Standards of Evidence for Drug Approval:

An FDA perspective

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Evidence Standards

- How do we learn about new drugs?
- Origins of evidence standards
  - Safety
  - Efficacy
- Role of clinical vs. nonclinical evidence
- Recent changes in U.S. laws and regulations
  - Fast Track

Evolution of Evidence about Disease

Basic Science

- Molecular Phenomenology
- Causal Links
- Causal Chain

Clinical Science

- Clinical Phenomenology
- Pathophysiology
- Prognosis
- Progression
- Intervention

Evolution of Evidence about a Drug

Basic Science

- Molecular Structure
- Binding Characteristics
- in vitro biologic effects
- Animal models for safety and effectiveness

Clinical Science

- Pharmacology
  - Kinetics
  - ADME
- Pharmacodynamics
- Exploratory Clinical Studies
- Confirmatory Clinical Trials

Regulatory Responsibilities

Evidence Standards:

- To safely test new drugs for first-in-human trials:
  - Preclinical studies
- To assess chronic or special toxicity, difficult to assess in human trials:
  - Reproductive toxicity
  - Carcinogenicity
- To determine if the drug is safe and effective for an intended use

Law: New Drug Approval Evidence

Food Drug and Cosmetic Act

Any person may file an application …

A) Full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use;

Law: New Drug Approval Evidence

Food Drug and Cosmetic Act

A drug will be approved unless …

1) Do not include adequate tests by all methods reasonably applicable to show whether a drugs is safe …

5) … there is a lack of substantial evidence that the drug will have the effect that it purports …

Substantial Evidence

Safety

- Adequate Tests
  - by all methods reasonable

Effectiveness

- Substantial Evidence
  - from full reports of investigations

Effectiveness: Adequate & Well Controlled Trials

§ 21 CFR 314.126 *

The purpose of conduction clinical investigations is to distinguish the effect of a drug from other influences …

Generally the following types of control are recognized:

- Placebo concurrent control
- Dose-comparison concurrent control
- No treatment concurrent control
- Active treatment concurrent control
- Historical control

* CFR: Code of Federal Regulations

Adequate & Well Controlled Trials

Pivotal Trial Examples (HIV)

- Placebo concurrent control
  - Zidovudine
- Dose-comparison concurrent control
  - Aerosolized Pentamidine
- No treatment concurrent control
  - Foscarnate
- Active treatment concurrent control
  - Didanosine
- Historical control
  - Itraconazole (parenteral)

Evidence for Regulatory Decisions

Pharmacological

- Early Drug Development
  - Formulation Development
  - Food Effects
  - Drug Interactions
- Special Populations
  - Pediatrics / Elderly
  - Organ dysfunction
- Generic Drugs
  "Bioequivalence"

Clinical Efficacy

- First Marketing
- New Clinical Indications
- New Formulations

← *(sometimes)*

- New Schedule
- New Population

← *(sometimes)*

Regulatory Decisions

What is needed for Pharmacology data to replace clinical efficacy data?

- Robust PK / PD data
  - averages, variability
  - clinical populations
- Understanding of relationship between PK/PD and clinical effectiveness (and safety)
  - AUC ?
  - time above minimum ?
  - minimum above threshold ?

Regulatory Decisions

Why replace clinical efficacy data with pharmacology data?

- Earlier Decision Making
  - Conditional (accelerated approval) / Final decisions
  - PK/PD effects may be evident long before clinical benefit develops
- Decisions based on smaller data sets
  - PK/PD effects may be observed in all participants while only a small fraction may develop a clinical end-point
- Make better decisions (?)
  - Clinical Trials are noisy
    - Sample sizes needed for small differences in effects are too large
    - Clinical trials drift toward null, making small differences undetectable

Regulatory Motivations to Accept PK/PD

Waxman-Hatch Act (PK)

"Bioequivalence" becomes the evidence needed for generic drugs

Accelerated Approval Rules (PD)

Surrogate Markers (often pharmacodynamic drug effects) as basis for early drug approval

Pediatric Drug Development Rules (PK)

