Selected Issues in HIV Clinical Trials

Judith S. Currier, M.D., MSc
Professor of Medicine
Division of Infectious Diseases
University of California, Los Angeles
Issues

• Evolving Global and Domestic Epidemic
• Evaluating new therapies
  – Non-inferiority trials
  – Composite Endpoints
  – Sex differences and clinical trials
### Global summary of the AIDS epidemic | 2012

#### Number of people living with HIV

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35.3 million</td>
<td>[32.2 million – 38.8 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>32.1 million</td>
<td>[29.1 million – 35.3 million]</td>
</tr>
<tr>
<td>Women</td>
<td>17.7 million</td>
<td>[16.4 million – 19.3 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>3.3 million</td>
<td>[3.0 million – 3.7 million]</td>
</tr>
</tbody>
</table>

#### People newly infected with HIV in 2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.3 million</td>
<td>[1.9 million – 2.7 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>2.0 million</td>
<td>[1.7 million – 2.4 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>260 000</td>
<td>[230 000 – 320 000]</td>
</tr>
</tbody>
</table>

#### AIDS deaths in 2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.6 million</td>
<td>[1.4 million – 1.9 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>1.4 million</td>
<td>[1.2 million – 1.7 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>210 000</td>
<td>[190 000 – 250 000]</td>
</tr>
</tbody>
</table>
Adults and children estimated to be living with HIV | 2012

North America 1.3 million
[980 000 – 1.9 million]

Caribbean 250 000
[220 000 – 280 000]

Latin America 1.5 million
[1.2 million – 1.9 million]

Western & Central Europe 860 000
[800 000 – 930 000]

Eastern Europe & Central Asia 1.3 million
[1.0 million – 1.7 million]

Middle East & North Africa 260 000
[200 000 – 380 000]

East Asia 880 000
[650 000 – 1.2 million]

Sub-Saharan Africa 25.0 million
[23.5 million – 26.6 million]

South & South-East Asia 3.9 million
[2.9 million – 5.2 million]

Oceania 51 000
[43 000 – 59 000]

Total: 35.3 million [32.2 million – 38.8 million]
Estimated number of adults and children newly infected with HIV | 2012

Total: 2.3 million [1.9 million – 2.7 million]
About 6,300 new HIV infections a day in 2012

- About 95% are in low- and middle-income countries
- About 700 are in children under 15 years of age
- About 5,500 are in adults aged 15 years and older, of whom:
  - almost 47% are among women
  - about 39% are among young people (15-24)
Targets for HIV Therapy

- **Virus adsorption**
- **Integrate inhibitors**
- **3' processing**
- **Reverse transcriptase inhibitors**
- **Reverse transcriptase**
- **DNA**
- **Integration (strand transfer)**
- **Uncoating**
- **Integrate inhibitors**
- **Viral proteins and RNA assemble at the cell membrane**
- **Translation**
- **Polypeptide**
- **Budding**

## Antiretroviral Drugs 2014

<table>
<thead>
<tr>
<th>Nucleoside Analogues</th>
<th>Nucleotide Analogue</th>
<th>Non-Nucleoside Analogues</th>
<th>Protease Inhibitors</th>
<th>Reverse Transcriptase Inhibitors</th>
<th>Integrase Inhibitors</th>
<th>Fusion Inhibitor</th>
<th>Entry Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine (AZT, ZDV)</td>
<td>tenofovir (TFV)</td>
<td>nevirapine (NVP)</td>
<td>saquinavir (SQV)</td>
<td>raltegravir (RAL)</td>
<td>raltegravir (RAL)</td>
<td>fuzeon (T20)</td>
<td>maravirocut (MV)</td>
</tr>
<tr>
<td>didanosine (ddI)</td>
<td></td>
<td>delavirdine (DLV)</td>
<td>ritonavir (RTV)</td>
<td>Elvitegravir</td>
<td>Elvitegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>zalcitabine (ddC)</td>
<td></td>
<td>efavirenz (EFV)</td>
<td>indinavir (IDV)</td>
<td>dolutegravir</td>
<td>dolutegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td></td>
<td>etravirine (ETV)</td>
<td>nelfinavir (NFV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lamivudine (3TC)</td>
<td></td>
<td>rilpivirine (RPV)</td>
<td>amprenavir (APV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td></td>
<td>truvada (FTC)</td>
<td>lopinavir/r (LPV/r)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td></td>
<td>tipranavir (TPV)</td>
<td>fosamprenavir (FPV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reverse Transcriptase Inhibitors (12)**

