

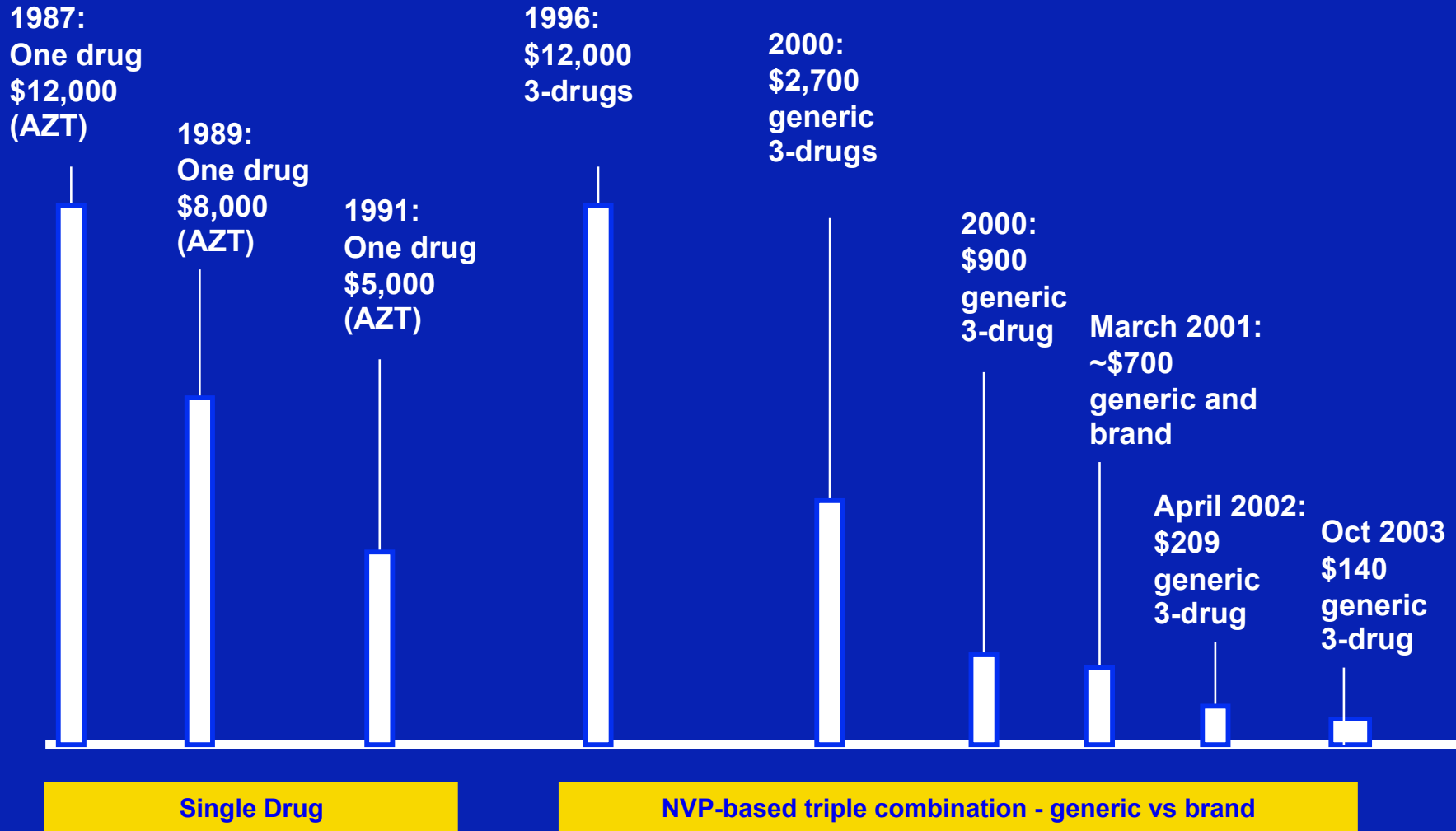
# Medical timeline

• Observation or research idea	Y0
• Pilot study	
- design, ethics approval, screen enroll	1-2 years
- run study, preliminary analysis	+6 months
• Conference abstract	+6 months
• Write up paper, submit to publication	+6 months
• Published data	+6 months
• Guidelines and clinical practice	???
Total	3-4 years

