



Inclusion of Women in HIV Clinical Trials

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FDA

U.S. Department of Health and Human Services

Food and Drug Administration





Objectives

- Describe key FDA regulatory policies regarding inclusion of women in clinical research
- Describe Women in HIV Trials Grant Project: A comprehensive review and meta-analysis update

Historical Perspective

General
Considerations
for the Clinical
Evaluation of
Drugs

Guideline for the
Study and
Evaluation of
Gender
Differences in
Clinical
Evaluation of
Drugs

Clinical
Hold Final
Rule

1977

'88

'93

'98

'00

Guideline for the
Format and
Content of the
Clinical and
Statistical
Sections of NDAs

Demographic
Final Rule



Background

- Prior to 1993, growing concerns drug development process did not have data about effects of drugs in women
- Concern arose from:
 - Analyses of published clinical trial data (e.g. cardiovascular disease) indicated limited participation of women in many clinical studies
 - Limited studies on effects of female physiology (menstrual cycle, menopause)
 - 1977 policy excluded women of childbearing potential from early drug studies



Background

- Women excluded in clinical research because:
 - General belief men and women do not differ significantly in response to treatment in most situations
 - Inclusion of women introduces additional variables (from hormonal cycles) and decreases homogeneity of study population
 - Women might not avoid pregnancy, and protecting fetus outweighs other possible interests



FDA's 1977 Guideline

- Excluded women of childbearing potential (WCBP) in clinical trials (phase 1 and early phase 2)
 - These trials do not have therapeutic intent except in cases of life-threatening diseases
- WCBP could participate in studies of effectiveness (later phase 2 and 3) if:
 - Adequate information on effectiveness and relative safety were collected during phase 1 and early phase 2
 - Animal teratogenicity and animal fertility (female) studies completed



Revisions to 1977 Policy

- Rationale for Revision:
 - 1977 guideline did not result in failure to include adequate numbers of women in later phases
 - Restricted early accumulation of information about women's responses to drugs that could have been used to design phase 2 and 3 trials.
 - Guideline may have delayed appreciation of gender-related variation in drug effects
 - FDA believed removing prohibition of WCBP in early development was consistent with congressional efforts to prevent unwarranted discrimination against women

■ ■ ■ Revisions to 1977 Policy

- Revision of policy did not mean lack of concern for potential fetal exposure or indifference to potential fetal damage
 - Excluding women is not medically necessary; patient behavior and lab testing can minimize risk of fetal exposure
 - FDA leaves initial determinations about whether risks are adequately addressed to patients, physicians, local IRBs and sponsors
- Appropriate precautions should be taken
 - Not pregnant at time of trial
 - Adequately informed about current state of animal reproduction studies and teratogenic potential of drugs
 - FDA considers adequacy of the precautions during protocol reviews



1988 Guideline

- “Guideline for the Format and Content of the Clinical and Statistical Sections of NDA”
 - Analyses of NDA data to identify variations among population subsets in favorable responses (effectiveness) and unfavorable responses (adverse reactions)
 - Gender
 - Age groups
 - Races
 - Persons receiving other drug therapy
 - Persons with concomitant illness



The 1993 Guideline

- Rationale:
 - Drugs should be studied prior to approval in subjects representing the full range of patients likely to receive the drug when marketed
 - Recognition of these differences can allow safer and more effective use of drugs
- Therefore sponsors are expected to:
 - Include a full range of patients in studies
 - Carry out appropriate analyses to evaluate potential subset differences in studied patients
 - Study possible PK differences in patient subsets
 - Carry out targeted studies to look for subset PD differences suggested by existing data, or would be particularly important if present



The 1993 Guideline

- Recommendations in 1993 guideline based on:
 - Variations in response to drugs, including gender-related differences (PK)
 - Gender-related variations
 - Effects of endogenous/exogenous hormones
 - Body weight, age, race
 - Underlying diseases
 - Concomitant therapies
 - Gender-related pharmacodynamic/effectiveness differences

■ ■ ■ The 1993 Guideline

- Inclusion of both genders in clinical studies
 - Both genders should be included in same trial
 - FDA is concerned about data variability – trials should include measure to reduce or adjust for variability
- Analysis of effectiveness and adverse events by gender
 - Analysis to detect influence of gender should be done for individual studies and overall integrated analyses.
 - Expected to detect relatively large gender-related differences; small differences not likely to be clinically important
 - Results of analyses may suggest need for more studies



