Future of PrEP and Microbicide Research

Non-Inferiority (NI) Clinical Trials: Some Key Considerations in PrEP and Microbicide Studies

January 7, 2013

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Fleming TR. *Statistics in Medicine*, 27: 317-332, 2008
Fleming TR, Powers JH. *Journal of CID*, 47: 108-120, 2008
Fleming TR et al. *Clinical Trials* 8:432-439, 2011

New product choices

- New daily oral drug
  - Higher or similar efficacy
  - Motivations
    - Fewer side effects, higher adherence
    - Avoid first line treatment drugs
    - Lower risk of community resistance
- Longer acting formulation (e.g. injectable)
  - Higher efficacy
    - Increased adherence and convenience
  - Safety concerns
- New dosing strategy for TDF/FTC (eg coitally dependent)
  - Equivalent efficacy
    - Increased ‘coverage’ (active drug at time of exposure)
    - Decreased cost and side effects

Possible PrEP Scenarios

Control	Experimental		
	New daily oral drug	New longer acting drug	New TDF/FTC dosing strategy
Daily TDF/FTC as an Active Control	**Scenario A**	Scenario B	Scenario C
Placebo add-on to Daily TDF/FTC	Scenario D	Scenario E	Scenario F N/A
Placebo add-on to 'Std. of Care'	Scenario G	Scenario H	Scenario I

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Non-Inferiority Trials

- A direct evaluation
  of the clinical efficacy/safety
  of **Exp** relative to **Std**

- Goal: To determine whether
  we can rule out that the efficacy of **Exp** is '*unacceptably worse than*' that of **Std**

…setting the **Margin**…

E.g.: Maraviroc (Exp) vs. TDF/FTC (Std)

Some Important Issues

- Some PrEP interventions provide *major* clinical benefit
- Serious issue if meaningfully less effective interventions were used instead
- There can be differences between interventions in either "on target" or "off target" effects including levels of adherence

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⇒ **Reliable evaluation of benefit-to-risk profile of new PrEP interventions is necessary**

Dual Goals of Non-Inferiority Trials

- To enable a direct evaluation
  of the clinical efficacy/safety
  of **Exp** relative to **Std**

- To contribute evidence to
  the evaluation of efficacy/safety
  of **Exp** relative to **Placebo**

E.g.: Maraviroc (EXP) vs. TDF/FTC (STD)

Non-Inferiority Trials… Some Requirements

ICH E9: Std should have clinical efficacy

- that is of **substantial magnitude**
- that is **precisely estimated**
- with estimates that are **relevant** to the setting in which the non-inferiority trial is being conducted

Factors invalidating Constancy Assumption
(Exp vs. Std NI Trial vs. Trials evaluating Std)

- ✓ patient characteristics

e.g., Participants less likely to be impacted by Std in NI Trial

- ✓ use of supportive care

e.g., Enhanced concomitant Rx attenuates effect of Std in NI Trial

- ✓ dose, schedule, level of adherence

e.g., Lower adherence to Std in NI trial

- ✓ efficacy and safety endpoints

~ well-defined & reliable *~ clinically meaningful* *~ sensitive*

Populations and Efficacy results for Daily TDF/FTC

Study	Risk/Gender	Adherence	# of Events	Efficacy; 95% CI
Partners PrEP	Discordant heterosexual couples	**~80%**	13 vs. 52	**75% (55%, 87%)**
TDF2	Heterosexual Men & Women	**~80%**	9 vs. 24	**63% (22%, 83%)**
iPrEx	**MSM**	**~50%**	48 vs. 83	**42% (18%, 60%)**
FemPrEP	Heterosexual Women	**~35%**	33 vs. 35	**6% (-69%, 41%)**
VOICE	Heterosexual Women	**To be Reported**	To be Reported	**To be Reported**

Illustration: Setting the Margin

Maraviroc (Exp) *vs* TDF/FTC (Std)
PrEP in MSM
(Rate of HIV Infection)

Non-Inferiority Trial **HIV INFECTION**

Maraviroc
TDF/FTC

Factors Influencing the Choice of Margin and Interpretation of NI Trial Results

- Active Control Effect
- Clinical Relevance of Changes in:

  Loss of *Benefits* (eg., 1.5 add'l MI/100 *people*)
  relative to changes in

  Risks/Tolerance, (eg, 2 fewer major bleeds)
  Convenience,
  Drug-Drug Interactions, *Cost*, etc.

