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BHIVA Community Symposium
Generic antiretrovirals: what will they mean for patients and HIV services?

UK clinician's perspective

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Introduction

- Number of HIV-infected persons continues to increase
- Most patients with HIV will be on cART for many decades
- The introduction of generic ARVs has the potential for significant cost savings
- Programs will be effective to promote switch to generic cART
- Barriers to the introduction of generic cART

Economic Savings Versus Health Losses: The Cost-Effectiveness of Generic Antiretroviral Therapy in the United States

Rochelle P. Walensky, MD, MPH; Paul E. Sax, MD; Yoriko M. Nakamura, BA; Milton C. Weinstein, PhD; Pamela P. Pei, PhD; Kenneth A. Freedberg, MD, MSc; A. David Paltiel, PhD; and Bruce R. Schackman, PhD

Background: U.S. HIV treatment guidelines recommend branded once-daily, 1-pill efavirenz–emtricitabine–tenofovir as first-line antiretroviral therapy (ART). With the anticipated approval of generic efavirenz in the United States, a once-daily, 3-pill alternative (generic efavirenz, generic lamivudine, and tenofovir) will decrease cost but may reduce adherence and virologic suppression.

Objective: To assess the clinical effect, costs, and cost-effectiveness of a 3-pill, generic-based regimen compared with a branded, co-formulated regimen and to project the potential national savings in the first year of a switch to generic-based ART.

Design: Mathematical simulation of HIV disease.

Setting: United States.

Patients: HIV-infected persons.

Intervention: No ART (for comparison); 3-pill, generic-based ART; and branded ART.

Measurements: Quality-adjusted life expectancy, costs, and incremental cost-effectiveness ratios (ICERs) in dollars per quality-adjusted life-year (QALY).

Results: Compared with no ART, generic-based ART has an ICER of \$21 100/QALY. Compared with generic-based ART, branded ART increases lifetime costs by \$42 500 and per-person survival gains by 0.37 QALYs for an ICER of \$114 800/QALY. Estimated first-year savings, if all eligible U.S. patients start or switch to generic-based ART, are \$920 million. Most plausible assumptions about generic-based ART efficacy and costs lead to branded ART ICERs greater than \$100 000/QALY.

Limitation: The efficacy and price reduction associated with generic drugs are unknown, and estimates are intended to be conservative.

Conclusion: Compared with a slightly less effective generic-based regimen, the cost-effectiveness of first-line branded ART exceeds \$100 000/QALY. Generic-based ART in the United States could yield substantial budgetary savings to HIV programs.

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For author affiliations, see end of text.

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Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease:

A Systematic Review and Meta-analysis

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Abstract

Context—Use of generic drugs, which are bioequivalent to brand-name drugs, can help contain prescription drug spending. However, there is concern among patients and physicians that brand-name drugs may be clinically superior to generic drugs.

Objectives—To summarize clinical evidence comparing generic and brand-name drugs used in cardiovascular disease and to assess the perspectives of editorialists on this issue.

Data Sources—Systematic searches of peer-reviewed publications in MEDLINE, EMBASE, and International Pharmaceutical Abstracts from January 1984 to August 2008.

Study Selection—Studies compared generic and brand-name cardiovascular drugs using clinical efficacy and safety end points. We separately identified editorials addressing generic substitution.

Data Extraction—We extracted variables related to the study design, setting, participants, clinical end points, and funding. Methodological quality of the trials was assessed by Jadad and Newcastle-Ottawa scores, and a meta-analysis was performed to determine an aggregate effect size. For editorials, we categorized authors' positions on generic substitution as negative, positive, or neutral.