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- amprenavir (APV)
- lopinavir/r (LPV/r)
- fosamprenavir (FPV)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)

**Protease Inhibitors (9)**

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- amprenavir (APV)
- lopinavir/r (LPV/r)
- fosamprenavir (FPV)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)

**Nucleoside Analogues**

- zidovudine (AZT, ZDV)
- didanosine (ddI)
- zalcitabine (ddC)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)

**Nucleotide Analogue**

- tenofovir (TFV)

**Non-Nucleoside Analogues**

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETV)
- rilpivirine (RPV)
New Formulations/Doses
Simplified Regimens

Circa 1996

One Pill/Day

2006
efavirenz
emtricitabine
tenofovir

2014
single tablet regimens
Elvitegravir/COBI/FTC/TDF
Also…
RPV/TDF/FTC
and
DTG/ABC/3TC coming soon
What is the role of newer agents in initial therapy?

CASTLE
Atazanavir/r vs Lopinavir /r

ARTEMIS
Darunavir/r vs LPV/r

Raltegravir vs Efavirenz
STARTMRK
Non-inferiority Design

Population of Patients

Randomize to Treatment

Investigational Treatment

Active Control

Response

SAMPLE

YES

NO

YES

NO
Objective

To show experimental therapy is “no worse” (in a practical sense) than active control

- Rule out important or relevant (clinical and statistical) differences with reasonable confidence
- Underlying implication is that the experimental therapy is thus superior to placebo

Cannot be demonstrated with non-significant p-values

- High p-value ≠ similarity
- Scientific method
- Absence of evidence is not evidence of absence
Rationale for Non-Inferiority in HIV Trials

Experimental therapy often better in other ways
– Better toxicity profile
– Less expensive
- Favorable adherence profile

Important for resource limited settings
– Less invasive or complicated (better adherence)
– Shorter treatment duration
Design Assumptions

Constancy
- Efficacy of active control has not changed since showing superiority to placebo
  - Changes could occur with the development of resistance or adjuvant therapies

Assay sensitivity
- Able to detect differences if they exist
  - E.g., poor adherence in both arms results in similarity

Composite endpoint (More on this later)
- Concern for dilution of effect
Selection of the NI Interval

Combination of statistical reasoning and clinical judgment
– Must be smaller than the effect size of active control over placebo
– Conceptually
  “Maximum treatment difference that is clinically irrelevant”
  “Largest treatment difference that is acceptable in order to gain other advantages of the experimental intervention”

• Context dependent
• Pre-specification important
• Ideally chosen independent of considerations of study power
  – But sample size is very sensitive to its selection, affecting feasibility
• Directly impacts study conclusions
Alternative: Estimation-based Design

Particularly useful when the acceptable NI margin is not universal

Estimate difference between arms with acceptable precision (as measured by the width of a CI)
Figure. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials.
Research article

Methodological standards in non-inferiority AIDS trials: moving from adherence to compliance

Jean-Jacques Parienti*1,2, Renaud Verdon3 and Véronique Massari1

Address: 1Inserm UMR-S 707, Paris, F-75012; Université Pierre et Marie Curie-Paris6, UMR-S 707, Paris, F-75012, France, 2Department of Biostatistics and Clinical Research, Côte de Nacre University hospital, 14033 Caen, France and 3Department of Infectious Diseases, Côte de Nacre University hospital, 14033 Caen, France

Email: Jean-Jacques Parienti* - parienti-jj@chu-caen.fr; Renaud Verdon - verdon-r@chu-caen.fr; Véronique Massari - massari@u707.jussieu.fr