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# ARV drug pricing

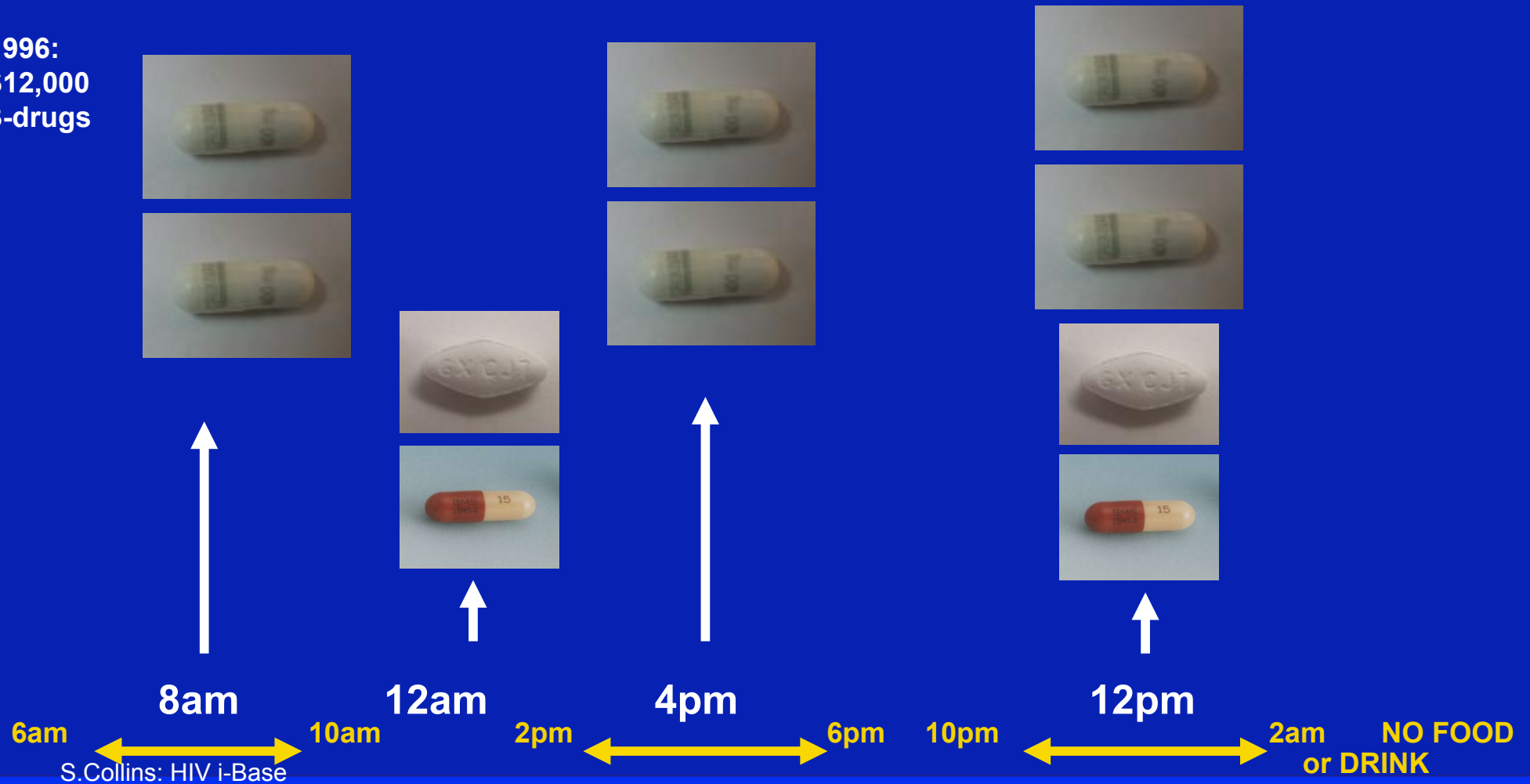


# Indinavir-based combination: 1996

Indinavir: Every 8 hours. No food for 2 hours before AND 2 hours after (ie 12 hours fasted through each day). PLUS drink 2 litres water to minimise risk of kidney stones

3TC: Every 12 hours; d4T: Every 12 hours

1996:  
\$12,000  
3-drugs



# Saquinavir-based combination: 1995

Saquinavir (INVIRASE)\*: Every 8 hours. Serious issues with absorption (originally recommended to take with grapefruit juice to boost levels. All patients in the Netherlands doubled the saquinavir dose.

ddl: 4 large chewable tablets, once daily. Taken on an empty stomach, with no food for 2 hours afterwards.

