ACTIVATE
The tribulations of a panobinostat/ interferon-α cure trial

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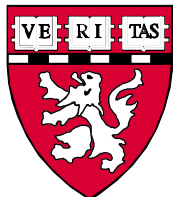
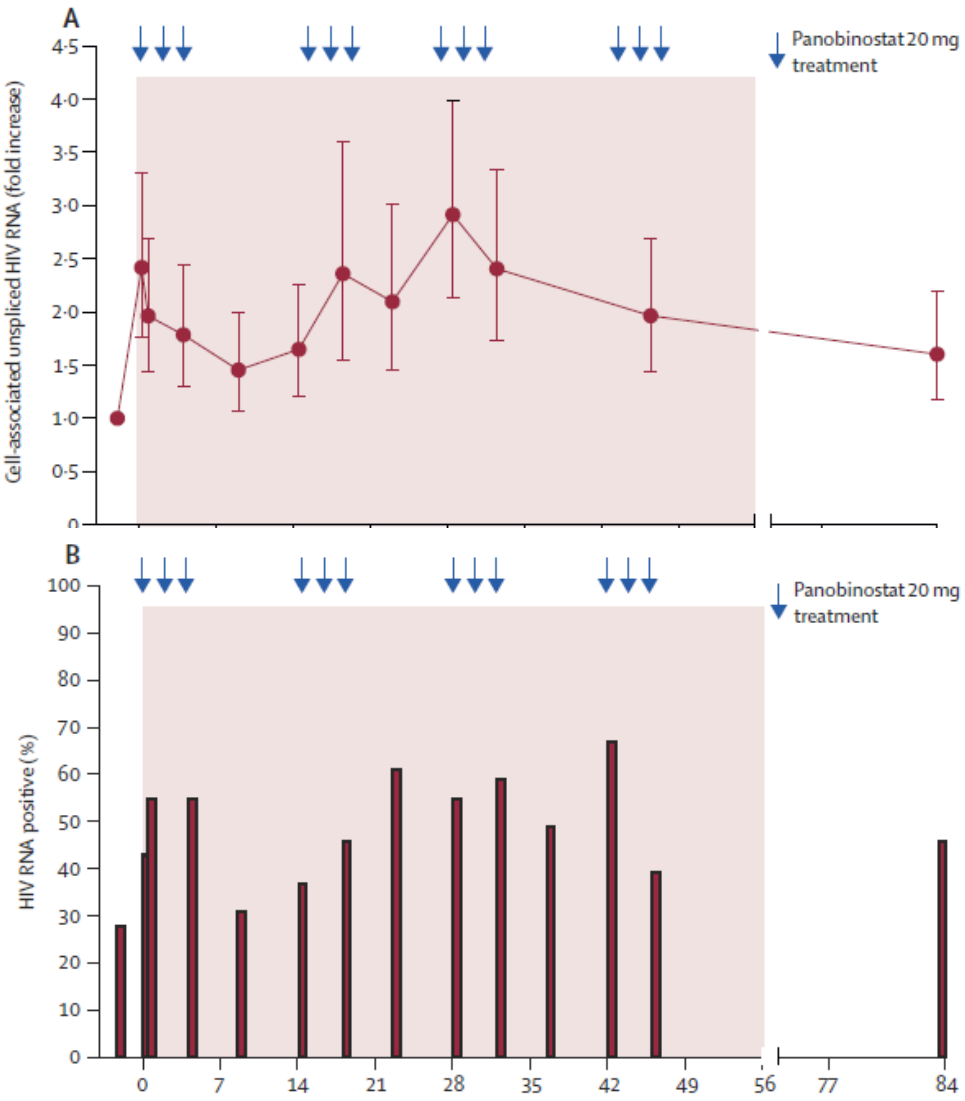


Background

- **HDACi are effective in reversing viral latency in 4 studies (Panobinostat, Vorinostat x2, Romidepsin)**
- **No significant HIV-1 DNA decline in any study**
- **Failure to reduce HIV-1 DNA attributed to insufficient immune-mediated clearance**
- **Two studies ongoing to test combinations of HDACi and CTL vaccines**
  - Denmark: Romidepsin + Vacc4x (see CROI 2016)
  - Oxford: Vorinostat + ChAdV63/MVA vaccine