PK to establish dose in children, extrapolating from adults

FDA Modernization Act and Evidence

Evidence

- Single Trial Standard
  - Heightened importance of prespecified end-points
- Abbreviated reports for some studies
  - Full safety data
  - Efficacy only from key study(ies)
- Fast Track
  - Accelerated Approval
  - Rolling BLA's

Fast Track Products

Food Drug & Cosmetic Act

- Amended by the FDA Modernization Act of 1997 to include section 506: Fast Track Products *
- Authorizes FDA to:
  - Facilitate Development
  - Expedite Review
- Incorporates:
  - Subpart E Regulations (21 CFR 312.80 – 312.88)
  - Priority Review Policy

* Http://www.fda.gov/cder/guidance

Priority Review Policy

CDER

Products which provide a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease.

(Not limited to drugs for serious or life-threatening disease.)

CDER MAPP 6020.3

CBER

Products which provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease.

CBER SOPP 8405

FDA Modernization Act of 1997

Permits approval for marketing under:

505(c) of the FD&C Act *or*

351 of the PHS Act

"upon determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit."

i.e., the accelerated approval regulation* becomes law

* 57 FR 58942 Dec 11, 1992

Accelerated Approval

Key Features

- Reliable Surrogate Markers from adequate and well controlled trials
  - Evidence that SM predicts clinical benefit
- Need over existing treatments
- Adequate safety information
- Confirmatory trials underway to demonstrate clinical benefit

Accelerated Approval: Evidence

CFR 21 § 314.510 (drugs) § 601.41 (biologicals)

FDA may grant marketing approval for a new drug on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.

1992

Accelerated Approval: Evidence

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1992

Surrogate Marker

Definitions

A **surrogate marker** is a laboratory measurement, sign or symptom, that if changed by a therapy, would not, in and of itself, be clinically significant enough as a basis to evaluate therapeutic success.

A **surrogate end-point** is a pre-defined change in a surrogate marker that is a primary or secondary outcome of a treatment trial.

Surrogate Markers

Aliases

- Pharmacodynamic outcomes
- Drug-mechanism based outcomes
- Proof of Concept outcomes
- Disease status measures
- Prognostic assessments
- Molecular Markers

Surrogate Markers Validation

Limitations:

- Need trials with clinical benefit
- Need trials that measure both SM and clinical outcomes
- Time sensitivity of SM's
- Specificity of SM's
- Power
  - If SM's imprecisely predict clinical outcome you need very strong clinical effects to detect SM's with precision

FDA Modernization Act of 1997

Permits FDA to:

"Accept for review portions of a marketing application prior to receipt of the complete application."

i.e., the rolling NDA/BLA become law

Fast Track Qualification

Two Criteria:

Intended to treat a serious or life threatening condition

Potential to address unmet medical needs for the condition

Serious or Life Threatening Conditions

Whether a Condition is Serious:

"… is a matter of judgement, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease if left untreated would progress from a less severe condition to a more serious one." *

Morbidity need not be irreversible providing it is persistent or recurrent.

* 57 FR 13234 Apr 15, 1992

Serious or Life Threatening Conditions

Whether a Condition is Serious:

Examples:

- AIDS and HIV Infection
- Alzheimer's Dementia
- Angina Pectoris
- Heart Failure
- Cancer
- Inflammatory Bowel Disease
- Asthma
- Rheumatoid Arthritis
- Diabetes Mellitus
- Systemic Lupus Erythematosus
- Depression
- Psychosis
- And Many Others

Serious or Life Threatening Conditions

Whether a drug is intended to treat serious conditions:

- a therapy directed at serious symptoms or serious manifestations of the condition;
- a diagnostic evaluated for the impact on a serious aspect of the condition;
- a preventive intended to prevent a serious aspect;
- a product which could ameliorate serious side effects of other treatments.