* Corresponding author
Non-inferiority Trials and HIV

- Reviewed 18 recent clinical trials of HIV therapy and evaluated the adherence to standards for reporting
- Pre-specified NI margins ranged from 10-15%
- 38% reported ITT results only
- Half of the studies had non-conclusive results for non-inferiority
Conclusions about non-inferiority should be drawn on the basis of the confidence interval analysis of an appropriate primary endpoint, using the predefined criteria for noninferiority, in both on treatment (OT) and intent to treat (ITT) analyses.
1 Report/justify NI margin
2 Sample size justified
3 Both ITT and AT
4 Report CI of difference
5.1 base conclusions of both ITT or AT
5.2 Restate NI margin in abstract
5.3 Interpret based on primary endpoint
5.4 conclusion matches aim of study- non-inferior or equivalent

Parienti *BMC Medical Research Methodology* 2006, 6:46
Reporting of Noninferiority and Equivalence Randomized Trials
An Extension of the CONSORT Statement
Maraviroc versus Efavirenz, Both in Combination with Zidovudine-Lamivudine, for the Treatment of Antiretroviral-Naive Subjects with CCR5-Tropic HIV-1 Infection

New drug MVC compared to standard
Noninferiority was defined as the lower bound of this 97.5% CI being above 10%.
A

Primary Analysis

![Graph showing patient analysis over time for different treatments.]

B

Post-hoc Reanalysis
(excludes patients with non-R5 virus at screening by the enhanced Trofile assay)

![Graph showing patient analysis over time for different treatments after post-hoc reanalysis.]

*Note: The graphs illustrate the percentage of patients maintaining less than 50 copies/mL and less than 400 copies/mL over time for EFV + CBV and MVC + ZDV/3TC treatments. The post-hoc reanalysis excludes patients with non-R5 virus at screening by the enhanced Trofile assay.*
Important Lessons: MERIT

• Lack of precision for entry criteria (sensitivity of CCR5 test) led to wider confidence interval around the difference in response

• Smaller pre-specified CI for NI (10%) led to rejection of NI

• MVC was not selected as a preferred initial regimen for treatment of HIV by guidelines
Composite Endpoints

- Combination of multiple endpoints
- Used to reduce sample size
- Usually includes a disease specific endpoint and all cause mortality
- Interpretation is problematic when outcome is driven by one component
- Often not reported accurately
  - Overstatement of benefit of treatment
Composite Outcomes in Randomized Trials
Greater Precision But With Greater Uncertainty?

Nick Freemantle, PhD
Melanie Calvert, PhD
John Wood, MSc
Joanne Eastaugh, PhD
Carl Griffin, MSc

Randomized controlled trials are central to the evaluation of pharmaceuticals. They are used to provide evidence for the efficacy of pharmaceuticals in the licensing process that aims to ensure that drugs only become available for widespread prescription if they have a positive impact on symptoms, prognosis, or both. Furthermore, they play a major role in the evaluation of the effectiveness of treatments, providing the evidence base on which, for example, decisions on the inclusion of treatments in clinical guidelines are made.

The choice of outcomes measured (the outcome variables or end points) in clinical trials is an important design consideration. The primary outcome in particular has much invested in it, because it is normally the outcome alone that indicates whether or not the trial provides evidence at an acceptable level that the treatment is efficacious.

Trials that examine treatments that are expected to have an effect on mortality and major morbidity often adopt a primary composite outcome measure that includes mortality along with other nondal end points. This article examines the use of composite outcomes in major clinical trials, focusing on those that include mortality. We assess the arguments for and against them and provide guidance on their application and reporting.

Composite outcomes, in which multiple end points are combined, are frequently used as primary outcome measures in randomized trials and are often associated with increased statistical efficiency. However, such measures may prove challenging for the interpretation of results. In this article, we examine the use of composite outcomes in major clinical trials, assess the arguments for and against them, and provide guidance on their application and reporting. To assess incidence and quality of reporting, we systematically reviewed the use of composite end points in clinical trials in Archives of Internal Medicine, BMJ, Circulation, Clinical Infectious Diseases, Journal of the American College of Cardiology, JAMA, Lancet, New England Journal of Medicine, and Stroke from 1997 through 2001 using a sensitive search strategy. We selected for review 167 original reports of randomized trials (with a total of 300,276 patients) that included a composite primary outcome that incorporated all-cause mortality. Sixty-three trials (38%) were neutral both for the primary end point and the mortality component. Sixty trials (36%) reported significant results for the primary outcome measure but not for the mortality component. Only 6 trials (4%) were significant for the mortality component but not for the primary composite outcome, whereas 19 trials (11%) were significant for both. Twenty-two trials (13%) were inadequately reported. Our review suggests that reporting of composite outcomes is generally inadequate, implying that the results apply to the individual components of the composite outcome rather than only to the overall composite. Current guidelines for the undertaking and reporting of clinical trials could be revised to reflect the common use of composite outcomes in clinical trials.