Demographic Rule - 1998

- Current rule revises IND annual report regulations and NDA format regulations
- Rationale:
 - Different population subgroups may respond differently to a specific drug product
 - Although an effort should be made to look for differences in effectiveness and AEs among such subgroups that effort is not being made consistently



Demographic Rule - 1998

- IND:
 - Require sponsors to tabulate the number of subjects in a trial by age, gender and race.
 - This action alerts FDA as early as possible to potential demographic deficiencies in enrollment that could lead to avoidable deficiencies in an NDA submission
- NDA:
 - Clearly defined requirement to present effectiveness and safety data for important demographic subgroups:
 - Gender, age, race and other subgroups, as appropriate





Demographic Rule - 1998

- Consistent with ICH guidelines
- This rule applies only to presentation of data already collected and does not address the requirement for the conduct of clinical studies
- If sponsors follow these rules, then a refuse to file action based on failure to carry out such critical analyses will be less likely



Clinical Hold Rule - 2000

- FDA can impose a clinical hold on any proposed or ongoing clinical trial if:
 - The trial is for a life-threatening disease or condition; and
 - The disease or condition affects both genders; and
 - Men or women of/with reproductive potential who have the studied disease or condition and were excluded from participating in any phase of the clinical investigation solely because of a risk or potential risk of reproductive or developmental toxicity from the use of the investigational drug
- Does not apply to trials conducted exclusively in healthy volunteers



■ ■ ■ Clinical Hold Rule - 2000

- Rationale:
 - FDA is committed to expanding access to and accelerating approval of new agents for life threatening diseases/conditions
 - Important ethical principles underlie that belief that neither gender should be excluded from early clinical trials involving a life threatening disease/condition because of reproductive potential
 - Mechanisms are in place, or are available to protect individuals participating in clinical trials from potential risks
 - FDA is committed to expanding the collection of gender-specific data on investigational agents, especially for those populations who will ultimately use the therapies





Clinical Hold Rule - 2000

- Is not meant to be punitive
- Clinical holds will be issued only as a last resort
- This rule is consistent with ICH initiatives
 - ICH notes that there are regional differences in the timing of reproductive studies to support inclusion of women with reproductive potential in clinical trials
 - In multi-country studies FDA does not intend to impose a hold for such exclusions on studies in foreign sites, provided there is no categorical exclusion based on reproductive potential in the US



Clinical Hold Rule - 2000

- HIV/AIDS
 - Many women affected by HIV/AIDS are WCBP
 - This rule will prevent their exclusion from participation solely because of a perceived risk or potential risk of reproductive or developmental toxicity
 - Division of Antiviral Drug Products (and CBER):
 - Encourages sponsors to include women of all age groups early in the drug development process and
 - Supports the concept of allowing each eligible female participation to make her own informed decision regarding the risks and benefits of participating in a trial.



Women in HIV Trials: A Comprehensive Review and Meta-analysis

Grant Received by FDA's
Office of Women's Health



FDA

U.S. Department of Health and Human Services

Food and Drug Administration





PROJECT I

Inclusion of Women in HIV
Trials and Presentation of
Gender Analyses in NDAs

Track inclusion of
women in trials

Monitor completion
and presentation of
sex analyses

PROJECT II

Meta-Analysis of the
Efficacy and Safety
Information by Gender

Identify potential
safety and efficacy
differences by
various parameters



Project I

Objectives

- Track inclusion and analyses of women in HIV trials
- Gain better understanding of the efficacy and safety data in HIV+ women
- Improve labeling for HIV+ women with regard to the safe and effective use of ARVs