Non-Inferiority Trials… Some Requirements

Active Control should have clinical efficacy

- that is of substantial magnitude
- that is precisely estimated
- with estimates that are relevant to the setting in which the non-inferiority trial is being conducted

Illustration: Setting the Margin

Maraviroc (Exp) *vs* TDF/FTC (Std)
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Non-Inferiority Trial **HIV INFECTION**

Maraviroc
TDF/FTC

iPrEx Trial **HIV INFECTION**

TDF/FTC Total events
Placebo ≈ 131

(TDF/FTC / Placebo) RR = 0.58 95% CI: (0.40, 0.82)

Factors invalidating Constancy Assumption
(Non-Inferiority Trial vs. iPrEx)

- ✓ patient characteristics

e.g., Participants less likely to be impacted by Std in NI Trial

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e.g., Enhanced concomitant Rx attenuates effect of Std in NI Trial

- ✓ dose, schedule, level of adherence

e.g., Lower adherence to Std in NI trial

- ✓ efficacy and safety endpoints

~ definition ~ validation process ~ missing data

…..as in maintaining conditions of a lab experiment…

“HIV Infection” Events

Placebo compared with TDF/FTC

Placebo better

TDF/FTC better

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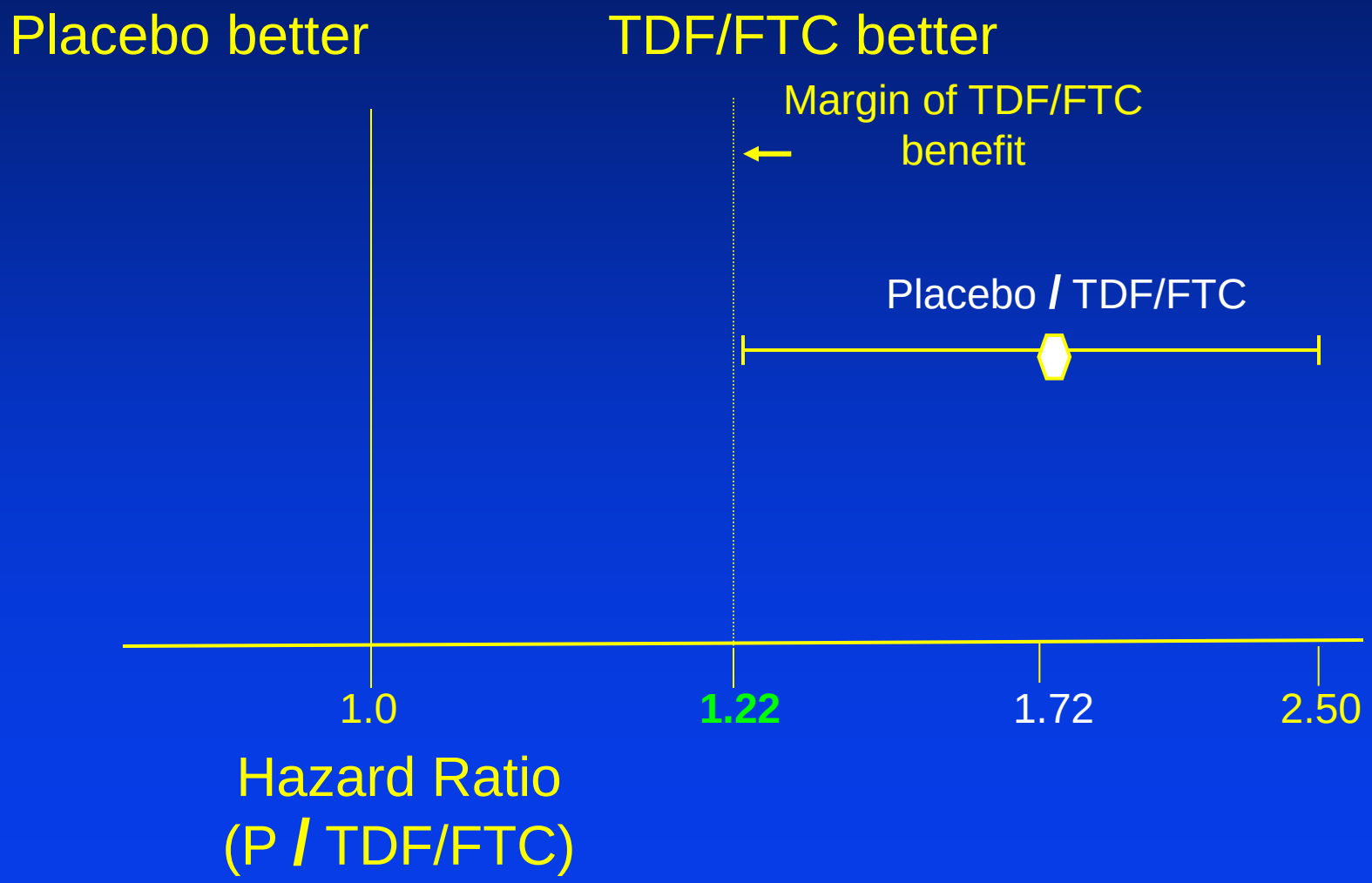
(TDF/FTC / Placebo) RR = 0.58 95% CI: (0.40, 0.82)

