Boffito, C Booth, P Cane, A Fakoya, AM Geretti, P Kelleher, N Mackie, D Muir, G Murphy, C Orkin, F Post, G Rooney, C Sabin, L Sherr, E Smit, W Tong, A Ustianowski, M Valappil, J Walsh, M Williams and D Yrrell on behalf of the BHIVA Guidelines Subcommittee*

British HIV Association (BHIVA), BHIVA Secretariat, Mediscript Ltd, London, UK

Part III

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<td>Type 2 Diabetes: Management</td>
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<td>Dyslipidaemia</td>
<td>36</td>
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</tbody>
</table>
Routine monitoring on ART (1)
(adapted from BHIVA monitoring guidelines 2011)

- History (patient reported outcomes):
  - Tolerability, toxicity
  - Adherence: assess and support

- Targeted physical examination
  - Plus annual weight/BP/BMI

- Investigations
  - Efficacy
  - Safety

- Other assessments
  - CVD risk (annual)
  - Fracture risk (FRAX score 3 yearly) +/- BMD
Routine monitoring on ART (2)
(adapted from BHIVA monitoring guidelines 2011)

- **Investigations**
  - **Efficacy**: Viral load and CD4 count

- **Safety**:
  - FBC (12 monthly)
  - Creatinine, eGFR, liver function, glucose, bone profile (3-6 monthly)
  - Lipids (6-12 monthly)
  - Urinalysis (all routine visits if on TDF, otherwise 12 monthly)
  - Urine protein:creatinine ratio (uPCR) (12 monthly)
### Screening for co-morbidities: EACS guidelines

<table>
<thead>
<tr>
<th>Assessment</th>
<th>At HIV diagnosis</th>
<th>Prior to starting CART</th>
<th>Follow up with CART</th>
<th>Frequency without CART</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>On transfer of care repeat assessment: Premature CVD, cardiovascular events in first degree relatives; male &lt;55, female &lt;65 years. Adverse lifestyle habits should be addressed more frequently.</td>
</tr>
<tr>
<td>Body composition</td>
<td>Body mass index</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Annual assessment on ART only.</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Risk assessment (Framingham score)</td>
<td>+</td>
<td>+</td>
<td>annual</td>
<td>Should be performed in every older patient without CVD (Men &gt; 40 years; Women &gt;50 yrs).</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure</td>
<td>+</td>
<td>+</td>
<td>annual</td>
<td>Repeat in fasting state if used for medical intervention (i.e. ≥8h without caloric intake).</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>TC, HDL-C, LDL-C, TG</td>
<td>+</td>
<td>+</td>
<td>annual</td>
<td>Consider oral glucose tolerance test if repeated fasting glucose levels of 6.1-6.9 mmol/L (110-125 mg/dL).</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Serum glucose</td>
<td>+</td>
<td>+</td>
<td>6-12 m</td>
<td>More frequent monitoring prior to starting and on treatment with hepatotoxic drugs.</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Risk assessment</td>
<td>+</td>
<td>+</td>
<td>annual</td>
<td>More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs. Every 6 months if eGFR &lt;60 ml/min; if proteinuria ≥1+ and/or eGFR&lt;60 ml/min perform UP/C or UA/C.</td>
</tr>
<tr>
<td>Renal disease</td>
<td>eGFR (aMDRD)</td>
<td>+</td>
<td>+</td>
<td>annual</td>
<td></td>
</tr>
<tr>
<td>Bone disease</td>
<td>Risk assessment</td>
<td>+</td>
<td>+</td>
<td>2 yrs</td>
<td>If not using FRAX®, consider DXA of spine and hip in specific patients; Repeat according to risk factors.</td>
</tr>
<tr>
<td>Neurocognitive impairment</td>
<td>Questionnaire</td>
<td>+</td>
<td>+</td>
<td>1-2 yrs</td>
<td>Perform screening assessment in at risk patients.</td>
</tr>
<tr>
<td>Depression</td>
<td>Questionnaire</td>
<td>+</td>
<td>+</td>
<td>1-2 yrs</td>
<td>Perform screening assessment in at risk patients.</td>
</tr>
<tr>
<td>Cancer</td>
<td>Mammography</td>
<td>+</td>
<td>1-3 yrs</td>
<td>1-3 yrs</td>
<td>Women 50-70 years. Sexually active women, frequency depending on CD4, controversial.</td>
</tr>
<tr>
<td></td>
<td>Cervical PAP</td>
<td>+</td>
<td>1-3 yrs</td>
<td>1-3 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>+</td>
<td>1-3 yrs</td>
<td>1-3 yrs</td>
<td></td>
</tr>
</tbody>
</table>