COMPOSITE OUTCOMES IN CLINICAL TRIALS

To assess the extent and nature of composite outcomes, we searched 9 journals...

See also pp. 2545 and 2575.
### Table 3. Significance of Primary Composite Outcome and Mortality Component in Included Trials by Journal

<table>
<thead>
<tr>
<th>Composite or Mortality</th>
<th>Annals</th>
<th>BMJ</th>
<th>Circulation</th>
<th>CID</th>
<th>JACC</th>
<th>JAMA</th>
<th>Lancet</th>
<th>NEJM</th>
<th>Stroke</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsignificant primary, nonsignificant mortality</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>8</td>
<td>5</td>
<td>15</td>
<td>17</td>
<td>5</td>
<td>63 (38)</td>
</tr>
<tr>
<td>Nonsignificant primary, significant mortality</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Significant primary, nonsignificant mortality</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>14</td>
<td>23</td>
<td>2</td>
<td>60 (36)</td>
</tr>
<tr>
<td>Significant primary, significant mortality</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Multiple primary outcomes</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Not clear</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>10 (6)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
<td><strong>21</strong></td>
<td><strong>1</strong></td>
<td><strong>16</strong></td>
<td><strong>13</strong></td>
<td><strong>43</strong></td>
<td><strong>58</strong></td>
<td><strong>9</strong></td>
<td><strong>167 (100)</strong></td>
</tr>
</tbody>
</table>

Composite Endpoints in HIV Trials

• Virologic failure and toxicity
  – A more comprehensive picture of the outcome
  – May be more efficient due to low rates of virologic failure endpoints
  – But does it really capture what we want to know?
    • Important that the severity of toxicity be captured – grade 3 and above?
    • One component may precede the other in time
**Box. Recommendations**

1. Trialists should follow the CONSORT guidelines\(^{18}\) and identify precisely the prespecified primary and secondary outcome measures, reporting the results clearly in publications that describe the trial.

2. When trials report composite variables as primary outcomes, these should be interpreted together rather than as demonstrating efficacy of individual components of the composite.

3. Components of composite outcomes should always be defined as secondary outcomes and reported alongside the results of the primary analysis, preferably in a table.

4. Authors and journal editors should ensure that the reporting of composite outcomes is clear and avoids the suggestion that individual components of the composite have been demonstrated to be effective.

5. Systematic overviews and quantitative meta-analysis should be used to identify the effects of treatments on rare but important end points that may be included as part of composite outcomes in individual trials.
Are There Sex Differences in Response to ARV Therapy?
Percent of adults (15+) living with HIV who are female, 1990–2007

- Sub-Saharan Africa
- GLOBAL
- Caribbean
- Asia
- E Europe & C Asia
- Latin America
Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2011—United States and 6 Dependent Areas

N = 50,007

- Male-to-male sexual contact: 62%
- Injection drug use (IDU) – Males: 18%
- Injection drug use (IDU) – Females: 10%
- Male-to-male sexual contact and IDU: 3%
- Heterosexual contact$^a$ – Males: 3%
- Heterosexual contact$^a$ – Females: 5%
- Other$^b$: <1%

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting.