(Placebo / TDF/FTC) RR = 1.72 95% CI: (**1.22**, 2.50)

“HIV Infection” Events

Placebo compared with TDF/FTC



Factors Influencing Choice of Margin

- Active Control Effect

(HIV Infection)

~ magnitude of Active Control effect

Eg: Estimated (P / TDF/FTC) Relative Risk = 1.72

~ precision of estimate

Eg: ± 2 s.e. = (**1.22**, 2.50) (131 events)

~ estimates relevant to setting of NI trial

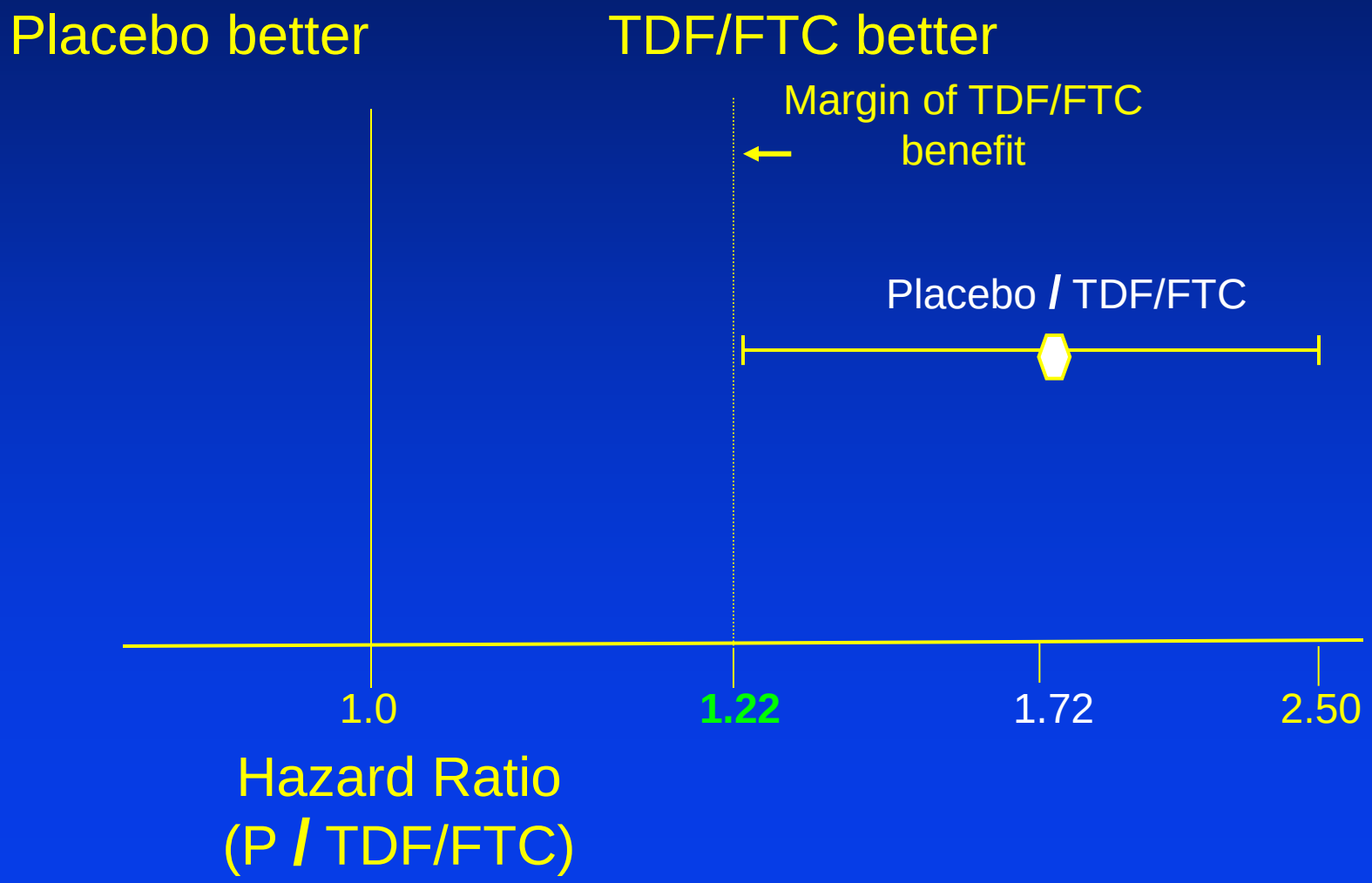
- Population
- Adherence
- Supportive care
- Endpoint assessment