AZT: One capsule every 12 hours

\* NOTE: when FORTOVASE, the new formulation of saquinavir was approved in 1997 the dose increased to



6am

8am

12am

4pm

12pm

4am



8am

NO FOOD or DRINK

S.Collins: HIV i-Base

# Saquinavir-based combination: 1998

Saquinavir (FORTOVASE): Approved as 6 capsules every 8 hours but in practice generally given as 8 capsules every 12 hours. This did not overcome the issue of absorption, which required boosting by zidovudine. Manufacturers of each drug promote research showing why higher doses of their respective drugs was the preferred dose. FORTOVASE was discontinued in 2006.

ddl: 4 large chewable tablets, once daily. Taken on an empty stomach, with no food for 2 hours afterwards.

AZT: One capsule every 12 hours



8am

12am

12pm

6am

← 10am

NO FOOD or DRINK

S.Collins: HIV i-Base

# First-line combination: 2006

Efavirenz: one 600mg capsule, once daily at night

+ Truvada: one tablet, once daily \*\*

OR

Efavirenz: one 600mg capsule, once daily at night

+ Kivexa: one tablet, once daily

\*\* A single pill, once-daily combination of efavirenz + Truvada has been filed with the FDA and is expected to be approved in 2006/7.



12pm

**DON'T TAKE WITH HIGH FAT MEAL**

# 20 Approved ARVs in US/Europe

## different access in Western countries

- ✦ AZT 1987
- ✦ ddl 1991
- ✦ ddC 1992
- ✦ d4T 1994
- ✦ 3TC 1995
- ✦ saquinavir 1995
- ✦ indinavir 1996
- ✦ ritonavir 1996
- ✦ nevirapine 1996
- ✦ delavirdine 1997
- ✦ nelfinavir 1997
- ✦ efavirenz 1998
- ✦ abacavir 1998
- ✦ amprenavir 1999
- ✦ lopinavir 2000
- ✦ tenofovir 2001
- ✦ T-20 2003
- ✦ atazanavir 2004
- ✦ Fosamprenavir 2004
- ✦ FTC 2004