EACS guidelines, 2009
Routine monitoring – discussion points

- Little evidence around optimal frequency of monitoring
- Should monitoring frequency depend on the drugs used?
- What to do with fluctuating values?
- Cost implications of monitoring
Virtual clinic (St Mary’s) May-July 2014

- 67 patients discussed in 3 month period
- 39/67 (58%) ‘undetectable’ viral load on ART

Reasons for discussion

- Simplification (38%)
- Renal dysfunction (19%)
- CNS/neurocognitive impairment (13%)
- GI/liver (8%)
- Potential interaction (5%)
- CV/lipids (5%)
- Lipoatrophy (2%)
- Other (10%)
67 patients discussed in 3 month period
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Reasons for discussion
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- Lipoatrophy (2%)
- Other including bone (10%)
Renal
Mild abnormalities very common

Several ARV associated with a higher risk of renal impairment (tenofovir, atazanavir, indinavir)

Usually multi-factorial
- Co-morbidities?
- Other drugs? It’s not always tenofovir!

2 urgent situations:
- Fanconi’s syndrome (severe proximal tubule dysfunction)
- Acute or chronic kidney injury requiring ARV dose adjustments
How do we measure renal function?

- **Creatinine**
  - Dependent on skeletal muscle mass
- **Creatinine-based formulae**
  - Cockroft Gault
  - Modification of Diet in Renal Disease (MDRD)
- **Urine**
  - Proteinuria (uPCR vs uACR)
- **Other blood markers**
  - Phosphate
Impact of tenofovir (TDF) on renal function (1)

- **Increased creatinine**
  - Filtered by glomerulus (TDF probably not glomerulo-toxic)
  - Smaller amounts secreted across proximal tubule
    - Proximal tubule injury may cause modest eGFR changes
  - TDF causes small, non-progressive increase in creatinine
  - More common in real life than trials but moderate/severe increases uncommon (2.2%/0.6% in one cohort)

Impact of TDF on renal function (2)

- **Proximal tubule (PT) dysfunction**
  - Main target of TDF nephrotoxicity: ‘leaky kidneys’
  - Most severe = Fanconi’s syndrome or acute renal injury
  - Urine protein key marker

- **Distal tubule dysfunction (nephrogenic DI)**

- **Phosphate leak**
  - TDF can increase urinary phosphate excretion
  - Can lead to osteomalacia
  - PT handling of phosphate very sensitive to mitochondrial toxicity
HIV drugs that increase creatinine

- Tenofovir
- Rilpivirine
- Ritonavir
- Cobicistat
- Dolutegravir
Fanconi’s syndrome

- TDF and proximal tubule dysfunction
- eGFR and proteinuria assessment routine
- 3 essential features of Fanconi’s
  - Proteinuria
  - Glycosuria
  - Hypophosphataemia
- Hypophosphataemia in a well patient with normal urine is NOT an emergency
**Baseline:**
- eGFR, urine dip + UPCR

**During clinical follow-up:**

**Not on ART**
- eGFR, urine dip + UPCR (annual)

**On ART (not TDF)**
- eGFR, urine dip + UPCR (annual)

**On ART-containing TDF**
- eGFR, urine dip + UPCR (all routine visits; 3-4x/yr)
- Serum phosphate (all routine visits; 3-4x/yr; fasting if low)
- More frequently if progressive decline in eGFR or persistent severe hypophosphatemia
• Check concomitant medication
• Care with drug doses in renal impairment
• Manage BP, glucose, lipids
• HIVAN will improve on any HAART
• Renal referral / joint clinics
When to stop TDF?

