Sperimentazioni cliniche in terapia antiretrovirale

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Summary

- Regulatory or strategic trials: informative or confounding for clinician?
- Changing landscape and evolving end point at regulatory level
- Inferior, not inferior, not non-inferior.....
- The minimum of evidence for clinic
- Which surrogate and surrogate only for the future
Regulatory and strategic trials: informative or confounding for clinician?
Choice of optimal end point. Basis for evaluation

- Virological success is frequent in naive patients
  - Difference between study arms will be weak

- Composite endpoints can consider more informations
  - Switch because of toxicity
  - Disease progression
  - CD4 count
  - Closer to clinical objective
Time to loss of virological response (TLOVR)

- Composite end point proposed by the FDA in the past years
- Includes
  - Virological failure (2 consecutive measurements above the detection limit)
  - Death = failure
  - Lost to follow up = failure
  - Switch/introduction of drugs (exceptions for OBR)
- Could be added
  - CD4
  - Disease progression
- Lost to follow up
  - Should they be included in a composite endpoint?
  - Censored
  - Failure
Relative advantages of a regimen termination end point (TLOVR)

- In studies of sequences of regimens, it more directly counts the costs of expending regimens
  - toxicity costs; non-adherence costs; drug resistance costs
- Higher event rate compared to a purely virologic endpoint
  - disseminate study results more quickly
- HIV-1 RNA alone (purely virologic endpoint) can be misleading when patients with tolerability problems on an inferior regimen are salvaged with a superior regimen
- TLOVR reflects the current belief that the longer the first regimen effectively suppresses HIV RNA with tolerable side effects the more patients will benefit.
Virologic failure / switch = failure (TLOVR)

- Standard for regulatory approval trials – to isolate effect of one drug
- Information on patients after switching often not collected.
- Only minority of failures are virologic. Endpoint is dominated by drug switching related to toxicity and convenience – not a true efficacy endpoint.
- Decision to switch is subjective - leaves a trial open to bias when treatments are not blinded. E.g. relative degree of concern a clinician has for toxic effects could influence a comparison of two NRTIs.

In a recent survey, only 27% of endpoints in trials of naive patients were due to virological failure, with the remaining 73% being due to discontinuation of study medication (32% for adverse events and 41% for loss to follow up). Given that trial outcomes can be dominated by nonvirological endpoints when analysed by the FDA TLOVR algorithm, it is important for HIV clinical trials to be re-analysed including only virological endpoints.

- The FDA guidelines state that, in addition to analyses using the TLOVR algorithm, an analysis comparing only the documented virological failures should be presented and any inconsistencies between the different analyses should be explored [9]. This is also called a ‘nonvirological failures censored’ analysis. Data from patients is censored after discontinuation for reasons other than virological failure.

Phillips AN, 2005

Virologic and Regimen Termination Surrogate End Points in AIDS Clinical Trials

Peter B. Gilbert, PhD
Victor DeGruttola, DSc
Scott M. Hammer, MD
Daniel R. Kuritzkes, MD

A CRITICAL STEP IN THE DESIGN of clinical trials to evaluate the efficacy of anti-human immunodeficiency virus (HIV) therapies or to compare treatment strategies is the selection of the appropriate primary study end point. A well-designed phase 3 trial definitively assesses the effects of treatment on the chosen primary end point, thereby defining the role of the therapies or strategies in clinical practice.

Suppression of plasma human immunodeficiency virus (HIV) RNA levels has been widely accepted as an appropriate surrogate end point for HIV disease progression, and it is currently used as the primary end point to determine efficacy in many antiretroviral trials. However, this end point does not always measure other important effects of treatment, such as induction of multidrug resistance, which depletes future therapy options, and toxic effects. An alternative that directly factors in these treatment costs is a composite regimen termination end point, defined as a protocol-determined change in regimen due to either virologic failure or treatment-related toxic effects. Pros and cons for using purely virologic vs various composite primary end points are discussed. Conclusions include (1) a trial’s clinical objective guides the choice of primary end point, (2) a purely virologic end point is often preferable, (3) it may be important to analyze both end point types in interpreting study results, and (4) long-term clinical outcome studies are needed for identifying the most predictive surrogate end points.