Results—We identified 47 articles covering 9 subclasses of cardiovascular medications, of which 38 (81%) were randomized controlled trials (RCTs). Clinical equivalence was noted in 7 of 7 RCTs (100%) of β -blockers, 10 of 11 RCTs (91%) of diuretics, 5 of 7 RCTs (71%) of calcium channel blockers, 3 of 3 RCTs (100%) of antiplatelet agents, 2 of 2 RCTs (100%) of statins, 1 of 1 RCT (100%) of angiotensin-converting enzyme inhibitors, and 1 of 1 RCT (100%) of α -blockers. Among narrow therapeutic index drugs, clinical equivalence was reported in 1 of 1 RCT (100%) of class 1 antiarrhythmic agents and 5 of 5 RCTs (100%) of warfarin. Aggregate effect size ($n = 837$) was -0.03 (95% confidence interval, -0.15 to 0.08), indicating no evidence of superiority of brand-name to generic drugs. Among 43 editorials, 23 (53%) expressed a negative view of generic drug substitution.

Conclusions—Whereas evidence does not support the notion that brand-name drugs used in cardiovascular disease are superior to generic drugs, a substantial number of editorials counsel against the interchangeability of generic drugs.

Knowledge

- Knowledge and information are utterly important when switching from brand to generics, as they may mitigate the impact on physicians and patients



Raphael: School of Athens

True or false 1?

- GD do not have the same therapeutic properties of brand-name drugs
- GD deliver a lower amount of drug and their action is delayed

True or false 1?

- 
- GD do not have the same therapeutic properties of brand-name drugs
 - GD deliver a lower amount of drug and their action is delayed
 - Generic and originator = same active ingredient, dosage, and route of administration
 - Therapeutic action depends on quantity of active substance reaching target
 - Same absorption (rate and extent) into the bloodstream AND same plasma concentrations over time = same safety and effectiveness

Bioequivalence

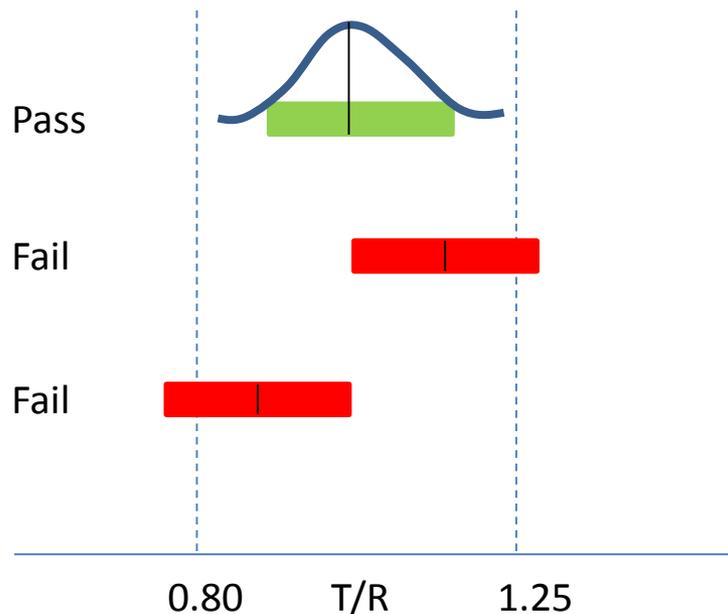
Bioequivalence may be the most misinterpreted criteria by both professionals and patients, and controversy arises from a misunderstanding of the statistical methods for determining bioequivalence

Bioequivalence

- Bioequivalence demonstrated compared to the originator by generic applicants
- Bioequivalence determination is based on the comparison of the ratio of the mean values of tested drug versus reference, for each PK variable
- The 90% confidence interval (90%CI) of the ratio must be within the acceptance interval of [0.80–1.25] (or [0.90–1.11] for drugs with narrow therapeutic index)
- Bioequivalence based on ratios where the nominal equality is 1 (or 100%), not based on differences in absolute values

Schematic diagram illustrating possible bioequivalence study outcomes

T/R = test/reference



True or false 2?

- GD have a different composition esp. excipients with noticeable effect
- GD look different: it is confusing
- GD are not evaluated as thoroughly as originators via clinical trials
- GD are cheaply manufactured at a lower quality

True or false 2?

