The Drug Development Process

- Drug Discovery: 10,000 Compounds
- Pre-Clinical: 250 Compounds
- Clinical Trials: 5 Compounds
- FDA Review
- Large Scale Manufacturing / Phase IV: 1 FDA Approved Drug

- Phase I: 20-100 Volunteers
- Phase II: 100-500 Volunteers
- Phase III: 1000-5000 Volunteers

- Drug Discovery: 5 years
- Pre-Clinical: 1.5 years
- Clinical Trials: 6 years
- FDA Review: 2 years
- Large Scale Manufacturing / Phase IV: 2 years
Target discovery

• The first stage of drug development is to identify the target.
• These are often proteins in the body or microorganism that are associated with a disease.
• With HIV the targets are things like the CCR5 co-receptors, or the mechanism that helps HIV change from a single strand of RNA into a double strand to DNA.
Drug discovery

• Once the targets are identified screening tools and computer databases are used to identify chemical compounds that could bind to the identified target.

• If a compound is found that affects the target in a way that could alter the disease it is then monitored to improve safety and effectiveness, eventually becoming a ‘drug candidate’.

• Of 10,000 ‘hits’ tested in early drug discovery only 1 will become a drug that reaches market.
Pre-clinical studies

• Prior to human clinical trials there are cell studies to look at activity and toxicity.

• Then animal studies to look at toxicity and elimination – rat, dog, macaque. Different animals used for different types of studies and different type of drug.

• Promising drugs often shelved based on rat or dog toxicity.

• Research into early formulations - tablet, capsule or injection.

• Pre-clinical results submitted to regulatory authorities (in the US, to the FDA), as an Investigational New Drug (IND) – needed before move to clinical phase.
Phase I studies

• Phase I studies are the first human studies. These usually enrol ‘healthy’ (HIV negative) people.

• Phase Ia: single-dose studies usually in HIV negative people.
  • A small group of patients (5-10) will take one single dose and be carefully monitored.
  • 1-2 patients usually get a placebo.
  • At this stage they’re just testing for safety—that the compound is not a poison.

• Phase Ib:
  • Short-term multi-dose studies, perhaps for 1-2 weeks
  • This where a slightly larger group (10-20) will take multiple doses and be carefully monitored.
Phase II Studies

Phase II studies are usually the first study to look at whether the investigational compound is actually active. (i.e. that it does what is needed)

Enrol HIV-positive people.

Can last one day, or 1-2 weeks or several months.

Phase IIa studies
• usually enrol 20-50 people with 8-12 people in each arm.
• may include different mg doses or dosing (once vs twice daily).
• Involve intensive PK monitoring.

Phase IIb studies
• also look at different doses of a drug called ‘dose finding’ studies.
• Often 200-300 people with 50-100 people in each arm.
Phase 3 studies

• For an HIV drug this is usually 800 – 1500 patients.

• large, randomised, double-blinded, often placebo controlled trials.

• safety monitored by an independent drug safety monitoring board (DSMB)

• Used to collect main efficacy and safety data and determine whether regulatory agencies like the EMA in Europe or the FDA in the U.S. will approve a new drug or new indication.

• Some drugs in phase III studies are not approved – recently this includes CCR5 inhibitor vivriviroc
Phase 4 studies

• Usually referred to as ‘post-marketing’ safety studies.

• Longer follow-up of looking at side effects and other safety concerns, perhaps in different populations to original studies.

• Sometimes to look for rare side effect, or a side effect that takes years to develop, not seen in Phase III or earlier studies.

• Phase IV studies are usually recommended by the regulatory agencies.

• Phase IV studies are now compulsory and the EMEA can withdraw a medication if safety commitments are not followed.
Promising Failures

- dOTC - monkeys died
- DPC-681 - toxicity
- DPC-684 - toxicity
- DPC 961 - suicidal pts
- emivirine - poor activity
- MK914 - kidney tox
- Reverset dFC - efficacy
- DMP450 - poor activity
- TMC 126 - dropped
- TMC 120 - dropped
- DPC 817 - toxicity
- adeovir - kidney toxic
- lodenesin - liver tox

Manufacturing problems:
- d4T once-daily;
- Nelfinavir 625mg
- Brecanavir - PI