~ preserve > half of the Active Control effect

$\sqrt{\mathbf{1.22}} = \mathbf{1.10}$

“HIV Infection” Events

Placebo compared with TDF/FTC



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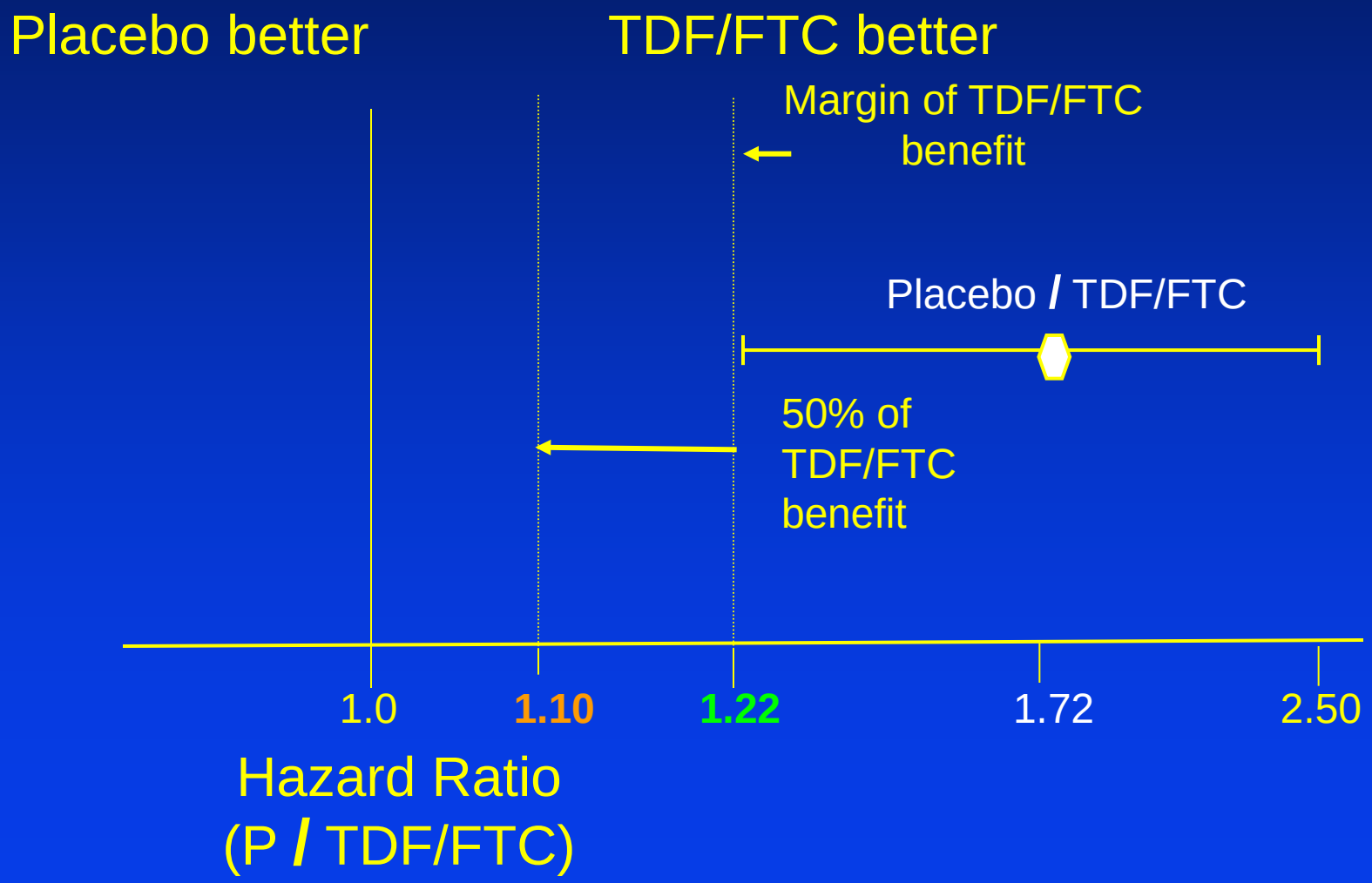