# Co-Formulations and combinations

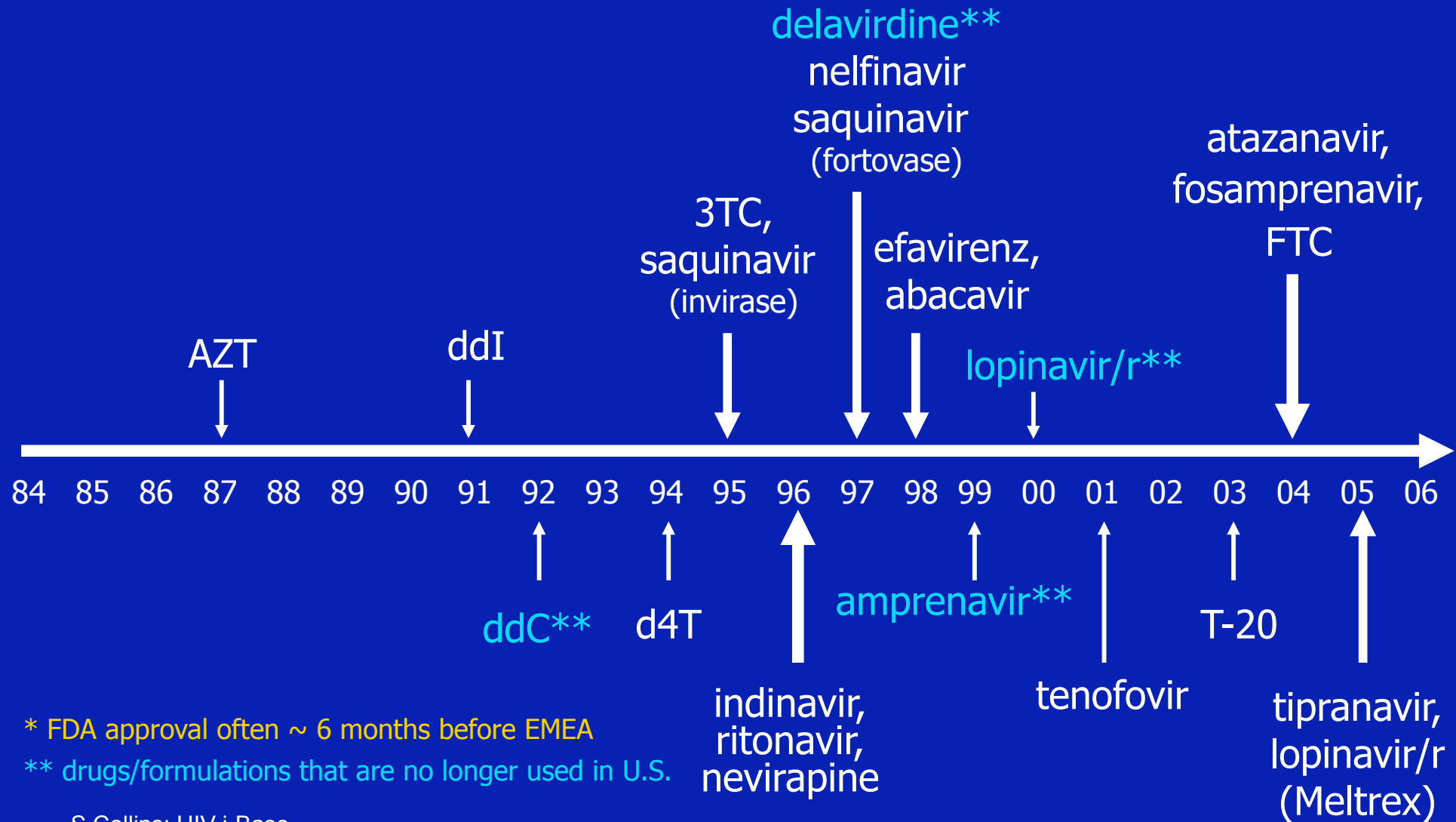
## US/Europe

- ✦ AZT+3TC
- ✦ AZT+3TC+abacavir
- ✦ abacavir+3TC
- ✦ Tenofovir+FTC
- ✦ Kaletra (lopinavir/r)

## Generic (via India etc)

- ✦ AZT+3TC
- ✦ d4T+3TC
- ✦ AZT+3TC+abacavir
- ✦ AZT+3TC+nevirapine
- ✦ d4T+3TC+nevirapine
- ✦ Kaletra (lopinavir/r)
  
