Emerging Therapy

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- The views presented are mine and do not represent those of DAIDS or NIH
- I have no conflicts of interest to disclose

Current Formulation

- **Guidelines: 2 nucleosides + NNRTI or PI**
- **Largely based on historically available agents**
- **Sequence:**
  - AZT, ddI, d4T first, 0.5-0.8 log VL decrease
  - 2 nucs > 1, up to 1.5 log VL decrease
  - Add PI, 2.5+ log VL decrease
  - NNRTI ~ 1.8 – 2.5 log VL decrease

ACTG 5142

- Explored the possibility of PI + NNRTI in one arm without nucs
- Showed no benefit (or had other problems) compared to nucs + NNRTI or PI

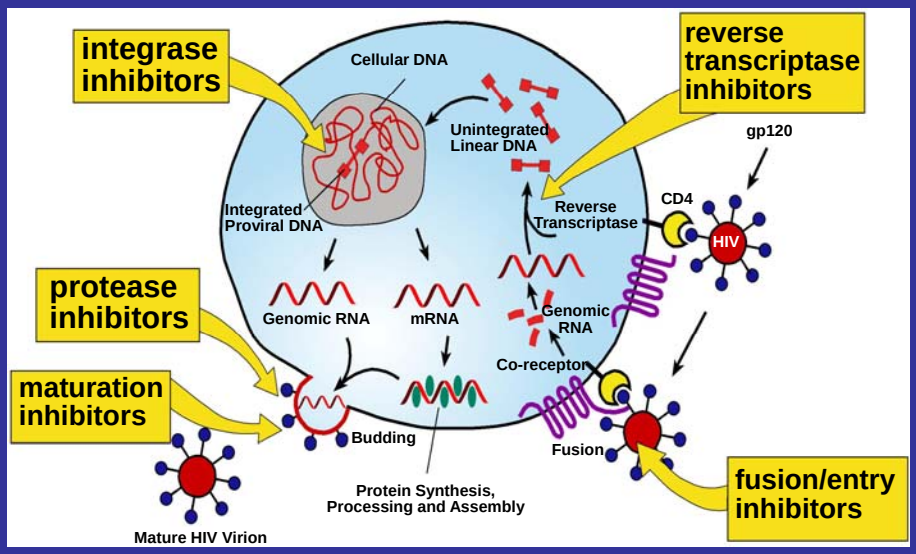
Newer Approaches, Since ~2001

- Better nucs (TDF, ABC)
  - Less toxicity
  - Improved tolerability
  - More convenient, especially with co-formulations
- Better PIs
  - Routine boosting
  - Greater intrinsic activity
  - Less resistance propensity

Newer Classes of Agents

- **CCR5 inhibitors**
  - Maraviroc approved
  - Vicriviroc in advanced trials
- **Integrase inhibitors**
  - Raltegravir approved
  - Elvitegravir in advanced development
- **Other potential agents – entry and assembly inhibitors**
  - PRO 140
  - Beviramat and Myriad agent

HIV Replication Cycle: Targets for Antiretroviral Therapy



FDA-Approved Antiretroviral Drugs

NRTI
- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

NNRTI
- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine

Fusion Inhibitor
- Enfuvirtide (T-20)

PI
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Entry Inhibitor
- Maraviroc

Integrase Inhibitor
- Raltegravir

Combinations
- 6 available, combining 2 or 3 drugs

Current Paradigm

- Current recommendations yield ~90% responses for a year or more
- Should we consider other approaches?
  - In the context of many years of therapy, with the challenges of behavior/adherence
  - Can a better approach to prevention of transmission use other agents
  - Cost issues, especially long-term

Combinations: which and why

- Siliciano proposes a log/log assessment of current drug activity (rather than semi-log)
  - Suggests activity of PIs may be greatest
  - DRV up to 8 logs activity (and IDV, SQV a bit less)
  - NNRTIs next (2-3 logs), then all others, including new agents (~2 logs)
- May explain why more than 3 drugs offers little, currently, but how to improve?

Studies with Newer Agents

STARTMRK

- Ral (no rtv) vs EFV, both + TDF/FTC
- 560 patients, mostly male and black (US epi)
- 86% vs 82% <50 copies at 48 weeks
- Slightly greater CD4 increase with ral

- Ral qd? Co-formulations? Next likely agent elvitegravir, with quad pill (ELV/TDF/FTC + proprietary booster) in studies

ARTEMIS

- QD darunavir vs LPV/r, both + TDF/FTC
- 800 subjects
- 84% vs 78% <50 at 48 weeks, 79% vs 71% at 96 weeks

- This and the next study mentioned may suggest LPV/r may not be as good after 1 – 2 years, considering tolerability and lipids

CASTLE

- ATV/r vs LPV/r, both + TDF/FTC
- 883 patients
- At 96 weeks 74% vs 68% <50 copies

MERIT

- MVC bid vs EFV, both with CBV
- 740 subjects
- 69% vs 65% <50 copies at 48 weeks
- Issues may be identification of R5 and use of CBV rather than TDF/FTC

When to Start?

- NA ACCORD
  - 8300 patients, 22 cohort collaboration
  - CD4 <350 vs above, 1.7 relative risk of illness if wait (1.4 if >500)
- Prospective studies
  - START, a population trial of >500, Rx or wait to <350?
  - Individualization approach, based on genomics, PK, host factors, etc.

New Agents - I

- What is their proper role? Should they be employed in initial therapy? Long-term effects need to be defined
- CCR5 inhibitors may be immunoadjuvants
  - Is this true? Are the cells functional?
- Integrase inhibitors
  - Does more rapid viral decline reflect the reservoir?

New Agents- II

- Should other potential targets (assembly, regulatory proteins) be pursued?
  - What is the pipeline?
- Pair new classes with new PIs – preserve NRTI/NNRTI (with simpler approach for promoting adherence, avoiding resistance) for second line?
  - Will this strategy prolong clinical response?
  - How to accomplish international roll-out?

"Really Radical" Thinking 1

- How about an R5 inhibitor + an integrase inhibitor, going to nuc/NNRTI or PI as second line?
  - Does it result in greater durability through 2nd line?
  - Is it more in line with current understanding of pathophysiology?
  - If BID, does this matter?
  - Do we need this? Who should fund studies?

"Really Radical" Thinking 2

- Can we identify (and then Rx) "true" acute infection?
  - Epi testing?
  - Feibig 1,2 pre-seroconversion
- Will this facilitate Rx of high-risk transmitters?
  - Can we identify other high-risk transmitters, besides the acutely infected?

"Really Radical" Thinking 3

- What may be the effect of adding or substituting suppression of
  - Immune activation
  - Inflammation
  - Gut translocation
- Can HIV reservoirs be purged, resulting in a true cure?

History will judge us as a global community by what we will do in the next 27 years as much as by what we have accomplished in the first 27 years.