Potential to Address Unmet Medical Needs

A medical need not met by existing therapy:

- no existing therapy;
- new therapy is better;
- new therapy for patients intolerant or unresponsive to existing therapy;
- new therapy is less toxic (with similar benefit);
- new therapy improves compliance (which is shown to improve effects on serious conditions)

Requesting Fast Track Designation

When

Any time prior to filing an NDA or BLA;

How

As an IND amendment

Guidance on Content

Sept 1998 Guidance on CBER and CDER web

FDA Response

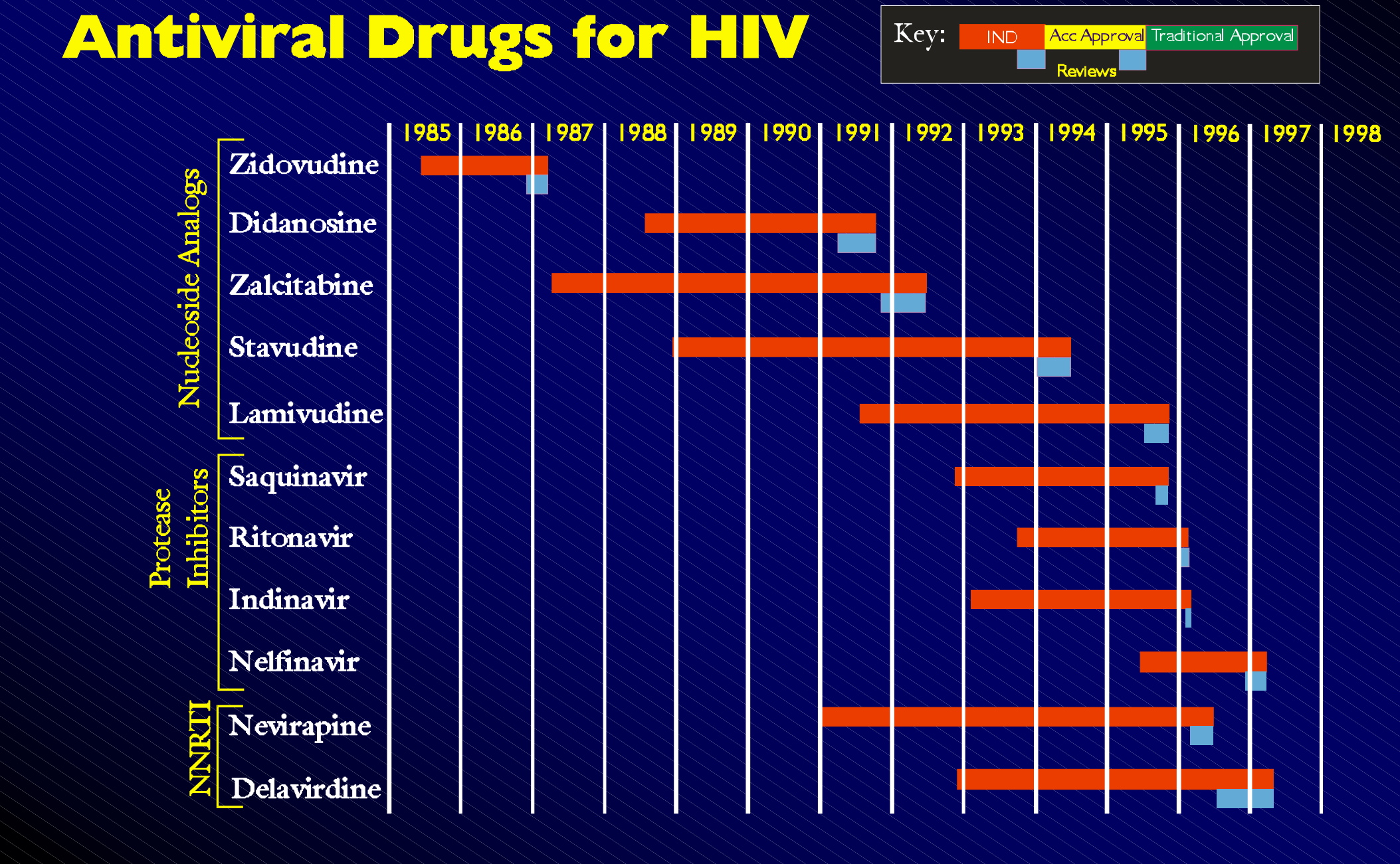
Within 60 days: Designation Letter

Programs for Expediting Development and Review

Meetings:

- Pre-IND consultations
- End of Phase 1
- End of Phase 2
- Pre NDA/BLA
- Early Labeling Meeting