Analyses for Project 1

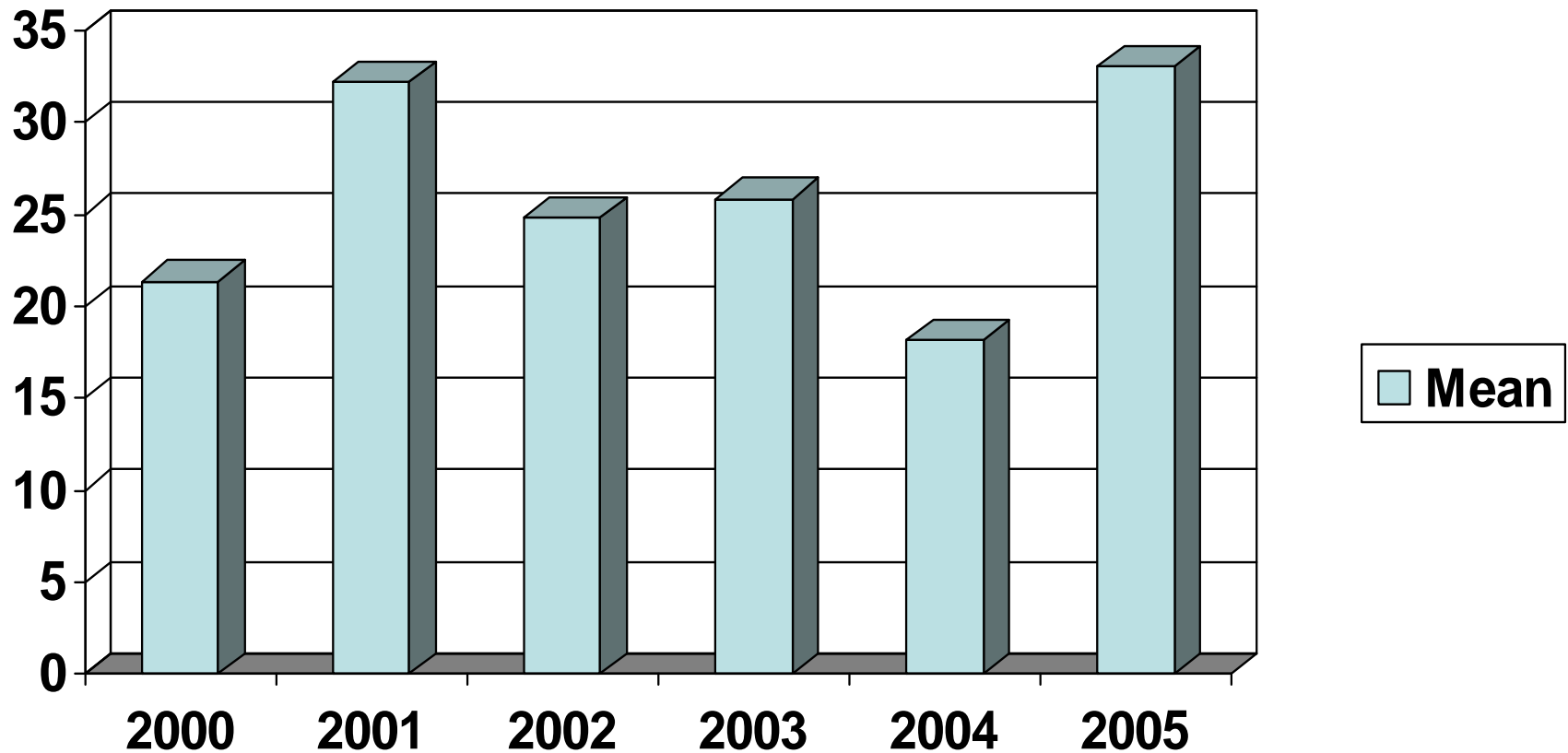
- Summarize % of women included in Phase II-IV trials submitted to FDA to support a new molecular entity or major labeling change (2000-2006)
- Review statistical and medical reviews to determine if proper gender analyses were included and if any significant findings were found
- Evaluate labels to determine if any gender specific statements regarding efficacy and safety exist



■ ■ ■ Analysis for Project I (cont)

- Compare % of women in trials by:
 - **Time:** to evaluate any potential trends over time with respect to inclusion of women (year of starting date of trial as the classifier)
 - **Continent:** to evaluate if North America differs from Europe, South America, and Africa vs ROW
 - **Disease stage:** to evaluate differences between treatment-experienced and naïve patients
 - **Drug class:** to evaluate if women are more inclined to participate in trials when certain regimens are available
 - **Age, Race**
 - **Pregnancy:** inclusion at baseline and rate of new pregnancies