Factors Influencing the Choice of Margin and Interpretation of NI Trial Results

- Active Control Effect
- Clinical Relevance of:

  Loss of *Benefit* (i.e. 2.4 add'l HIV inf / 1000 p.y.)

  relative to changes in:

  Fewer side effects
  Avoid first line treatment drugs
  Lower risk of community resistance

Illustration: Setting the Margin

Maraviroc (Exp) *vs* TDF/FTC (Std)
PrEP in MSM
(Rate of HIV Infection)

Non-Inferiority Trial **HIV INFECTION**

Maraviroc	2 yr f.u.
TDF/FTC	2 yr f.u.
	2.25/100 p.y.

iPrEx Trial **HIV INFECTION**

TDF/FTC	Total events
Placebo	≈ 131

(TDF/FTC / Placebo) RR = 0.58 95% CI: (0.40, 0.82)

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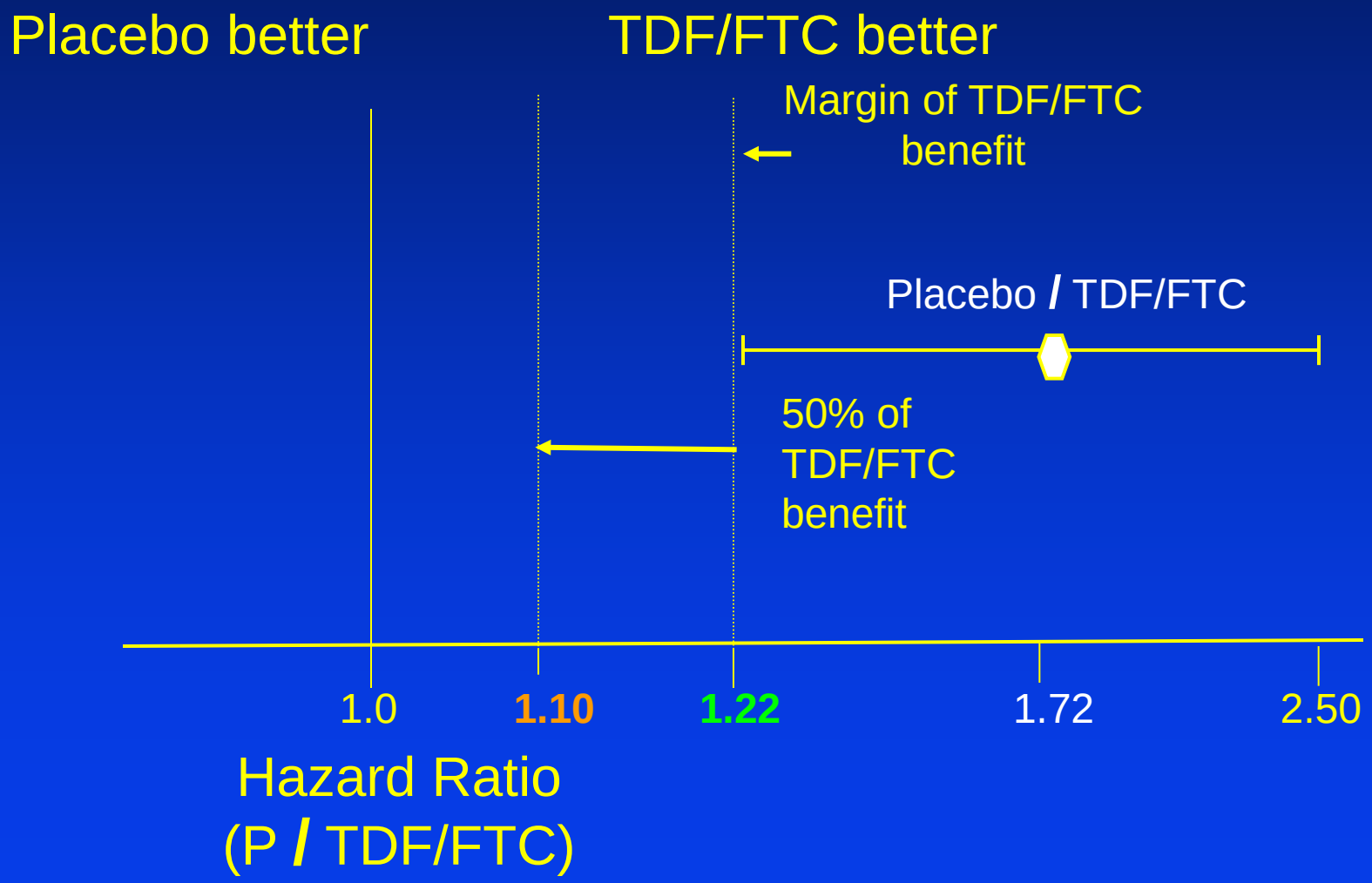

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Maraviroc (Exp) *vs* TDF/FTC (Std)
PrEP in MSM
(Rate of HIV Infection)

Non-Inferiority Trial	**HIV INFECTION**	
Maraviroc	133/3200 (4.2%)	2 yr f.u.
TDF/FTC	153/3200 (4.8%)	2 yr f.u.
	RR = 0.87 (0.69, **1.09**)	2.25/100 p.y.

iPrEx Trial	**HIV INFECTION**
TDF/FTC	Total events
Placebo	≈ 131

(TDF/FTC / Placebo) RR = 0.58 95% CI: (0.40, 0.82)