$^a$ Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

$^b$ Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.
Treatment discontinuation or modification greater in women

- Royal Free Clinic: Women 1.5x more likely to d/c EFV than men (naives)\(^1\)
- CASTLE (ATV/r vs LPV/r): Women more likely to d/c (21% vs 14%; 29% vs 18%); sex differences in efficacy in ITT\(^2\)
- Meta-analysis- earlier and greater d/c or change of HCV tx in HIV+ women\(^5\)

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1Smith. JAIDS 2007; 2Johnson. Gender-based differences in antiretroviral-naïve patients treated with ritonavir-boosted protease inhibitors: results from the CASTLE study through 96 weeks. 12th European AIDS Conference, 2009; 3Bhattacharyya. JAIDS Oct 2010
Higher rates of side effects on HIV therapy in women

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Adverse event</th>
<th>Ratio</th>
<th>Statistical analysis</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richter et al. (38)</td>
<td>Dyslipidemia</td>
<td></td>
<td>AHR</td>
<td>1.39 (1.05–1.45)</td>
</tr>
<tr>
<td>Richter et al. (38)</td>
<td>Glucose abnormalities</td>
<td></td>
<td>AHR</td>
<td>0.65 (0.45–0.93)</td>
</tr>
<tr>
<td>Galli et al. (39)</td>
<td>Lipoatrophy</td>
<td></td>
<td>AHR</td>
<td>1.84 (0.47–7.14)</td>
</tr>
<tr>
<td>Galli et al. (39)</td>
<td>Lipohypertrophy</td>
<td></td>
<td>AHR</td>
<td>3.23 (1.17–8.91)</td>
</tr>
<tr>
<td>Bonfanti et al. (40)</td>
<td>Lipodystrophy</td>
<td></td>
<td>ARR</td>
<td>1.5 (1.20–2.10)</td>
</tr>
<tr>
<td>Heath et al. (41)</td>
<td>Lipoatrophy</td>
<td></td>
<td>AOR</td>
<td>2.06 (1.03–4.12)</td>
</tr>
<tr>
<td>Heath et al. (41)</td>
<td>Lipohypertrophy</td>
<td></td>
<td>AOR</td>
<td>2.36 (1.17–4.74)</td>
</tr>
<tr>
<td>Santos et al. (42)</td>
<td>Lipohypertrophy</td>
<td></td>
<td>AOR</td>
<td>1.84 (1.17–2.91)</td>
</tr>
<tr>
<td>Florida et al. (45)</td>
<td>Rash</td>
<td></td>
<td>AOR</td>
<td>1.65 (1.00–2.72)</td>
</tr>
<tr>
<td>Boulasse et al. (44)</td>
<td>Hypersensitivity reactions</td>
<td></td>
<td>AHR</td>
<td>4.4 (2.10–9.30)</td>
</tr>
<tr>
<td>van Leth et al. (46)</td>
<td>Rash</td>
<td></td>
<td>UOR</td>
<td>2.0 (1.20–3.40)</td>
</tr>
</tbody>
</table>

Ratios (+/- 95% CI) of different adverse events by sex with HAART (2002-07)¹

Nicastri. Sex issues in HIV-1 infected persons during HAART: a systematic review. JACC 2007
Limitations of Current Data

- Most randomized trials of ARV are underpowered to detect sex differences in primary endpoint
- Would need studies with large sample size over 20% women
  - Need to adjust for age, race/ethnicity
  - As treatments improve, overall response rates are high and differences more difficult to detect
- Large Cohorts provide the best data currently
Sample Size Calculations to Detect a 50% Reduction in 2-Year Failure Rates Between Women and Men (1-beta=.8, alpha=.025)

J Currier et al., VIII Int Conference on AIDS, Amsterdam 1992, Abstract 4705
### Sample Sizes Required to Detect 2-Fold Differences in Toxicity Rates Between Men and Women

<table>
<thead>
<tr>
<th>Rate in Men</th>
<th>Rate in Women</th>
<th>Accural of Women</th>
<th>Total Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>10%</td>
<td>10%</td>
<td>2353</td>
</tr>
<tr>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>1689</td>
</tr>
<tr>
<td>5%</td>
<td>10%</td>
<td>20%</td>
<td>1367</td>
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<td>20%</td>
<td>10%</td>
<td>1095</td>
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<td>20%</td>
<td>15%</td>
<td>785</td>
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<td>20%</td>
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<td>879</td>
</tr>
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<td>20%</td>
<td>40%</td>
<td>10%</td>
<td>466</td>
</tr>
<tr>
<td>20%</td>
<td>40%</td>
<td>15%</td>
<td>333</td>
</tr>
</tbody>
</table>