- New onset or worsening proteinuria and/or glycosuria may indicate tubular injury
- Monitor carefully
- If abnormalities persist:
  - Additional biochemistry including fasting serum/urine phosphate
  - Additional investigations
  - Discontinue TDF and/or refer to nephrology
Bone
# Prevalence of Reduced BMD Higher in HIV+ than HIV- Subjects

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of patients</th>
<th>Overall prevalence of reduced BMD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+</td>
<td>HIV–</td>
</tr>
<tr>
<td>Amiel et al 2004</td>
<td>148</td>
<td>81</td>
</tr>
<tr>
<td>Brown et al 2004</td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td>Bruera et al 2003</td>
<td>111</td>
<td>31</td>
</tr>
<tr>
<td>Dolan et al 2004</td>
<td>84</td>
<td>63</td>
</tr>
<tr>
<td>Huang et al 2002</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Knobel et al 2001</td>
<td>80</td>
<td>100</td>
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<tr>
<td>Loiseau-Peres et al 2002</td>
<td>47</td>
<td>47</td>
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<tr>
<td>Madeddu et al 2004</td>
<td>172</td>
<td>64</td>
</tr>
<tr>
<td>Tebas et al 2000</td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td>Teichman et al 2003</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Yin et al 2005</td>
<td>31</td>
<td>186</td>
</tr>
</tbody>
</table>

*Brown et al, AIDS 2006*

Derived from Brown TT & Qaqish RB. *AIDS* 2006; **20**:2165-2174
Fractures are more common in HIV+ patients

Healthcare Registry study
8,525 HIV-infected patients
2,208,792 non HIV-infected patients
Fracture rates in women demonstrated

Overall comparison p=0.002

Triant VA et al, JCEM 2008;93:3499-3504
Potential causes of low BMD

- HIV infection*
- Traditional osteoporosis risk factors (poor nutrition, low weight, physical inactivity)
- High rates smoking and alcohol/opiate use
- Low Vit D levels
- Antiretroviral therapy

*ART-naïve subjects also have high prevalence of osteopenia – effect of uncontrolled viraemia and systemic inflammation on bone remodelling
ART initiation is associated with bone loss

Greater loss in BMD with ART containing NRTI

- Changes in BMD accompanied by increases in markers of bone turnover

Within group and between-group differences all $P<0.05$

Lumbar spine Z score

- ZDV/3TC/LPV/r
- NVP/LPV/r

ART and bone loss - ABC/3TC vs TDF/FTC

**Hip**

- No. of subjects
  - TDF/FTC: 126, 109, 105, 96, 85, 53

**Lumbar Spine**

- No. of subjects
  - TDF/FTC: 128, 111, 106, 97, 87, 53
  - ABC/3TC: 130, 122, 106, 101, 80, 53

McComsey GA et al. CROI 2010
BMD monitoring: BHIVA 2011

- Assess risk factors for reduced BMD at diagnosis and prior to ART
- Reassess if on ART and ≥50 every 3 years
- BMD assessment (usually by DXA):
  - All men ≥ 70 years
  - All women ≥ 65 years
  - Consider in all >50 years if intermediate to high FRAX score
- Biochemical markers (calcium, phosphate, alkaline phosphatase) have limited use as screening tools for reduced BMD

**Conservative approach compared with EACS who recommend DXA in all postmenopausal women and men ≥ 50 years**
Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: UK
Name/ID:

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: [ ] Y: [ ] M: [ ] D: [ ]

2. Sex
   Male
   Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture
   No
   Yes

6. Parent fractured hip
   No
   Yes

7. Current smoking
   No
   Yes

8. Glucocorticoids
   No
   Yes

9. Rheumatoid arthritis
   No
   Yes

10. Secondary osteoporosis
    No
    Yes

11. Alcohol 3 or more units per day
    No
    Yes

12. Femoral neck BMD (g/cm²)
    Select DXA

Calculate

Weight Conversion

Pounds: [ ] Kgs: [ ] Convert

Height Conversion

Inches: [ ] Cms: [ ] Convert

Having trouble with the FRAX tool?

If you experience any problems with the FRAX tool please upgrade your version of Adobe Flash. Click here to upgrade.
Should we switch ART?

- Little evidence to suggest switching will improve BMD and decrease fracture risk.
- Some data suggesting discontinuing TDF associated with improvements in BMD (Bloch HIV med 2014).
- Preliminary data suggesting TDF-associated BMD reductions may translate into increased fracture risk (Bedimo AIDS 2012).
Recommend DXA, vitamin D and PTH if patients on TDF with hypophosphatemia and phosphaturia

Consider stopping TDF if:

- Progressive eGFR decline; no other cause found
- Confirmed significant hypophosphatemia of renal origin; no other cause found
- Significant osteopenia in the presence of phosphaturia/renal tubulopathy
Central nervous system (CNS)
HIV and the CNS

- Persistent CNS side effects related to ART, particularly efavirenz
- HIV associated neurocognitive disorders (HAND)
Central Nervous System (CNS) adverse events (AE) are common on EFV based regimens