Panobinostat



Rasmussen TA et al Lancet HIV 2014

Study Hypotheses

- Panobinostat reverses HIV-1 latency
- IFN-α activates innate effector cells and induces ISG expression
- Combined use of both agents leads to innate immunity-dependent elimination of cells in which viral reactivation is induced by panobinostat

Rationale

- **Panobinostat increases HIV-1 RNA in CD4 T cell in prior study (Rasmussen et al, Lancet HIV 2014)**
- **Some patients experienced 70-80% decline of HIV-1 DNA**
- **HIV-1 DNA decline during panobinostat treatment associated with delayed viral rebound kinetics during ATI**
- **Decline of HIV-1 DNA during panobinostat treatment associated with**
  - Higher numbers of activated NK cells
  - Higher frequencies of pDC
  - Distinct ISG expression patterns
  - IL28B “CC” genotype

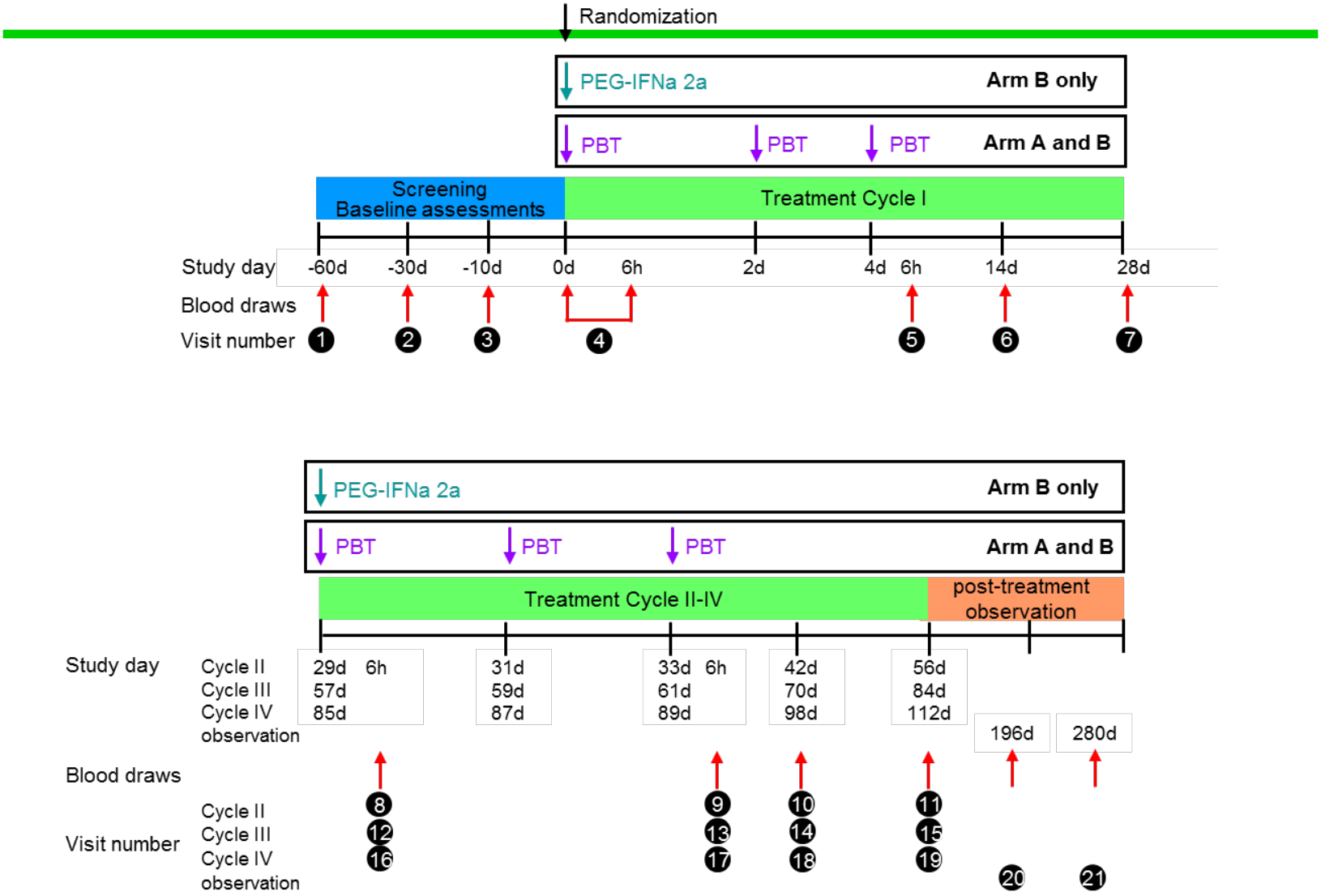
Design

- Prospective, randomized, single-center, open-label phase II clinical trial
- Treatment arm A: panobinostat
- Treatment arm B: panobinostat + PEG-IFN-α2a
- 1:2 randomization

Participants

- N=30 total
- All patients on suppressive ART for at least 24 months
- Participants with early and late initiation of ART eligible
- No major pre-existing comorbidities
- Pregnant or breastfeeding patients not eligible
- All participants must use effective contraception
- Cannot take medication known to prolong QTc or strong/moderately strong CYP3A4 inhibitors

Study scheme



Treatment regimen

- Panobinostat 20mg po QOD (M, W, F) p. o.
- PEG-IFN-α2a one s. c. shot during each treatment week (Arm B only)
- Each treatment week interrupted by three weeks off-treatment
- Four treatment cycles in total
- ART continued for entire study; only NRTI, NNRTI and Integrase Inhibitors permitted

Endpoints and Statistics

- Primary efficacy: HIV-1 DNA levels in CD4 T cells at end-of-study in comparison to baseline, in Arm A vs Arm B.
- Primary efficacy endpoint will be met if $p<0.05$ between treatment arm A vs B (Wilcoxon test)
- Primary safety: Number of AEs and SAEs; study not powered for safety comparisons between Arm A and B.