- ✦ ddl+3TC+efavirenz - KIT

# ARV approval timeline (FDA\*)

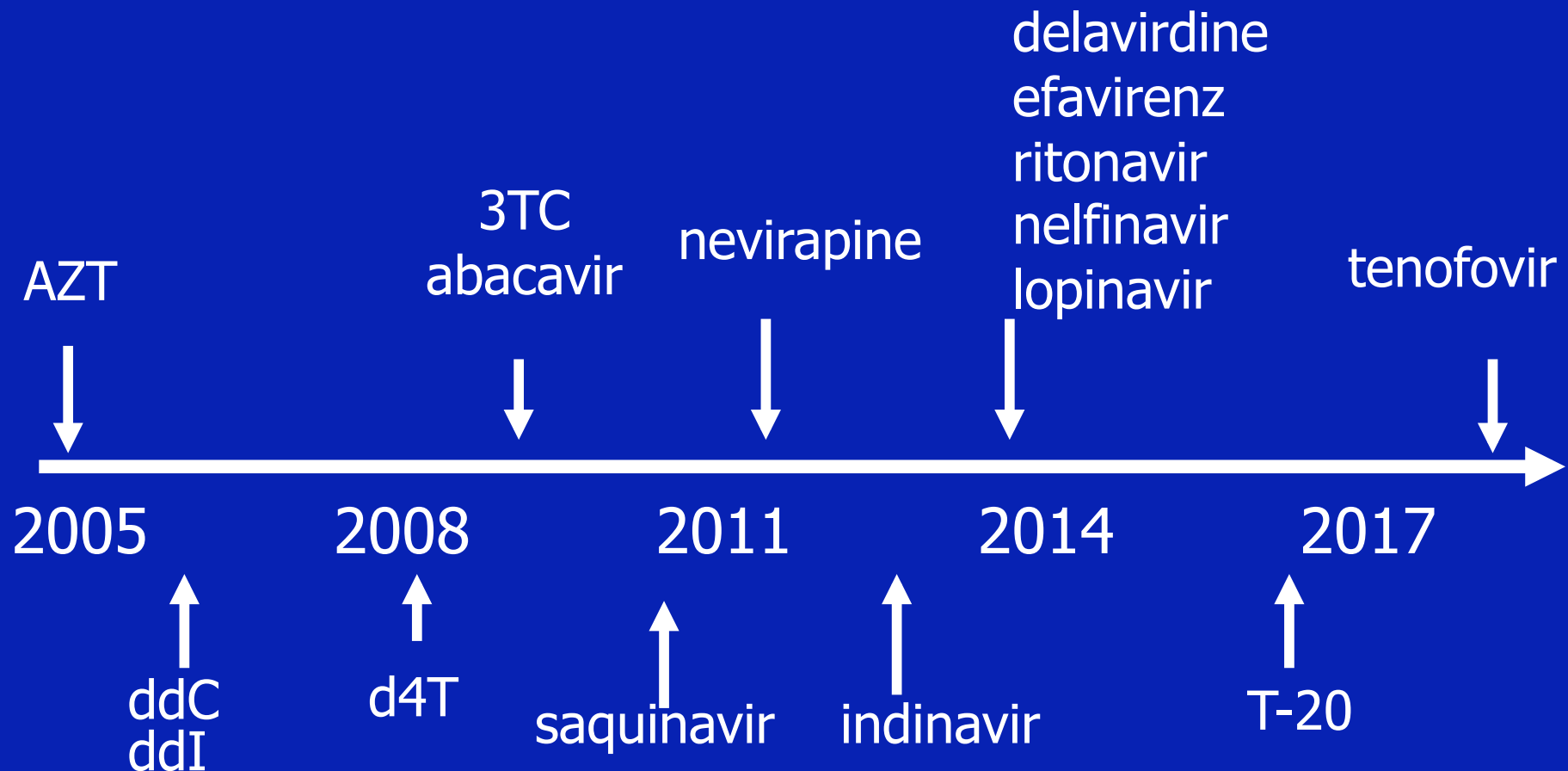


\* FDA approval often ~ 6 months before EMEA

\*\* drugs/formulations that are no longer used in U.S.

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# Approx patent expiry dates



# HIV Drug Pipeline Compounds

## Nukes:

Reverset (D-D4FC)

Amdoxovir (DAPD)

GS 7340 (tenofovir prodrug)

## NNRTIs:

capravirine - PIII

TMC 125

TMC 278 (rilpivirine)