Definitions of Primary End Point Types

**Purely Virologic End Point.** Time from randomization to virologic failure, with virologic failure defined by a confirmed rise in plasma human immunodeficiency virus (HIV) RNA levels above a threshold such as 200 copies/mL. Virologic failure may also include early virologic failure events such as lack of initial virologic response within 4 to 12 weeks or early virologic relapse, defined by a confirmed 1 log$_{10}$ (10-fold) increase above a subject’s lowest HIV RNA measurement (nadir) or by a rise above an absolute threshold.

**Regimen Terminating End Point.** (1) Time from randomization to earliest event of virologic failure, permanent study treatment discontinuation, acquired immunodeficiency syndrome–defining event, and death. All treatment discontinuation events are counted as end points, regardless of the reason for discontinuation. (2) Time from randomization to earliest event of virologic failure and permanent study treatment discontinuation due to protocol-defined toxic effects. Only the subset of treatment discontinuation events confirmed to be due to protocol-defined toxic effects are counted as end points.
Relative advantages of a purely virologic failure end point (Time-to-VF)

- Allows separate investigation of efficacy and safety
- Defined more objectively than a regimen termination endpoint
  - less dependent on physician/patient choice
  - less subject to bias in open-label studies
- Its use as a primary endpoint assures that a secondary analysis of a regimen termination endpoint can be carried out
The two primary objectives of the study were to perform pairwise comparisons of the time to virologic failure and the time to regimen failure among the three study groups.

Virologic failure was defined as a lack of suppression of plasma HIV-1 RNA by 1 log10 or rebound before week 32 or a lack of suppression to less than 200 copies per milliliter or rebound after week 32. Confirmation of suspected virologic failure was required within 4 weeks. Data from patients whose confirmation sample was missing were included among failure end points.

Regimen failure was defined as the first of either virologic failure or toxicity-related discontinuation of any component of the initial randomized treatment regimen.
A5202: Primary Study Endpoints

- **Efficacy**: Time to confirmed virologic failure
  - HIV-1 RNA $\geq 1000$ copies/mL at or after 16 and before 24 weeks, or
  - $\geq 200$ copies/mL at or after 24 weeks

- **Safety**: Time to safety event
  - first Grade 3 or 4 sign, symptom or lab abnormality at least one grade higher than baseline (excludes unconj. hyperbili and CPK)

- **Tolerability**: Time to tolerability event
  - modification of originally randomized regimen

NEAT001/ANRS143 - Primary endpoint

Time to clinical or virologic failure, as the first occurrence of any of the following components:

- Failure to achieve virologic response by W32 (defined as HIV-1 RNA ≥ 50 cp/ml at W32, confirmed within 4 weeks)
- Change of any component of the initial randomised regimen before W32 because of documentation of insufficient virologic response, defined as HIV-1 RNA reduction < 1 log10 cp/ml by W18 or HIV-1 RNA ≥ 400 copies/ml at W24 (confirmed within 4 weeks)
- Confirmed HIV-1 RNA ≥ 50 cp/ml (two consecutive measurements) at any time after W32
- Death due to any cause
- Any new or recurrent AIDS defining event confirmed by the Endpoint Review Committee
- Any new serious non AIDS defining event confirmed by the Endpoint Review Committee
Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy

In patients with screening HIV-1 RNA levels of 100,000 copies per milliliter or more, the times to virologic failure and the first adverse event were both significantly shorter in patients randomly assigned to abacavir–lamivudine than in those assigned to tenofovir DF–emtricitabine.

Similar Efficacy of INSTIs (RAL or DTG) + ABC/3TC or TDF/FTC, Even For High BL VL

- In SPRING-2, similar efficacy with ABC/3TC or TDF/FTC + RAL or DTG, including with high BL HIV-1 RNA
- In pooled analysis (SPRING-2 and SINGLE), high response rates with ABC/3TC or TDF/FTC at low and high BL HIV-1 RNA levels