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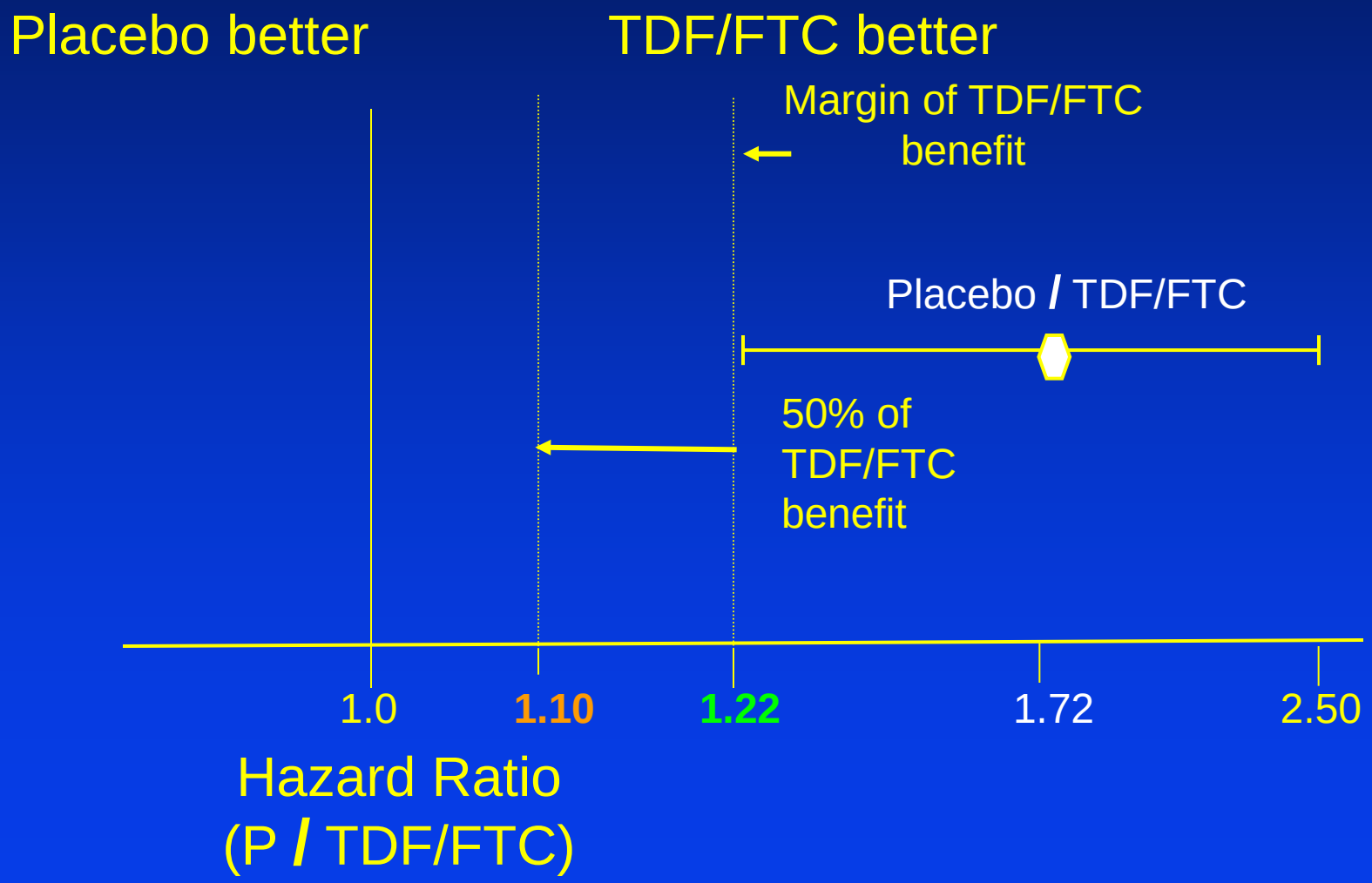