## PIs:

tipranavir - PIII

TMC 125

## Other targets:

### Integrase Inhibitors

S1360 - GSK

L-870,810 - Merck

## Entry inhibitors:

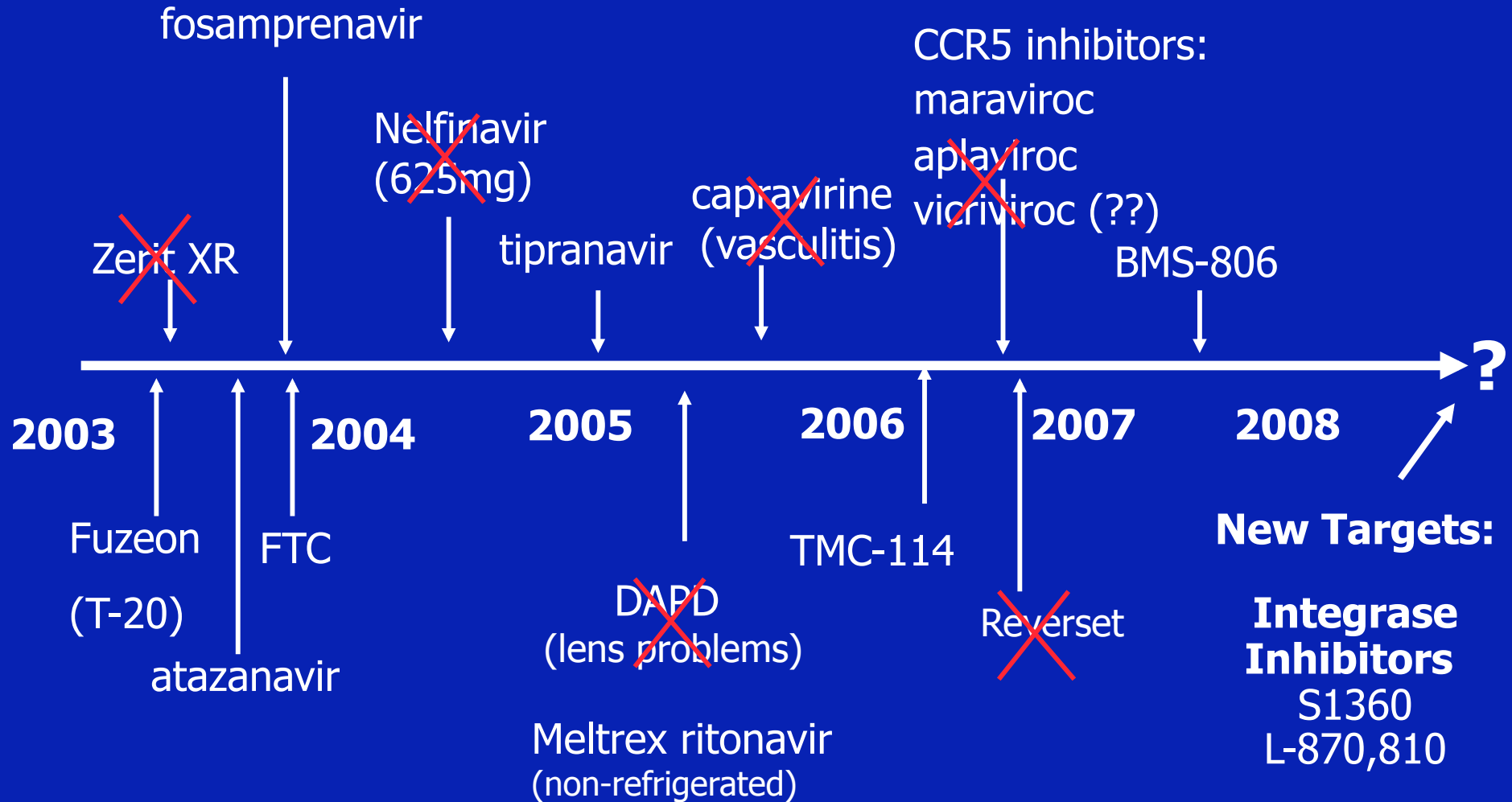
- (1) attachment inhibitors  
PRO 542 and BMS 806
- (2) co-receptor antagonists of CXCR4 (T-22, PA-14 and TAK-779 and CCR5 T-22, PA-14 and TAK-779
- (3) fusion inhibitors (T-1249)

## Microbicides

## Vaccines

## PreExposure Prophylaxis

# Recent HIV Drug Pipeline



# Recent promising failures

Development stopped after clinical studies due to toxicity (T), efficacy (E) or formulation (F)

- **dOTC - monkeys died**
- **DPC-681- toxicity**
- **DPC-684 - toxicity**
- **DPC 961- suicidal patients**
- **emivirine (MKC442) - efficacy**
- **MK914 - kidney toxicity**
- **nelfinavir 625mg form. (2004)**
- **d4T ER - formulation (2004)**
- **DAPD, amdoxovir (2004)**
- **DMP450 - efficacy**
- **TMC 126 - dropped**
- **TMC 120 - dropped**
- **DPC 817- toxicity**
- **adefovir - kidney toxicity**
- **Iodenesine - liver toxicity**
- **capravirine - efficacy (2005)**
- **aplaviroc - liver toxicity**
- **reverset - pancreatic tox (2006)**