**Graph:**
- Proportion Free of Protocol-Defined Virologic Failure
- Data from both studies and both INSTIs pooled

**Table:**

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA (c/mL)</th>
<th>Group (events/N)</th>
<th>ABC/3TC, ≤ 100K</th>
<th>ABC/3TC, &gt; 100K</th>
<th>TDF/FTC, ≤ 100K</th>
<th>TDF/FTC, &gt; 100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100k</td>
<td></td>
<td>88/225</td>
<td>91/257</td>
<td>86/306</td>
<td>82/335</td>
</tr>
<tr>
<td>100K-&lt;250K</td>
<td></td>
<td>36/42</td>
<td>72/88</td>
<td>13/16</td>
<td>29/38</td>
</tr>
<tr>
<td>250K-500K</td>
<td></td>
<td>81/13</td>
<td>76/29</td>
<td>13/18</td>
<td>18/28</td>
</tr>
<tr>
<td>&gt; 500K</td>
<td></td>
<td>72/18</td>
<td>64/18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Changing landscape and evolving end point at regulatory level
Snapshot Analysis
Differences between TLOVR & SNAPSHOOT (simplified explanation)

SNAPSHOT analysis considers only what is happening during the defined time window

- **FAILURE** = single blip
- **SUCCESS** = virologic re-suppression
### Snapshot Analysis

#### SNAPSHO Typ Approach: Definitions

<table>
<thead>
<tr>
<th>Category*</th>
<th>In Window</th>
<th>Prior to Window</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virologic Success</strong></td>
<td>HIV RNA &lt; 50 copies/mL</td>
<td>NA</td>
</tr>
</tbody>
</table>
| **Virologic Failures** | HIV RNA ≥ 50 copies/mL | 1. Discontinued due to lack/loss of efficacy  
2. OBT changes: to new class OR those not permitted in protocol OR due to lack of efficacy |
| **No Virologic Data in Window** | Missing HIV RNA data but on study | 1. Discontinued due to AE or death**  
2. Discontinued for other reasons (e.g. withdrew consent, lost to follow-up) with last HIV RNA < 50 copies/mL*** |

* Note that the categorization follows “virology first” hierarchy in that success and failure are assessed first then “no virologic data” is assessed. These 3 categories total to 100%.

** If HIV RNA data is available then it is used to categorize virologic outcome as success or failure. This limits the utility of the SNAPSHO Typ approach as a comprehensive safety analysis.

*** If last HIV RNA ≥ 50 copies/mL then categorize as failure, despite no virologic data in window.

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FDA letter on file. 3/30/10
STaR
Virologic Suppression at Week 48 FDA Snapshot Analysis by Baseline HIV-1 RNA Stratified by 100,000 c/mL

RPV/FTC/TDF compared to EFV/FTC/TDF
Superior for subjects with baseline HIV-1 RNA <100,000 c/mL
Non-inferior for subjects with baseline HIV-1 RNA >100,000 c/mL

STaR & ECHO/THRIVE
Virologic Failure at Week 48 per FDA Snapshot Overall and by Baseline HIV-1 RNA

ECHO/THRIVE: Two Phase III double-blinded, double dummy, multicenter 96 week studies in treatment-naïve HIV-1 infected subjects randomized to receive either RPV (25mg) or EFV (600mg) in combination with 2 NRTIs (ECHO, FTC/TDF; THRIVE, Investigator’s choice [FTC/TDF, n=406; 3TC/AZT, n=204; 3TC/ABC, n=68]). In the pooled TVD subset analysis (N=1096), RPV+TVD was non-inferior to EFV+TVD (HIV-1 RNA <50 c/mL [83%, 81%]).
Until recently, the paradigm guiding the pivotal studies of above mentioned agents in treatment experienced patients has been superiority trials comparing an optimized background treatment regimen (OBT) + placebo vs. OBT + the investigational agent.

The pivotal studies included patients infected with HIV with a range of calculated phenotypic or genotypic sensitivity scores (PSS/GSS). The current guideline effectively states that studies that evaluate agents in the treatment experienced population should compare test agent and placebo in patients with viruses having an OBT PSS/GSS score of 2.

This approach avoids the possibility that those with scores of 0 or 1 might be exposed to functional monotherapy and also addresses the fact that superior virological efficacy with the investigational agent might not be demonstrable in case of a PSS/GSS >2.
• Since it is now difficult to recruit treatment-experienced patients who are failing on their regimen, and also as it may now not be possible to demonstrate superiority of viral efficacy for a new agent + OBT vs. OBT alone in an unselected treatment experienced population, a re-consideration of the regulatory pathway is needed.
A new HIV trial design pathway for treatment-experienced HIV patients?

Table 1. Rate of patient recruitment for recent HIV trials.