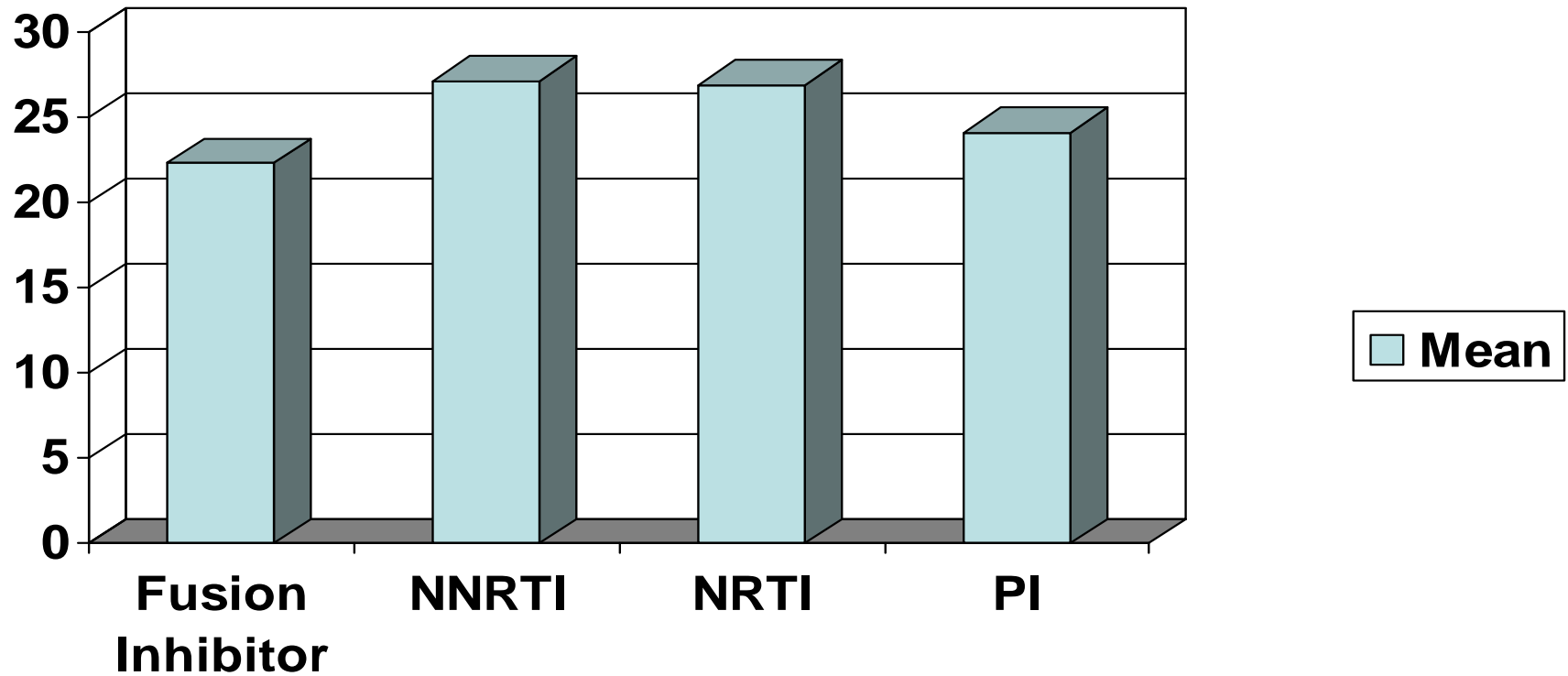
Results by Year – Mean Proportion of Females



Total # of pts	2261	2194	6407	6595	4188	2683
Min – Max	6–61	8.5-68	8-77	14-48	9-26	9-52