Many CNS AE are transient

BUT a significant proportion of individuals experience on-going CNS AE
UK cohort studies of efavirenz

- Brighton\(^1\)
  - Bimodal discontinuation of efavirenz
    - 39% discontinued EFV (59% due to AE)
    - 12% in first 6 weeks
    - 47% 6 weeks–12 months
    - 41% >12 months

- Chelsea and Westminster\(^2\)
  - 71% switched therapy due to CNS AEs
    - 10% in first 4 weeks
    - 6% in first 3 months
    - 48% 3–12 months
    - 36% > 12 months

Zhou et al, HIV Medicine 2011; Scourfield et al, AIDS 2012
Central Nervous System (CNS) adverse events (AE) are common on EFV based regimens

Many CNS AE are transient

BUT a significant proportion of individuals experience on-going CNS AE

Differentiating drug AE from other causes of CNS problems can be difficult

Remember to ask about other drugs including alcohol and recreational drugs
Switching from efavirenz

- Concerns re enzyme induction
- Few good studies to guide clinical practice
- Early toxicity switch when still detectable VL
  - Switch to bPI recommended
- Switch when VL < 50
  - Nevirapine\(^1\):
    - packet insert recommends dose escalation. BHIVA also endorses switch to full dose\(^2, 3\)
  - bPI/raltegravir/etravirine/rilpivirine\(^4\):
    - Straightforward switch

\(^1\) Ward et al AIDS Patient Care STDS 2006; \(^2\) Winston et al AIDS 2004; \(^3\) Laureillard et al HIV Med 2008; \(^4\) Crauwels et al CROI 2011
A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine.

HIV associated neurocognitive disorders (HAND)

- **Asymptomatic NCI**
  - does not interfere with daily life

- **Symptomatic NCI** (neurocognitive impairment)
  - interferes with daily life

- **HAD (HIV associated dementia)**
  - Marked interference with daily life

*Neurology* 2007;69;1789-1799
HIV associated neurocognitive impairment (BHIVA 2013)

- Start ART (any CD4) if symptomatic HIV-associated neurocognitive disorders
- Suggest avoidance of PI monotherapy in neurologically symptomatic patients
- Ongoing or worsening NC impairment despite ART
  - re-assessment for confounding conditions
  - assessment of CSF HIV RNA with genotyping
  - modifications to ART should be based on plasma and CSF genotypic results
Algorithm for diagnosis and management of HIV-associated Neurocognitive Impairment (NCI)

1. All patients without highly confounding conditions
   - Screening for NCI: 3 questions
     - Normal
     - Abnormal
       - IADL questionnaire
         - Normal
         - Repeat 3 questions after 2 ys
       - Abnormal
         - NP Examination
           - Normal
           - Neurological examination
             - Brain MRI
             - CSF examination
               - Additional causes of NCI other than HIV excluded
                 - HAND diagnosis (HAD, MND)

2. Off ART
   - Start plasma and CSF GDR-guided ART
   - Consider inclusion of potentially CNS-active drugs
     - Repeat 3 questions after 6 months
     - If CSF VL > 50 c/mL consider repeating after 3-6 months

3. On ART
   - Plasma VL > 50 c/mL
     - Optimise ART by plasma (CSF, if VL > 50 c/mL) GDR testing
   - Plasma VL < 50 c/mL
     - Optimise ART by CSF GDR testing
     - Include potentially CNS-active drugs
     - Repeat 3 questions after 6 months
     - Repeat CSF after 3-6 months

4. CSF VL < 50 c/mL
   - Continue ongoing ART
   - Consider inclusion of potentially CNS-active drugs
   - Reconsider other causes of NCI
   - Repeat 3 questions after 6 months
EACS 2013 Guidelines – algorithm for NCI

3 screening questions (ref. Simioni et al., AIDS 2009)

1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?

2. Do you feel that you are slower when reasoning, planning activities, or solving problems?

3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

For each question, patients can answer: a) never, b) hardly ever, or c) yes, definitely. Patients are considered to have an “abnormal” result when answering “yes, definitely” on at least one question.