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Number of participants</th>
<th>Number of countries</th>
<th>Number of sites</th>
<th>Recruitment period</th>
<th>Recruitment rate/patient/site/months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENCHMRK-1 (three-class resistant) [8]</td>
<td>350</td>
<td>12</td>
<td>61</td>
<td>~5 months (2006)</td>
<td>1.15</td>
</tr>
<tr>
<td>VICTOR E-3, E-4 (two-class resistant or ≥6 month treatment experienced) [9]</td>
<td>857</td>
<td>North America, Europe, Latin America, South Africa</td>
<td>160+</td>
<td>~12 months (2007/2008)</td>
<td>0.45</td>
</tr>
<tr>
<td>Elvitegravir (any resistance or ≥6 month experience of two classes) [35]</td>
<td>700</td>
<td>14</td>
<td>183</td>
<td>~14 months (2008/2009)</td>
<td>0.27</td>
</tr>
<tr>
<td>Lersivirine phase 2 (NNRTI resistance; preprotocol amendment) [36]</td>
<td>189</td>
<td>11</td>
<td>55</td>
<td>~8 months pre-amendment (2009/2010)</td>
<td>0.02</td>
</tr>
<tr>
<td>ING111762 (two-class resistance) (currently recruiting)</td>
<td>688</td>
<td>20</td>
<td>226+</td>
<td>Ongoing</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Diagram:

- Randomize to current “failing regimen”
- Add: Placebo
- New drug + new background
- Multiple doses
- 10 days – 2 weeks
- Primary efficacy assessment
- Safety assessment
- Dose comparison
- Resistance assessments

Inferior, not inferior, not non-inferior.....
Design of HIV non-inferiority trials: where are we going?

Historical improvement of antiretroviral efficacy has changed the HIV drug development design from superiority to non-inferiority establishing now an 80–90% viral suppression rates in recent studies. Applying FDA’s approach would naturally lead to reduce the non-inferiority margin as it was pointed out that ‘there is a powerful tendency to be conservative in the choice of margin’.

In the HIV area, however, the tendency is opposite keeping a 12% margin and adopting a 95%-power design. Non-inferiority HIV trials are often overpowered assuming lower success rates than those observed, enrolling a large number of patients and choosing a large margin.

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Summary of hypotheses of five HIV non-inferiority trials published in 2011

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Patients</th>
<th>Endpoint</th>
<th>Success rates</th>
<th>N</th>
<th>Margin</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECHO</td>
<td>RLV + TDF/FTC</td>
<td>EFV + TDF/FTC</td>
<td>Treatment-naive</td>
<td>&lt;50 copies/ml W48 (TLOVR)</td>
<td>p_c = p_e = 75%</td>
<td>346 vs. 344</td>
<td>12%</td>
<td>95%</td>
</tr>
<tr>
<td>THRIVE</td>
<td>RLV + 2 NRTIs</td>
<td>EFV + 2 NRTIs</td>
<td>Treatment-naive</td>
<td>&lt;50 copies/ml W48 (TLOVR)</td>
<td>p_c = p_e = 75%</td>
<td>340 vs. 338</td>
<td>12%</td>
<td>95%</td>
</tr>
<tr>
<td>QDMRK study</td>
<td>RAL once daily + TDF/FTC</td>
<td>RAL twice daily + TDF/FTC</td>
<td>Treatment-naive</td>
<td>virologic success W48</td>
<td>p_c = p_e = 80%</td>
<td>382 vs. 388</td>
<td>10%</td>
<td>90%</td>
</tr>
<tr>
<td>Study 145</td>
<td>ELV + OBR</td>
<td>RAL + OBR</td>
<td>Treatment-experienced</td>
<td>&lt;50 copies/ml W48 (TLOVR)</td>
<td>p_c = p_e = 75%</td>
<td>351 vs. 351</td>
<td>10%</td>
<td>85%</td>
</tr>
<tr>
<td>SENSE</td>
<td>ETR + 2 NRTIs</td>
<td>EFV + 2 NRTIs</td>
<td>Treatment-naive</td>
<td>&lt;50 copies/ml W48 (TLOVR)</td>
<td>p_c = p_e = 75%</td>
<td>79 vs. 78</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>

EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; NRTIs, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; p_c, proportion of success in the control arm; p_e, proportion of success in the experimental arm; RAL, raltegravir; RLV, rilpivirine; TDF, tenofovir; TLOVR, time to loss of virological response.
Statistical methods used to estimate confidence intervals in noninferiority trials have a strong impact on the conclusion of the trials.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Analysis</th>
<th>Margin</th>
<th>Results</th>
<th>$\delta$</th>
<th>Wald</th>
<th>Exact CZ</th>
<th>Newcombe</th>
<th>FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIRAL</td>
<td>ITT</td>
<td>−12.5%</td>
<td>89.2% vs. 86.6%</td>
<td>2.6%</td>
<td>−5.1% to 10.4%</td>
<td>−5.5% to 10.9%</td>
<td>−5.2% to 10.6%</td>
<td>−5.6% to 10.9%</td>
</tr>
<tr>
<td>SPIRAL</td>
<td>OT</td>
<td>−12.5%</td>
<td>96.9% vs. 95.1%</td>
<td>1.8%</td>
<td>−3.9% to 7.5%</td>
<td>−3.7% to 7.6%</td>
<td>−3.5% to 7.5%</td>
<td>−5.0% to 8.6%</td>
</tr>
<tr>
<td>Switchmrk 1</td>
<td>ITT</td>
<td>−12%</td>
<td>80.8% vs. 87.4%</td>
<td>−6.54%</td>
<td>−14.2% to 1.14%</td>
<td>−14.4% to 1.3%</td>
<td>−14.3% to 1.2%</td>
<td>−14.3% to 1.2%</td>
</tr>
<tr>
<td>Switchmrk 2</td>
<td>ITT</td>
<td>−12%</td>
<td>88.0% vs. 93.8%</td>
<td>−5.82%</td>
<td>−11.8% to 0.15%</td>
<td>−12.2% to 0.3%</td>
<td>−12.1% to 0.3%</td>
<td>−12.2% to 0.5%</td>
</tr>
<tr>
<td>ODIN</td>
<td>ITT</td>
<td>−12%</td>
<td>72.1% vs. 70.9%</td>
<td>1.2%</td>
<td>−6.1% to 8.5%</td>
<td>−6.2% to 8.6%</td>
<td>−6.1% to 8.4%</td>
<td>−6.1% to 8.5%</td>
</tr>
<tr>
<td>M06-802</td>
<td>ITT</td>
<td>−12%</td>
<td>55.3% vs. 51.8%</td>
<td>3.5%</td>
<td>−4.5% to 11.5%</td>
<td>−4.6% to 11.6%</td>
<td>−4.5% to 11.4%</td>
<td>−4.4% to 11.4%</td>
</tr>
<tr>
<td>M06-802</td>
<td>Observed</td>
<td>−12%</td>
<td>76.0% vs. 72.2%</td>
<td>3.8%</td>
<td>−4.3% to 11.9%</td>
<td>−4.4% to 12.1%</td>
<td>−4.3% to 11.9%</td>
<td>−4.3% to 12.0%</td>
</tr>
</tbody>
</table>

Original results are bolded and values in italic indicate inconclusive results (noninferiority not demonstrated).

Confidence intervals can be quite different according to the method used. In many situations, however, conclusions of the trials are not altered because point estimates of the treatment difference were too far from the prespecified noninferiority margins. Nevertheless, in few trials the use of different statistical methods led to different conclusions.

Interpreting the possible outcomes from noninferiority trials.

The outcomes described above may arise when a trial has been designed to show noninferiority. A further possible outcome of a trial, where noninferiority is demonstrated in a study originally designed to show superiority, is not recommended by European guidelines.

Hill A & Sabin C. AIDS, 2008
The Ethics of Switch/Simplify in Antiretroviral Trials: Non-Inferior or Just Inferior?

Andrew Carr¹,²*, Jennifer Hoy³,⁴, Anton Pozniak⁵

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Summary Points

- The high efficacy of antiretroviral therapy has resulted in more trials that switch or simplify existing therapy in patients whose HIV is fully controlled.
- The primary outcome of about half of these trials is virological non-inferiority. As participants already have fully controlled HIV on existing therapy, these trials offer no virological benefit.
- Many trials (i) enrol patients who cannot benefit with the switch, (ii) do not capture (or report) all potential risks, and (iii) are designed with a view to a pharmaceutical company’s profits rather than participant benefit.
- A switch/simplification trial is only ethical if participants can meaningfully benefit from the treatment change and are more likely to benefit than suffer harm, and if the study is powered to assess the key expected benefit and reports all end points.
Simplification of ARV therapy to a single tablet regimen consisting of EFV/FTC/TDF