Results by Drug Class

Mean Proportion of Females

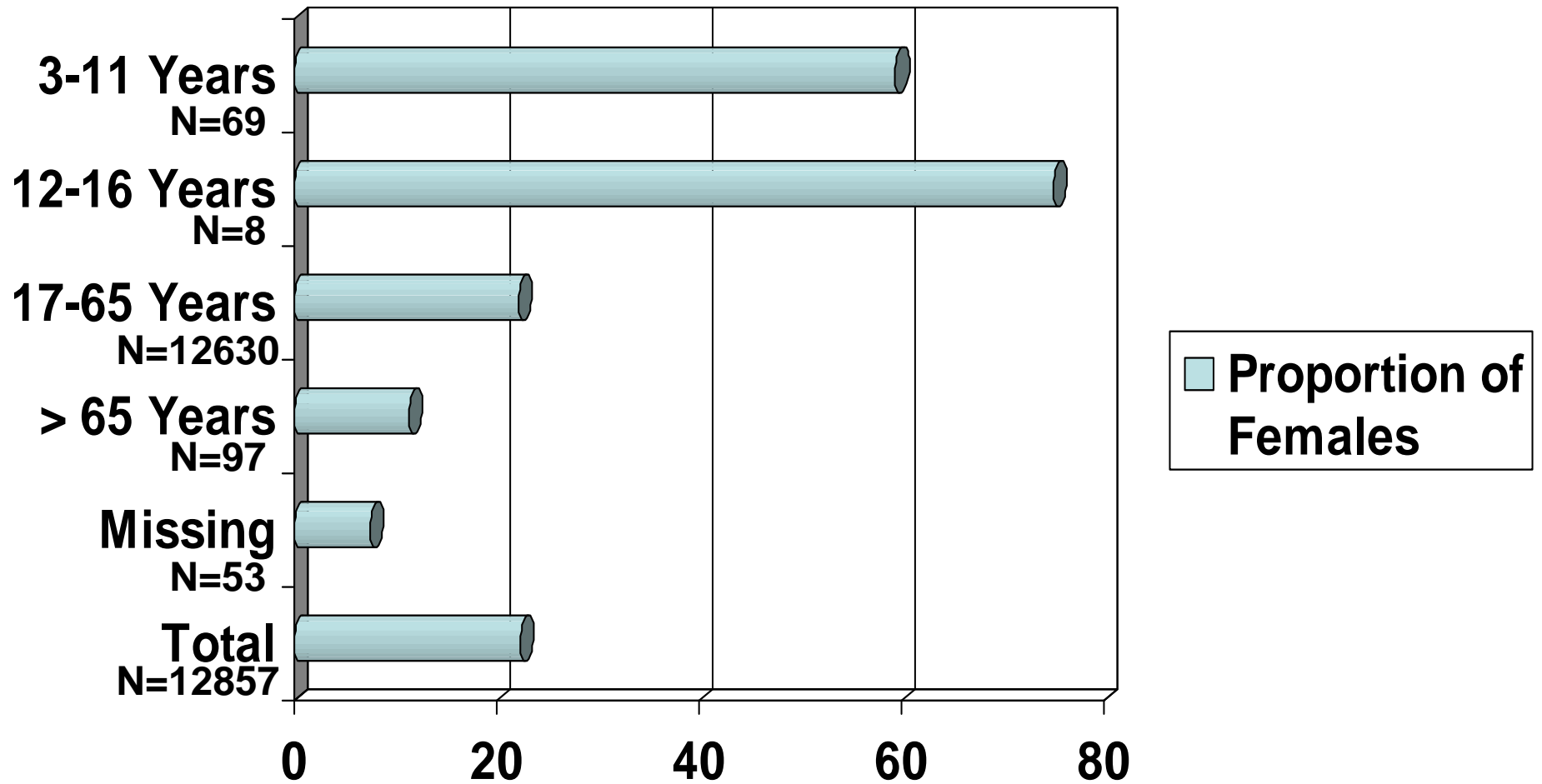


Total # of pts	1065	4609	11139	10859
Min – Max	8-46	13-61	8-68	6-77

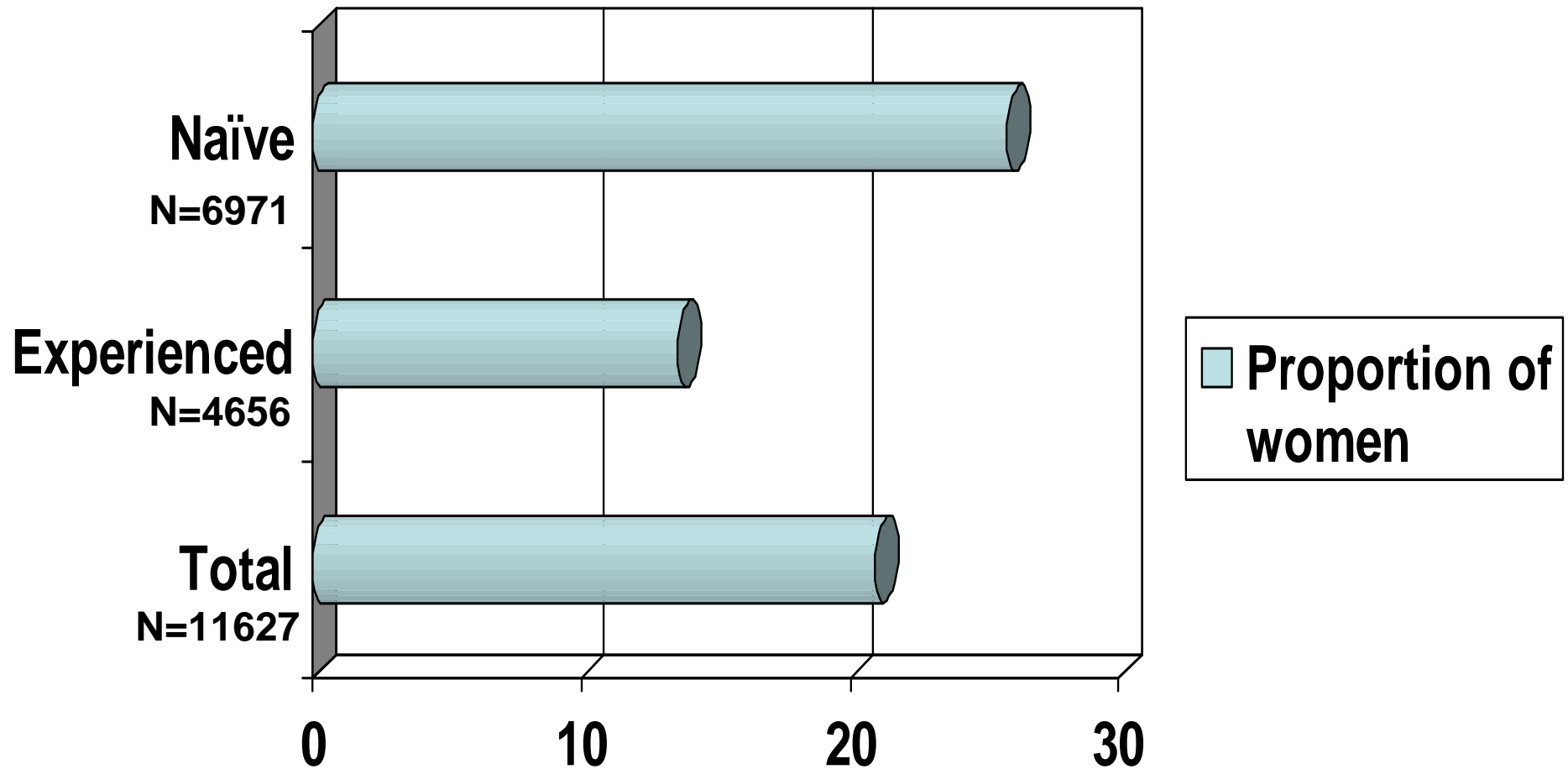
Results by Race/Ethnicity

Race/ethnicity	Proportion of Female	Total Number of Patients
Asian/Pacific Islander	52.6%	549
Black	39.01%	2556
Hispanic	22.23%	2015
Missing	10.73%	177
Native American/Alaska	12.5%	8
Other	35.77%	274
White	13.97%	7278
Total	22.31%	12857

Results by Age Group



Results by Disease State*



*excludes unknown or mixed populations



Objectives for Project II

- Conduct meta-analysis on Phase II-IV trials submitted to FDA to support a new molecular entity or major labeling change (2000-2006)
- Identify any potential systematic safety and efficacy differences between men and women

■ ■ ■ Analysis for Project II

1. Overall distribution of the relative effect size of women vs men across trials to determine if any systematic pattern exists by the following factors (singly or in combination)
 - **Drug class** (PI, NNRTI or triple NRTI based regimens)
 - **Continent**
 - **Treatment-experience** (naïve vs ≤ 2 regimens vs > 2 regimens)
 - **Types of treatment regimen** (e.g., all Kaletra containing regimens)
2. Identify differences between men and women by baseline HIV RNA, CD4, treatment-experience, weight
3. Identify and compare any safety and efficacy differences between men and women in #1 and determine if differences are due to baseline covariates such as CD4, HIV RNA or weight

■ ■ ■ Miscellaneous

- Compare % of women enrolled with % of women in HIV population to determine if the % of women in trials are representative of the epidemic worldwide for the given stage of disease
- Examine datasets to determine if:
 - trials included information on all patients screened to identify potential causes of low enrollment
 - Any gender-specific criteria impeded enrollment of women (birth control, hemoglobin, etc)



Conclusions

- Optimal use of drugs requires identification of demographic, disease-related and individual patient related factors so that appropriate adjustments in dose, concomitant therapy or monitoring can be made.
- In the US, FDA has implemented various regulations and guidelines in order to determine if there are gender related PK or PD differences.
- This information will ultimately aid in the individualization of drug treatment.