Highly confounding conditions
1. Severe psychiatric conditions
2. Abuse of psychotropic drugs
3. Alcohol abuse
4. Sequelae from previous CNS-OIs or other neurological diseases
5. Current CNS-OIs or other neurological diseases
What to switch to – general principles
Considerations in switching ART

‘do no harm’

Patient preference and clear discussion
Considerations in switching ART


**Table 1. Switching and simplifying antiretroviral therapy in a patient with controlled HIV replication.**

<table>
<thead>
<tr>
<th>Treatment Aspect</th>
<th>Potential Advantages of Switching or Simplification</th>
<th>Potential Disadvantages of Switching or Simplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Improved drug effectiveness</td>
<td>New drug may be greater than toxicity of existing drugs</td>
</tr>
<tr>
<td></td>
<td>(improved virological control)</td>
<td>New drug may be greater than toxicity of existing drugs</td>
</tr>
<tr>
<td>Pill burden</td>
<td>Reduce dosing regimen (improved compliance)</td>
<td>Older drugs have less long-term safety data than older drugs</td>
</tr>
<tr>
<td></td>
<td>(improved compliance)</td>
<td>New drug may be greater than toxicity of existing drugs</td>
</tr>
<tr>
<td>Toxicty</td>
<td>Prevent drug toxicity, e.g. dyslipidaemia</td>
<td>New drug may be greater than toxicity of existing drugs</td>
</tr>
<tr>
<td></td>
<td>Prevent drug toxicity, e.g. dyslipidaemia, hypercholesterolaemia, smoking cessation for cardiovascular disease</td>
<td>New drug may be greater than toxicity of existing drugs</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Prevent new interaction</td>
<td>New interaction, e.g. lipid increase in patient with cardiovascular disease</td>
</tr>
<tr>
<td>Co-morbid disease</td>
<td>Prevent co-morbid drug interaction, e.g. lipid increase in patient with cardiovascular disease</td>
<td>New toxicity to mother or foetus</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Prevent toxicity to mother or foetus</td>
<td>New toxicity to mother or foetus</td>
</tr>
<tr>
<td>Costs</td>
<td>Reduce costs for patients and improve community coverage with same level of expenditure</td>
<td>Increase costs because of greater virological failure, toxicity with new therapy</td>
</tr>
<tr>
<td></td>
<td>(improved compliance)</td>
<td>Future market prices may change</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>Improve confidentiality by not requiring pill refrigeration or dosing at work</td>
<td>Reduce future options—the number of new HIV drugs in clinical development is small and reducing</td>
</tr>
<tr>
<td>Treatment options</td>
<td>Enable use of a drug previously avoided because concerns about medication safety or efficacy no longer apply</td>
<td>Patient takes the wrong dose or pills</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>Lower pharmacy costs</td>
<td>Pharmacy prescribes the wrong agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Forgotten drug interactions or superimposed toxicities</td>
</tr>
</tbody>
</table>
SWITCHMRK 1 and 2 (P032 & 033) Study Design

- Identical, multicenter, double-blind, randomized, active-controlled studies

- **Study population**
  - Well controlled on a stable LPV/r regimen (b.i.d.) in combination with at least 2 NRTIs (and no other active PI) for ≥ 3 months
    - HIV RNA <50 copies/mL (US PCR) or <75 copies/mL (bDNA)
    - Patients were not required to be intolerant of LPV/r
    - Patients with prior virologic failure were not excluded
      - No limit on number of prior ART regimens
  - No lipid lowering therapy for at least 12 weeks

- Randomized (1:1) to continue LPV/r or switch to RAL

NRTI = nucleoside reverse transcriptase inhibitor
PI = protease inhibitor
Protocols 032, 033
Percent of Patients (95% CI) With HIV RNA <50 Copies/mL (NC = F)

In P032,
- 149 patients on RAL had HIV RNA < 50 copies/mL at Week 12; 134/149 (90%) remained suppressed (< 50 copies/mL) at Week 24.
- 152 patients on LPV/r had HIV RNA < 50 copies/mL at Week 12; 145/152 (95%) remained suppressed (< 50 copies/mL) at Week 24.