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>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Improved drug levels may improve efficacy</td>
</tr>
<tr>
<td>Pill burden</td>
<td>Reduce doses per day, tablets per day or meal restrictions (improve quality of life)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Prevent or reverse toxicity</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Prevent or reduce drug interactions</td>
</tr>
<tr>
<td>Co-morbid disease</td>
<td>Prevent or reduce co-morbidities</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Prevent toxicity to mother or foetus</td>
</tr>
<tr>
<td>Costs</td>
<td>Reduce costs for patient or improve community coverage with same health-care expenditure</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>Improve confidentiality by not requiring pill refrigeration or dosing at work</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>
</tr>
<tr>
<td>Pharmacy</td>
<td>Lower pharmacy costs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential Disadvantages of Switching or Simplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of virological control</td>
</tr>
<tr>
<td>Increase pill doses or number</td>
</tr>
<tr>
<td>Toxicity of new drug may be greater than toxicity of existing drug (new drugs have less long-term safety data than older drugs)</td>
</tr>
<tr>
<td>Toxicity may not reverse</td>
</tr>
<tr>
<td>Switching may be less effective than other approaches, e.g., statins for hypercholesterolaemia, smoking cessation for cardiovascular risk</td>
</tr>
<tr>
<td>Unforeseen new interaction</td>
</tr>
<tr>
<td>Adverse interaction, e.g., lipid increase in patient with cardiovascular disease</td>
</tr>
<tr>
<td>New toxicity to mother or foetus</td>
</tr>
<tr>
<td>Increase costs because of greater virological failure, toxicity with new therapy</td>
</tr>
<tr>
<td>Future market prices may change</td>
</tr>
<tr>
<td>Reduce future options—the number of new HIV drugs in clinical development is small and reducing</td>
</tr>
<tr>
<td>Patient takes the wrong dose or pills</td>
</tr>
<tr>
<td>Pharmacy prescribes the wrong agent</td>
</tr>
<tr>
<td>Forgotten drug interactions or superimposed toxicities</td>
</tr>
</tbody>
</table>
The minimum of evidence for clinic
Evidence for use DRV/r+ABV/3TC in the first line

The efficacy and safety of once-daily darunavir/ritonavir and fixed-dose abacavir/lamivudine was examined in 22 treatment-naive patients with HIV-1 infection. Three patients discontinued antiretroviral therapy due to mild adverse events. Among 18 patients who continued therapy, 66.7% had viral load less than 50 copies/ml at week 48. Only two patients experienced virologic failure with the emergence of resistant virus.  

*Nishijima T, et al. AIDS, 2012*

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**Table 1. Recommended and Alternative Initial Antiretroviral Regimens, Including Strength of Recommendations and Quality of Evidence**

<table>
<thead>
<tr>
<th>Recommended Regimens</th>
<th>Alternative Regimens</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI plus NRTIs</td>
<td>Efavirenz/tenofovir/emtricitabine (Ala)</td>
<td>Nevirapine plus tenofovir/emtricitabine or abacavir/lamivudine (Bla)</td>
</tr>
<tr>
<td></td>
<td>Efavirenz plus abacavir/lamivudine (Ala) in HLA-B*5701-negative patients with baseline plasma HIV-1 RNA &lt;100,000 copies/mL.</td>
<td>Filtruvirine/tenofovir/emtricitabine (Ala) (or rilpivirine plus abacavir/lamivudine) (Bla)</td>
</tr>
</tbody>
</table>

| PI/r plus NRTIs       | Darunavir/r plus tenofovir/emtricitabine (Ala) | Darunavir/r plus abacavir/lamivudine (Bla) | Other alternative PIs include fosamprenavir/r and saquinavir/r but indications to use these options for initial treatment are rare. |
|                       | Atazanavir/r plus tenofovir/emtricitabine (Ala) | Lopinavir/r plus tenofovir/emtricitabine (Bla) (or abacavir/lamivudine) (Bla) |
|                       | Atazanavir/r plus abacavir/lamivudine (Ala) in patients with plasma HIV-1 RNA <100,000 copies/mL. |

| InSTI plus NRTIs      | Raltegravir plus tenofovir/emtricitabine (Ala) | Raltegravir plus abacavir/lamivudine (Bla) | Raltegravir is given twice daily; experience with elvitegravir/cobicistat/tenofovir/emtricitabine is limited to 48-week data. |
|                       | Elvitegravir/cobicistat/tenofovir/emtricitabine (Bla) |

*Thompson MA, et al. JAMA 2012;308:387-402*
Switching the third drug of antiretroviral therapy to maraviroc in aviraemic subjects: a pilot, prospective, randomized clinical trial.