Antiviral Drugs for HIV



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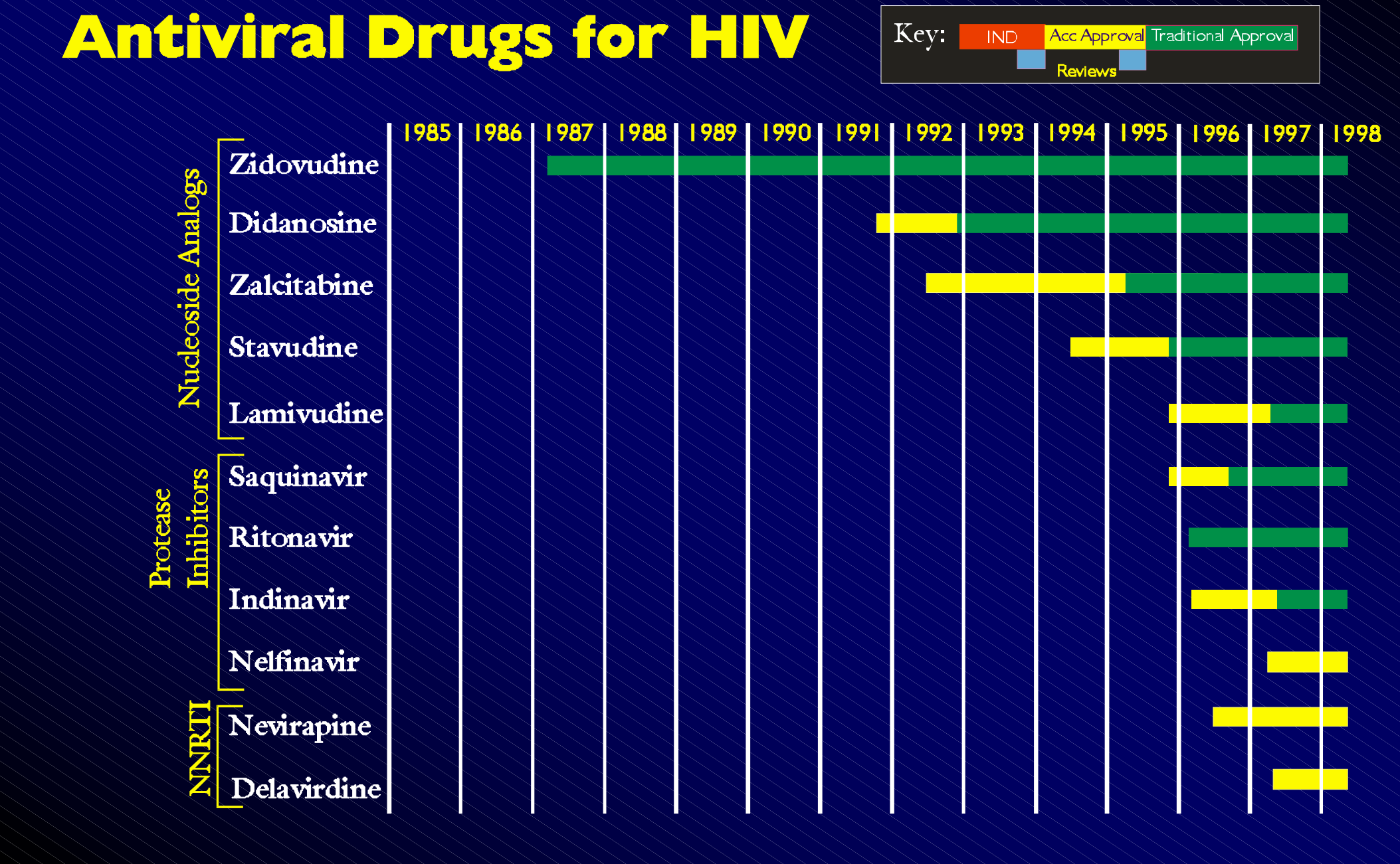

Acceleration: Options

- Intensify
- Telescope
- Combine
- Shorten
- Simplify
- Skip
- Postpone

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Lower Standards?