In P033,
- 157 patients on RAL had HIV RNA < 50 copies/mL at Week 12; 148/157 (94%) remained suppressed (< 50 copies/mL) at Week 24.
- 167 patients on LPV/r had HIV RNA < 50 copies/mL at Week 12; 161/167 (96%) remained suppressed (< 50 copies/mL) at Week 24.
Efficacy at 24 Weeks: Subgroup analysis – SWITCHMRK-1 and -2 combined data

If considering switch in suppressed patients with history of treatment failure or potential archived resistance, avoid regimens with a low genetic barrier.
“What to switch to will be dependent on the reason for the switch”
How to switch and with what

- **Virological failure**
  - Based upon resistance testing
  - Ideally 3 drugs that are effective, at least 1 new class

- **Toxicity**
  - Switch within class: if drug-specific
  - Switch between class: if class-specific

- **Potential drug-drug interactions**
  - Dependent upon interaction

- **Better treatment options**
  - New agents/formulations with better tolerability/toxicity/adherence profile
Switch studies
STB = Stribild® = EVG/COBI/FTC/TDF
TVD = Truvada® = FTC/TDF

**Primary Endpoint: HIV-1 RNA < 50 c/mL**

<table>
<thead>
<tr>
<th>CD4 Cell Count (cells/mm³)</th>
<th>STRATEGY-PI</th>
<th>STRATEGY-NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>603</td>
<td>625</td>
</tr>
<tr>
<td>∆Week 48 (mean)</td>
<td>+40</td>
<td>+32</td>
</tr>
<tr>
<td>P-value (∆ W48-BL)</td>
<td>&lt;0.001</td>
<td>0.025</td>
</tr>
</tbody>
</table>

**STRATEGY-PI**
- STB (n=290)
- PI/r+TVD (n=139)

**STRATEGY-NNRTI**
- STB (n=290)
- NNRTI+TVD (n=143)

In STRATEGY-PI, pre-specified sequential testing demonstrated statistical superiority (p = 0.025)

- Driven by a higher rate of discontinuation in the PI group due to non-virologic reasons

No subject in either treatment arm developed treatment-emergent resistance
Conclusions

Switching to STB from PI/r+TVD or NNRTI+TVD at Week 48:

- STB was non-inferior in maintaining virologic suppression
  - 94% STB (statistically superior) vs. 87% PI/r+TVD
  - 93% STB vs. 88% NNRTI+TVD
- No treatment-emergent resistance after switching to STB
- STB was well-tolerated with adverse events consistent with known safety profile
  - Adverse events leading to discontinuation were uncommon
  - Rates of investigator-reported AEs were similar between STB and PI/r+TVD; and higher rates of headache and nausea were reported in the STB compared to NNRTI+TVD group
  - Patient-reported symptoms of diarrhoea and bloating symptoms were lower after switching to STB from an PI/r+TVD regimen and lower rates of neuropsychiatric symptoms were reported in those who switched from an EFV-based regimen
  - Changes in SCr and CrCl were small and non-progressive; consistent with the known cobicistat inhibition of MATE-1 transporters, which mediate renal creatinine secretion

GS-264-106: SPIRIT

Study Design

Switching boosted PI to Rilpivirine In-combination with Truvada as a STR
Multicenter, international, randomized, open-label, Phase 3b, 48-week study

- Stable PI + RTV + 2 NRTI ≥ 6 months with VL <50 c/mL
- On 1st or 2nd regimen
- No prior NNRTI use
- No known resistance to study agents

(N=476)

2:1

n=317

RPV/FTC/TDF STR

n=159

PI + RTV +2 NRTIs

24 weeks
Primary Endpoint

48 weeks
Secondary Endpoint

RPV/FTC/TDF STR

RPV/FTC/TDF STR

Primary Endpoint:
Non-inferiority (12% margin) of RPV/FTC/TDF to PI+RTV+2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 24 weeks

Secondary Endpoints:
Proportion of subjects who have HIV1 RNA <50 copies/mL (missing=excluded) through Week 48, change in fasting lipid parameters and CD4 cell count at 24\(^2,3\) and 48\(^1\) weeks, safety and tolerability to PI+RTV+2NRTIs at 24\(^2,3\) and 48\(^1\) weeks

Adherence & Patient Reported Outcomes:
Visual Analog Scale Adherence, HIV Symptom Index and HIV Treatment Satisfaction Questionnaire

Ad Hoc Analysis:
Outcome at 24 weeks for patients with pre-existing resistance mutations

SPIRIT

Week 24 and 48 Virologic Suppression (Snapshot Analysis) Stratified by HIV-1 RNA at ART Initiation

FDA Snapshot at 24 Weeks¹

<table>
<thead>
<tr>
<th>HIV-1 RNA at ART Initiation (Historical)</th>
<th>RPV/FTC/TDF (immediate switch, Day 1 to W24)</th>
<th>PI+RTV+2NRTIs (delayed, Day 1 to W24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100K</td>
<td>95.0%</td>
<td>89.2%</td>
</tr>
<tr>
<td>≥ 100K</td>
<td>95.5%</td>
<td>92.3%</td>
</tr>
</tbody>
</table>