- GD have a different composition esp. excipients with noticeable effect
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-
- GD and originators can differ in nature and quantity of excipients, provided that the excipients in the generic do not affect bioequivalence
 - We are experienced in changing drugs: i.e. DRV 400 x 2 to 800; RTV soft gel to RTV Meltrex, etc
 - GD have same therapeutic properties than brand-name drugs
 - GD deliver the same amount of drug, in the same time-span as an originator

True or false 3?

- GD cause more AEs
- Less efficacious and less tolerated, especially when treating long-term conditions

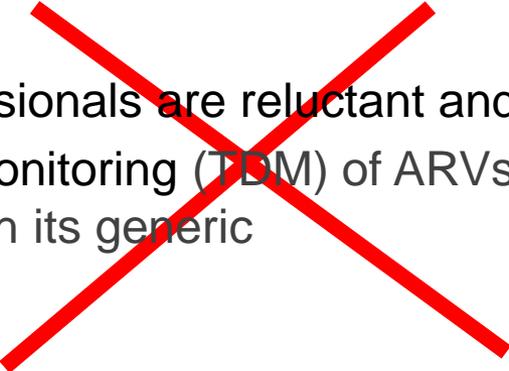
True or false 3?

- 
- GD cause more AEs
 - Less efficacious and less tolerated, especially when treating long-term conditions
 - AEs occur to the same extent and in the same conditions between generics and originators (health authorities reports)
 - Same efficacy, as same amount of active agent

True or false 4?

- Some health professionals are reluctant and fear changes
- Therapeutic drug monitoring (TDM) of ARVs should be systematic when replacing a drug with its generic

True or false 4?

- 
- Some health professionals are reluctant and fear changes
 - Therapeutic drug monitoring (TDM) of ARVs should be systematic when replacing a drug with its generic
-
- This is not a real change, not something we haven't done before
 - Guidelines on HIV treatment do not recommend routine TDM

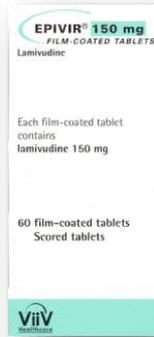
Regulations

- ❖ All major health authorities require:
 - generic drugs to have same quality, dosage, purity, and stability as originators
 - bioequivalence trials to demonstrate bioavailability equivalence of new formulation vs originator
- ❖ Redundancy of testing in human subjects is unethical and scientifically unnecessary
- ❖ Controls of the production of generics do not show an increased risk compared to the production of originators

Virological response in patients, who for economic reasons were changed from Atripla to a multi-tablet cART regimen

- ✓ STR changed to a cheaper multi-tablet regimen (MTR) after April 1, 2011, n = 509
- ✓ Switch from Atripla to a MTR did not reduce virological response or CD4 count

Highly managed process



Doctor to sign home care prescription:

Switching to generic lamivudine tablets

(For patients using 150mg tablets only)

Patient counseled on switch to generic lamivudine and is aware that the generic product may come on next or subsequent home delivery

Doctor sign: date:

Given leaflet via pharmacy initial:..... date:.....

Switching to generic lamivudine tablets

(For patients using 150mg tablets only)

	Sign	Date	
Counseled on switch to generic drug	

Given switch leaflet (by pharmacy)

Home care: Aware generic may come on next or subsequent home delivery

What factors should clinicians consider before switching a patient to GD?

- Is the patient stable on cART?
 - Importance of evaluating the need of switch: is it good practice to switch only for cost?
- Would a switch cause patient anxiety?
 - Importance of involving the patient in the decision
- Would a switch affect adherence to cART?
 - Importance of assessing pt adherence (current and Hx of adherence)
- Will GD increase the pill burden for patients?
 - Importance of being informed on available options

Examples of individuals suitable or non suitable for switch to GD

- YES

- Those who are stable on the brand-name drug that has become generic
- Those who request to

- NO

- Those with baseline resistance
- Those with a history of AEs to the GD

Conclusions

It is common sense if appropriately managed process

It has already happened in many medical specialties

If no harm in switching to GD, there is a duty of considering the switch in view of the available resources