- Secondary: QVOA, innate immunity, adaptive immunity, ISG expression profile, T cell subset reservoirs, immunogenetic studies, immune activation
- Secondary analysis of virologic and immunologic parameters between carriers of specific HLA and IL-28B genotypes

Safety and Toxicity

- Investigator Safety Review Committee: Kuritzkes, Lichterfeld, Gandhi, Lu
- Non-investigator Safety Monitoring Committee: Hirsch (MGH), Gallant (JHU), Bosch (HSPH)
- All AEs and SAEs recorded at each visit
- Possible side effects: Fatigue, N/V, CBC changes, LFT increases, QTc prolongation – all expected to be minor (<or equal to grade 2) based on prior experience
- Toxicity further minimized by three week off-treatment between each treatment week
- General: tolerate grade 1/2 toxicity; d/c treatment in case of grade 3/4 toxicity unless limited to laboratory abnormalities

FDA Discussions

- **Initial input from FDA (9/12/14)**
  - Concern re: panobinostat toxicities
    - Mutagenicity
    - Hematological toxicity
    - Cardiac toxicity
    - GI toxicity
  - Participants should have alternative ART regimens available
  - More conservative management of AEs

FDA response to IND applicaton

- **Full clinical hold (7/31/15)**
  - Black box warning in panobinostat label
    - Cardiovascular toxicity
    - Severe diarrhea
  - Hemorrhage, myelosuppression, infection
  - CLEAR study too small to provide reassurance
  - Lack of equipoise
  - Require *new data* regarding panobinostat safety

FDA conference

- **Teleconference (10/23/15)**
  - FDA, investigators, DAIDS, Novartis
  - Primary concern is potential for cardiac toxicity
  - Secondary concern is mutagenicity
  - Suggest starting with lower doses, shorter courses

Protocol modifications

- **Three graded steps with increasing panobinostat dosages**
  - 5 mg (6 participants)
  - 10 mg (6 participants)
  - 15 mg (15 participants)
- **First two cohorts are for safety (randomized 2:1 to receive IFN-α or control)**
- **Third cohort is for activity (randomized 2:1 to receive IFN-α or control)**
- **Additional screening tests required**
  - Stress-ECHO

Resolution

- **Full clinical hold removed (2/12/16)**