152/160* 83/93* 128/134* 48/52*

FDA Snapshot at 48 Weeks²

<table>
<thead>
<tr>
<th>HIV-1 RNA at ART Initiation (Historical)</th>
<th>RPV/FTC/TDF (immediate switch, Day 1 to W48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100K</td>
<td>90%</td>
</tr>
<tr>
<td>&gt;100K</td>
<td>94%</td>
</tr>
</tbody>
</table>

147/163 123/131

Switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs regardless of HIV-1 RNA while ARV naïve (a post-hoc analysis)

*23 (8%) RPV/FTC/TDF and 14 (9%) PI+RTV+2NRTIs subjects were excluded from this analysis due to unavailable HIV-1 RNA while ARV naïve
2. Data on file, Gilead Sciences, Inc.
**SPIRIT**

**Patient Reported Outcomes at Week 24**

---

### Gastrointestinal Symptom

- **Diarrhea**: 17.4% (RPV/FTC/TDF) vs 18.3% (PI+RTV+2NRTIs)
- **Stomach Pain or Bloating**: 45.3% (RPV/FTC/TDF) vs 32.1% (PI+RTV+2NRTIs)
- **Nausea or Vomiting**: 7.9% (RPV/FTC/TDF) vs 10.7% (PI+RTV+2NRTIs)

* $p<0.001^*$

---

### HIV Symptom Index

- Subjects that switched to RPV/FTC/TDF were significantly less likely to report the following symptoms compared to baseline:
  - Fatigue ($p=0.002$)
  - Memory loss ($p=0.022$)
  - Headache ($p=0.003$)
  - Depression ($p<0.001$)

---

### Treatment Satisfaction Questionnaire

- Reported higher satisfaction with their treatment regimen by HIV-TSQ than those who stayed on PI+RTV+2NRTIs ($p<0.001^*$)

---

* $P$-value for comparison between treatment groups at Week 24 using Chi-square

† $P$-value for comparison between treatment groups at Week 24 from ANCOVA

Novel strategies
Recommend against the use of protease inhibitor monotherapy as initial therapy for treatment-naïve patients*. (1C)

However as with other novel strategies there may be specific circumstances where a rationale for its use may be made.

*Same applies to PI based dual therapy
Recommend continuing standard combination ART as the maintenance strategy in virologically suppressed patients (1C)

No significant clinical benefit of PI monotherapy vs standard cART, which might offset the disadvantage of a lower rate of viral suppression with PI monotherapy. For this reason PI monotherapy should not be used in unselected patient populations.
PI/r monotherapy with od DRV/r or bd LPV/r might represent an option for:
- Persons with intolerance to NRTIs
- Treatment simplification

This only applies to:
- those without a history of failure on prior PI-based therapy
- VL<50 cp/ml for ≥ 6 months
- Those who do not have hepatitis B
## Forest plots for comparisons of PI monotherapy versus combination therapy.

**Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.1 Virological suppression.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PI monotherapy</th>
<th>Combination therapy</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.1.1 Lopinavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arribas 2005 (OK Pilot)</td>
<td>17</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Cahn 2011 (wk51.4)</td>
<td>39</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Gutmann 2010 (MOST)</td>
<td>23</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Hasson 2011 (KAMON 2)</td>
<td>8</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Meynard 2010 (KALESOL0)</td>
<td>73</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Nunes 2009 (KaiMo wk 96)</td>
<td>24</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Pulido 2008 (OKD4 wk48)</td>
<td>85</td>
<td>103</td>
<td>90</td>
</tr>
<tr>
<td>Waters 2008 (wk48)</td>
<td>18</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>287</td>
<td>322</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 6.99, df = 7 (P = 0.43); I² = 0%

**Test for overall effect: Z = 2.12 (P = 0.03)**

### 1.1.2 Darunavir

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PI monotherapy</th>
<th>Combination therapy</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Arribas 2010 (MONET wk48)</td>
<td>107</td>
<td>127</td>
<td>110</td>
</tr>
<tr>
<td>Katlama 2010 (MONOI)</td>
<td>82</td>
<td>112</td>
<td>91</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>189</td>
<td>201</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%

**Test for overall effect: Z = 0.94 (P = 0.35)**

Total (95% CI) 591 607 100.0% 0.95 [0.90, 0.99]