HIV Unit & Fundació Lluita contra la SIDA, Hospital Universitari Germans Trias i Pujol, Barcelona, Catalonia, Spain.

Abstract

OBJECTIVES: To evaluate the safety and efficacy of switching the third drug of antiretroviral treatment to maraviroc in aviraemic subjects infected with R5 HIV.

PATIENTS AND METHODS: This is a pilot, prospective, randomized clinical trial (ClinicalTrials ID: NCT00966329). Eighty HIV-1-infected aviraemic adults on stable antiretroviral treatment for ≥1 year and no antiretroviral drug resistance were screened for the presence of non-R5 HIV by triplicate proviral V3 population sequencing. From them, 30 subjects with R5 HIV-1 were randomized 1:1 to switch the non-nucleoside reverse transcriptase inhibitor or ritonavir-boosted protease inhibitor to maraviroc (n=15) or to continue the same antiretroviral treatment (controls, n=15). The principal endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48. Ultrasensitive proviral HIV-1 tropism testing (454 sequencing) was performed retrospectively at weeks 0, 4, 12, 24, 36 and 48.

RESULTS: One subject in the maraviroc arm and one control had non-R5 HIV in proviral DNA by retrospective 454 sequencing. The subject receiving maraviroc was the only individual to develop virological failure. However, plasma HIV at failure was R5. Switching to maraviroc was well tolerated and associated with small, but statistically significant, declines in total, high-density lipoprotein and low-density lipoprotein cholesterol. Median (IQR) triglyceride [1 (0.67-1.22) versus 1.6 (1.4-3.1) mmol/L, P=0.003] and total cholesterol [4.3 (4.1-4.72) versus 5.4 (4-5.7) mmol/L, P=0.059] values were lower in the maraviroc arm than in controls at week 48.

CONCLUSIONS: In this pilot, prospective, randomized clinical trial, switching the third drug to maraviroc was safe, efficacious and improved lipid parameters.

PMID: 23354282 [PubMed - as supplied by publisher]
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:
1. Proportion of subjects on RPV/FTC/TDF who have HIV1 RNA <50 copies/mL at Week 48
2. Change in fasting lipid parameters and CD4 cell count at 24 and 48 weeks
3. Safety and tolerability to PI+RTV+2NRTIs at 24 and 48 weeks
4. Proportion of subjects who have HIV1 RNA <50 copies/mL (missing = excluded) through Week 48

**SPIRIT Study Design**

Switching boosted PI to Rilpivirine In-combination with Truvada as an 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

2. Tebas P, et al. LIPO 2012; Washington, DC. #018*
Switching to RPV/FTC/TDF was non-inferior* to remaining on PI+RTV+2NRTIs for 24 weeks (difference 3.8, 95% CI [-1.6, 9.1]). Similar rates of virologic suppression were also seen with 48 weeks of treatment with RPV/FTC/TDF.

A 48-week course of ART in patients with primary HIV infection delayed disease progression, although not significantly longer than the duration of the treatment. ART given during primary HIV infection could confer a durable beneficial effect by limiting HIV mediated immunologic damage, which was the main hypothesis underpinning our trial. Whether the lower HIV RNA levels after cessation of 48-week ART or the improved CD4+ recovery after initiation of long-term ART can be maintained and will translate into a clinical benefit in the years ahead requires longer follow-up, which is planned.
**START. Sensitivity of the sample size to assumptions**

The sample size has been estimated as 4000 participants to be followed for an average of 4.5 years. The primary analysis will be according to the intention to treat principle, using a stratified two-sided log-rank test with strata defined by geographical region (North America, South America, Europe, Australasia, and Africa) and type 1 error 0.05.