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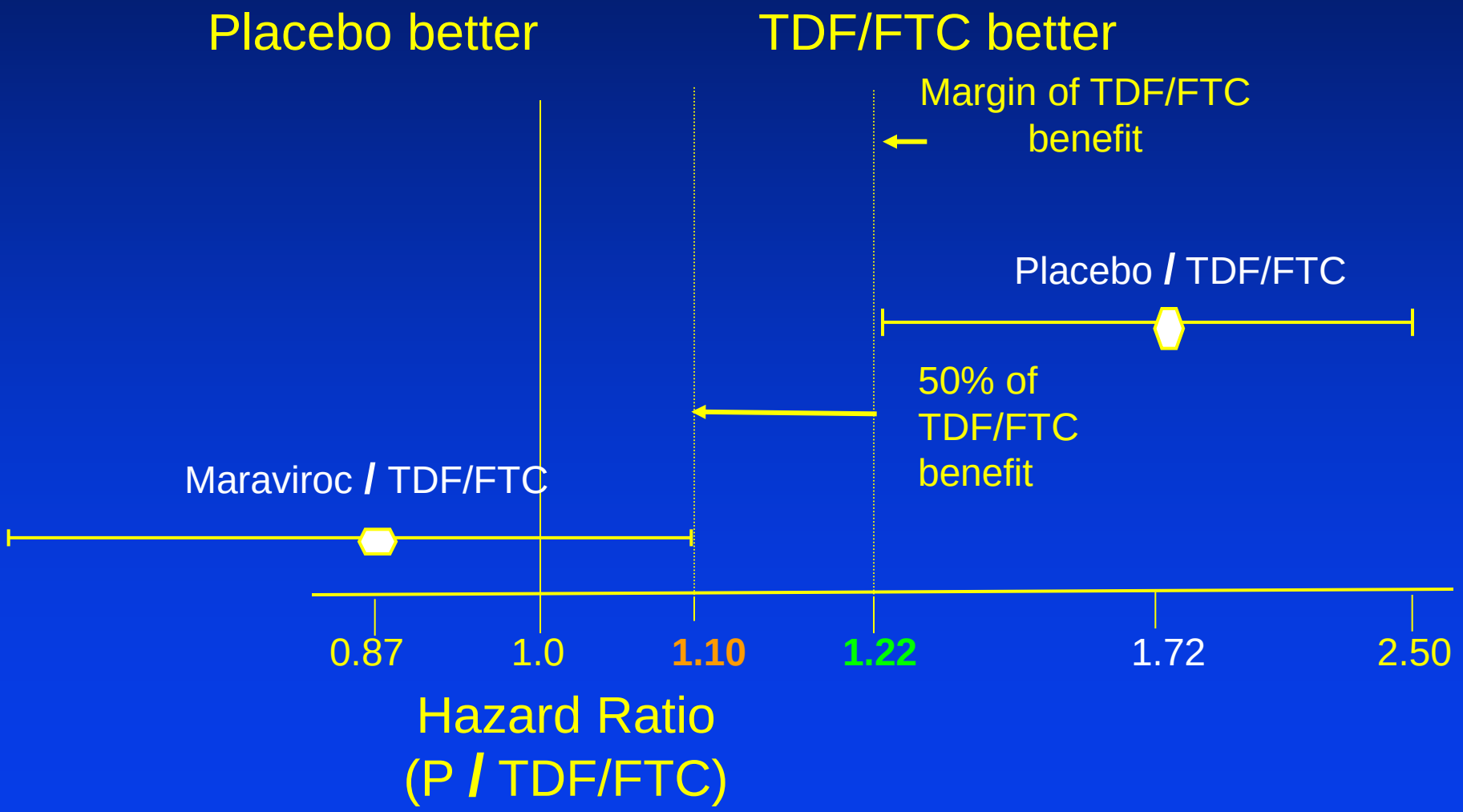

Determining the **Margin** in NI Trials

Goal in NI trials: Ruling out the new intervention (Exp) is unacceptably worse than a standard (Std) regimen having *reliable* evidence of *substantial* effects…

⇒ Need an 'evidence based' NI **Margin**

Determining the NI margin: Two Key considerations

- The NI margin should be formulated using adjustments to account for bias or inherent unreliability in the estimate of the effect of Std in the non-inferiority trial setting.
  (…*as in superiority trials that are not randomized*…)
- The NI margin should be formulated to preserve an appropriate percentage of the effect of Std.

Community Acquired Pneumonia: Mortality
(Non-bacteremic patients, Age > 50)

- *Sulfonamide derivatives & penicillin. (Fleming, Powers. *CID*, 2008)

	21-day Mortality
➢ Antibiotics*	16.1%
➢ No Specific Rx	49.4%

- Consider an Exp *in patients who are candidates for Antibiotics*:

	21-day Mortality
➢ Experimental Rx	37%
➢ No Specific Rx	49%

- Is a statistically significant, but clinically modest, ↓ in mortality acceptable *in patients who are candidates for Antibiotics*?

Clinton-Gore (April 1995)

– "it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when:

1. the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack); or
2. the disease to be treated is a contagious illness that poses serious consequences to the health of others (e.g., sexually transmitted disease)."

The Choice of the Margin in a NI Trial

ICH E10: "The determination of the **margin** in a non-inferiority trial is based on both *statistical reasoning* & *clinical judgment*, and should reflect uncertainties in the evidence on which the choice is based, and should be *suitably conservative*."

Future of PrEP and Microbicide Research

"Non-inferiority trials with non-rigorous margins allow substantial risk for accepting inadequately effective experimental regimens, leading to the risk of erosion in quality of health care…

Due to the inherent uncertainties in non-inferiority trials, alternative designs should be pursued whenever possible."

* Fleming TR, Odem-Davis K, Rothmann MD, Shen YL
Some essential considerations in the design and conduct of non-inferiority trials. *Clinical Trials* 8: 432-439, 2011