Total events 476 523

Heterogeneity: Tau² = 0.00; Chi² = 7.91, df = 9 (P = 0.54); I² = 0%

**Test for overall effect: Z = 2.28 (P = 0.02)**

**Test for subgroup differences: Not applicable**

Combination therapy was superior to monotherapy for virological suppression.
Randomisation 1:1

On triple ART
VL < 50 for >6m

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

Primary Endpoint: Loss of future drug options, defined as: new intermediate/high level resistance to ≥1 drug to which the patient’s virus was considered to be sensitive at trial entry
# PIVOT – baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OTT (n=291)</th>
<th>PIIm (n=296)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>43 (37-49)</td>
<td>45 (39-50)</td>
<td>44 (38-49)</td>
</tr>
<tr>
<td><strong>Mode of infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>175 (60%)</td>
<td>176 (60%)</td>
<td>351 (60%)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>108 (37%)</td>
<td>108 (36%)</td>
<td>216 (37%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (3%)</td>
<td>12 (2%)</td>
<td>17 (3%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>64 (22%)</td>
<td>73 (25%)</td>
<td>137 (23%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>206 (71%)</td>
<td>195 (66%)</td>
<td>401 (68%)</td>
</tr>
<tr>
<td>Black</td>
<td>73 (25%)</td>
<td>90 (30%)</td>
<td>163 (28%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (4%)</td>
<td>11 (4%)</td>
<td>23 (4%)</td>
</tr>
<tr>
<td><strong>HCV infected (Ab +ve)</strong></td>
<td>7 (2%)</td>
<td>14 (5%)</td>
<td>21 (4%)</td>
</tr>
<tr>
<td><strong>Baseline CD4</strong></td>
<td>512 (386, 658)</td>
<td>516 (402, 713)</td>
<td>513 (392, 682)</td>
</tr>
<tr>
<td><strong>CD4 nadir</strong></td>
<td>181 (90, 258)</td>
<td>170 (80, 239)</td>
<td>178 (86, 250)</td>
</tr>
<tr>
<td><strong>Years since ART start</strong></td>
<td>3.9 (2.0, 6.4)</td>
<td>4.2 (2.4, 6.9)</td>
<td>4.0 (2.2, 6.7)</td>
</tr>
<tr>
<td><strong>No. drugs ever received</strong></td>
<td>5 (3.6)</td>
<td>4 (3.6)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td><strong>PI or NNRTI at entry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>134 (46%)</td>
<td>139 (47%)</td>
<td>273 (47%)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>127 (54%)</td>
<td>155 (53%)</td>
<td>314 (53%)</td>
</tr>
</tbody>
</table>
# PIVOT - 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 (%) ¹</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 (%) ²</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 (%) ²</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>NRTI</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) ³</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 (%) ⁵</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)³</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)⁴</td>
<td>30,230 (860)</td>
<td>21,260 (700)</td>
<td>-8970 (-6,790 to -11,160)</td>
<td>-</td>
</tr>
</tbody>
</table>
PI monotherapy – discussion points

- Will results of PIVOT change prescribing guidelines?
- Who are the best candidates for PI monotherapy?
- Cost effectiveness of PI monotherapy when total management/monitoring costs factored in as well as drug costs
## NRTI-sparing regimens – the search goes on?

<table>
<thead>
<tr>
<th>Study</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 5142 (2008)</td>
<td>bPI + NNRTI</td>
</tr>
<tr>
<td>PROGRESS (2011)</td>
<td>bPI + RAL</td>
</tr>
<tr>
<td>SPARTAN (2012)</td>
<td>bPI + RAL</td>
</tr>
<tr>
<td>ACTG 5262 (2012)</td>
<td>bPI + RAL</td>
</tr>
<tr>
<td>NEAT 001/ANRS 143 (2014)</td>
<td>bPI + RAL</td>
</tr>
<tr>
<td>A4000178 (2011)</td>
<td>bPI + MVC</td>
</tr>
<tr>
<td>MODERN (2014)</td>
<td>bPI + MVC</td>
</tr>
</tbody>
</table>
When would you consider using such novel strategies?
In conclusion

- Patients are living longer – this is good news!
- Emerging co-morbidities and drug toxicities
- Aggressive management of modifiable risk factors
- It’s not always the antiretrovirals!
- Reviewing the patient in front of you is key!
- Switch ART safely and wisely
Thank you