<table>
<thead>
<tr>
<th>Ratio: nonfatal SNA to fatal SNA</th>
<th>% AIDS* events accepted by the ERC</th>
<th>Composite primary event rate per 100 person-years (deferred arm)</th>
<th>Hazard ratio (average over follow-up)</th>
<th>Sample size</th>
<th>Expected number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>65</td>
<td>2.40</td>
<td>0.706</td>
<td>4,244</td>
<td>351</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>2.81</td>
<td>0.712</td>
<td>3,822</td>
<td>369</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>3.23</td>
<td>0.717</td>
<td>3,472</td>
<td>383</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>2.49</td>
<td>0.700</td>
<td>3,900</td>
<td>333</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>2.91</td>
<td>0.707</td>
<td>3,545</td>
<td>353</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>3.33</td>
<td>0.712</td>
<td>3,245</td>
<td>367</td>
</tr>
</tbody>
</table>

AIDS: acquired immunodeficiency syndrome; SNA: serious non-AIDS.

In the deferred ART group, the average rate of the primary endpoint is 2.8 per 100 person-years over the follow-up period. Based on the computer simulations, early ART is predicted to reduce the primary endpoint average rate by 28.8% compared to deferred ART. This reduction in the hazard assumes (1) AIDS events represent 23% of the primary events in the deferred arm, and early ART will, on average, reduce this hazard by 43%; and (2) SNA events will represent 77% of events in the deferred ART group, and early ART will, on average, reduce this hazard by 24%.

Which surrogate and surrogate only for the future
Total and integrated HIV DNA monitor reservoirs and ongoing replication in eradication trials

Appearance of unintegrated HIV DNA reflects residual HIV expression and de-novo reverse transcription. Concurrent measurements of total and integrated HIV DNA provide information regarding reservoir size and ongoing replication in trials targeting HIV.
**ASSERT.** Randomized Comparison of Renal Effects, Efficacy, and Safety

A5202. Mean fold change in sICAM-1, sVCAM-1, TNF-a, sTNFR-I, and sTNFR-II by ITT analysis

Reported serious non-AIDS events in ESPRIT and classification by Endpoint Review Committee in meeting diagnostic categories

<table>
<thead>
<tr>
<th>Serious non-AIDS event</th>
<th>Confirmed</th>
<th>Probable</th>
<th>Does not meet criteria</th>
<th>Adjudicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI (n = 83)</td>
<td>55 (66%)</td>
<td>3 (4%)</td>
<td>25 (30%)</td>
<td>33 (40%)</td>
</tr>
<tr>
<td>Cirrhosis (n = 56)</td>
<td>17 (30%)</td>
<td>22 (39%)</td>
<td>17 (30%)</td>
<td>33 (59%)</td>
</tr>
<tr>
<td>CAD requiring therapeutic procedure (n = 92)</td>
<td>85 (92%)</td>
<td>—</td>
<td>7 (8%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>ESRD (n = 1)</td>
<td>1 (100%)</td>
<td>—</td>
<td>0 (0%)</td>
<td>—</td>
</tr>
<tr>
<td>Non-AIDS malignancy (n = 270)</td>
<td>211 (78%)</td>
<td>46 (17%)</td>
<td>13 (5%)</td>
<td>57 (21%)</td>
</tr>
<tr>
<td>Pulmonary embolism (n = 23)</td>
<td>17 (74%)</td>
<td>3 (13%)</td>
<td>3 (13%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Stroke (n = 38)</td>
<td>21 (55%)</td>
<td>2 (5%)</td>
<td>15 (39%)</td>
<td>14 (37%)</td>
</tr>
<tr>
<td><strong>Total (n = 563)</strong></td>
<td><strong>407 (72%)</strong></td>
<td><strong>76 (13%)</strong></td>
<td><strong>80 (14%)</strong></td>
<td><strong>155 (28%)</strong></td>
</tr>
</tbody>
</table>

*Note: AMI = Acute myocardial infarction; CAD = coronary artery disease; ESRD = end-stage renal disease

*Not applicable.
Finally...
The design of clinical trials for new antiretroviral agents poses unique challenges, given the availability of highly active antiretroviral therapy (HAART). Throughout, science and ethics are tightly woven elements in study designs for ARV drug trials. Fast-track drug approval status and successful lobbying by advocates for patients with acquired immunodeficiency syndrome aimed at the US Food and Drug Administration, the National Institutes of Health, the Centers for Disease Control and Prevention, university teaching centers, pharmaceutical companies, and members of Congress undoubtedly contributed to the development and swift regulatory approvals of the 17 antiretroviral medications now available in the United States for the treatment of human immunodeficiency virus infection.