J Currier et al., VIII Int Conference on AIDS, Amsterdam 1992, Abstract 4705
Further barriers to HIV treatment in women- LIFE

• Sex differences in HIV treatment utilization still exist (in US, not global)\(^1,2\)
  – Lower education levels
  – Lower rates of having health insurance
  – Competing priorities (food\(^3\), childcare, etc.)
  – Depression\(^4\)
  – Substance use\(^5,6\)
  – Domestic violence

\(^1\)Sohler et al. Gender Disparities in HIV Health Care Utilization among the Severely Disadvantaged: Can We Determine the Reasons? AIDS Patient Care and STDs, 2009;  
\(^2\)Braitstein. J Women’s Health 2008; \(^3\)Weiser. JAIDS 2009; \(^4\)Ickovics. JAMA 2001;  
\(^5\)Ghebremichael M AIDS Care 2009; \(^6\)Cook et al. AIDS 2008
Sex-Based Outcomes of Darunavir–Ritonavir Therapy
A Single-Group Trial

Judith Currier, MD, MSc; Dawn Averitt Bridge, BIS; Debbie Hagins, MD; Carmen D. Zorrilla, MD; Judith Feinberg, MD; Robert Ryan, MSc; Ron Falcon, MD; Alan Tennenberg, MD, MPH; Joseph Mrus, MD, MSc; and Kathleen Squires, MD, on behalf of the GRACE (Gender, Race, And Clinical Experience) Study Group

Background: Women account for an increasing proportion of patients with HIV-1 but remain underrepresented in antiretroviral clinical trials.

Objective: To evaluate sex-based differences in efficacy and adverse events in treatment-experienced, HIV-positive women and men receiving darunavir–ritonavir therapy over 48 weeks.

Design: Multicenter, open-label, phase 3b study designed to enroll a high proportion of women, with sample size determined on the basis of a noninferiority design with a maximum allowable difference of 15% in virologic response favoring men. (ClinicalTrials.gov registration number: NCT00381303)

Setting: 65 sites in the United States, Puerto Rico, and Canada.

Patients: 287 women and 142 men.

Intervention: Patients received darunavir–ritonavir, 600/100 mg twice daily, plus an investigator-selected optimized background regimen.

Measurements: Virologic response (HIV RNA <50 copies/mL using a time-to-loss of virologic response [TLOVR] algorithm) and adverse events were assessed over 48 weeks.

Results: 67% of patients were women; 84% of patients were black or Hispanic. A higher proportion of women discontinued treatment than men (32.8% vs. 23.2%; P = 0.042); more women than men discontinued treatment for reasons other than virologic failure. Response rates in women and men at week 48 were 50.9% and 58.5%, respectively (intention-to-treat TLOVR), and 73.0% and 73.5%, respectively (TLOVR censored for patients who withdrew for reasons other than virologic failure). The absolute difference in response, based on logistic regression and adjusted for baseline log_{10} viral load and CD4+ cell count, was −9.6 percentage points (95% CI, −19.9 to 0.7 percentage points; P = 0.067) for intention-to-treat TLOVR and −3.9 percentage points (CI, −13.9 to 6.0 percentage points; P = 0.438) for TLOVR population that censored patients who withdrew for reasons other than virologic failure. Adverse events were similar between the sexes. The most common grade 2 to 4 adverse events that were considered at least possibly treatment related in women and men were nausea (5.2% and 2.8%, respectively), diarrhea (4.5% and 4.9%, respectively), and rash (2.1% and 2.8%, respectively).

Limitation: Baseline characteristics differed between sexes.

Conclusion: Nonsignificant, sex-based differences in response were found during the 48-week study; however, these differences were probably due to higher discontinuation rates in women, suggesting that additional efforts are needed to retain women in clinical trials.

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For author affiliations, see end of text.
Study flow diagram.* “Other” classification was selected by the investigator as the reason for discontinuation.† Older patient taking too many concomitant medications.

Confirmed virologic response in ITT population (top) and population that censored patients who withdrew for reasons other than virologic failure (bottom). Virologic response was defined as viral load less than 50 copies/mL, confirmed by 2 consecutive assessments at

Confirmed virologic response in ITT population (top) and population that censored patients who withdrew for reasons other than virologic failure (bottom). Virologic response was defined as viral load less than 50 copies/mL confirmed by 2 consecutive assessments at least 14 days apart.

The absolute difference in response, based on logistic regression and adjusted for baseline log10 viral load and CD4 cell count, was 9.6 percentage points (95% CI, 19.9 to 0.7%; $P = 0.067$) for intention-to-treat TLOVR and 3.9 percentage points (CI, 13.9% to 6.0%; $P = 0.438$) for TLOVR population that censored patients who withdrew for reasons other than virologic failure.

“It is preferable to conduct adequately powered studies that will yield knowledge that will help both men and women than to do more studies that systematically provide poorer information for more than half the population.”

-Nancy E Adler, JAMA, December 22/29, 2010
Generalizability of Results: A Modeling Approach

Practice of Epidemiology

Generalizing Evidence From Randomized Clinical Trials to Target Populations
The ACTG 320 Trial

Stephen R. Cole* and Elizabeth A. Stuart

* Correspondence to Dr. Stephen R. Cole, Department of Epidemiology, Gillings School of Global Public Health and Center for AIDS Research, CB7438, University of North Carolina, Chapel Hill, NC 27599 (e-mail cole@chline.edu).

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Properly planned and conducted randomized clinical trials remain susceptible to a lack of external validity. The authors illustrate a model-based method to standardize observed trial results to a specified target population using a seminal human immunodeficiency virus (HIV) treatment trial, and they provide Monte Carlo simulation evidence supporting the method. The example trial enrolled 1,156 HIV-infected adult men and women in the United States in 1996, randomly assigned 577 to a highly active antiretroviral therapy and 579 to a largely ineffective combination therapy, and followed participants for 52 weeks. The target population was US people infected with HIV in 2000, as estimated by the Centers for Disease Control and Prevention. Results from the trial apply, albeit modestly, to the target population, under the assumption that the authors have measured and correctly modeled the determinants of selection that reflect heterogeneity in the treatment effect. In simulations with a heterogeneous treatment effect, a conventional intent-to-treat estimate was biased with poor confidence limit coverage, but the proposed estimate was largely unbiased with appropriate confidence limit coverage. The proposed method also compared observed trial results to a specified target population and thereby provides information regarding the generalizability of trial results.

Abbreviations: ACTG, AIDS Clinical Trial Group; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Properly planned and conducted randomized clinical trials (henceforth referred to as trials) typically provide stronger internal validity than observational study designs, such as prospective cohort studies. Such trials accomplish heightened internal validity by ensuring that the conditions necessary for proper inference are met. Specifically, trials ensure consistency (1–3) and positivity (1, 4) by design and no unmeasured confounding in expectation by randomization (5, 6). Trials and cohort studies constrain the amount of selection bias (7) due to dropout when near-complete patient follow-up is attained. However, even such trials are susceptible to a lack of external validity, or generalizability (8, 9), as recently discussed (10–12). This susceptibility is a function of the extent to which trial participants do not represent the target population. For an example of when trials might selectively enroll from the target population, a recent study (13) applied eligibility criteria from 32 human immunodeficiency virus (HIV) trials (largely funded by the National Institutes of Health) to the Women’s Interagency HIV Study (14) (the largest observational cohort of HIV-infected women in the United States) and found that, across trials, a median of 59% of women would have been eligible for a given trial (range: 32.4%–90%).

In simple settings, trial results may be mapped to a target population by using nonparametric direct standardization (15, 16 (p. 49)). However, when there are many covariates, or some covariates are continuous, direct standardization will fail. Here, we illustrate a model-based method to standardize observed trial results to a specified target population. Thereby, this method provides information regarding...
Summary

• Major advances in HIV therapeutics have made it more difficult to evaluate the role of newer agents
• Non-inferiority designs are important in many areas of therapeutics - beware of pitfalls
• Composite endpoint trials are attractive but need to be reported properly
• Sex differences in outcome are important across all therapeutic areas