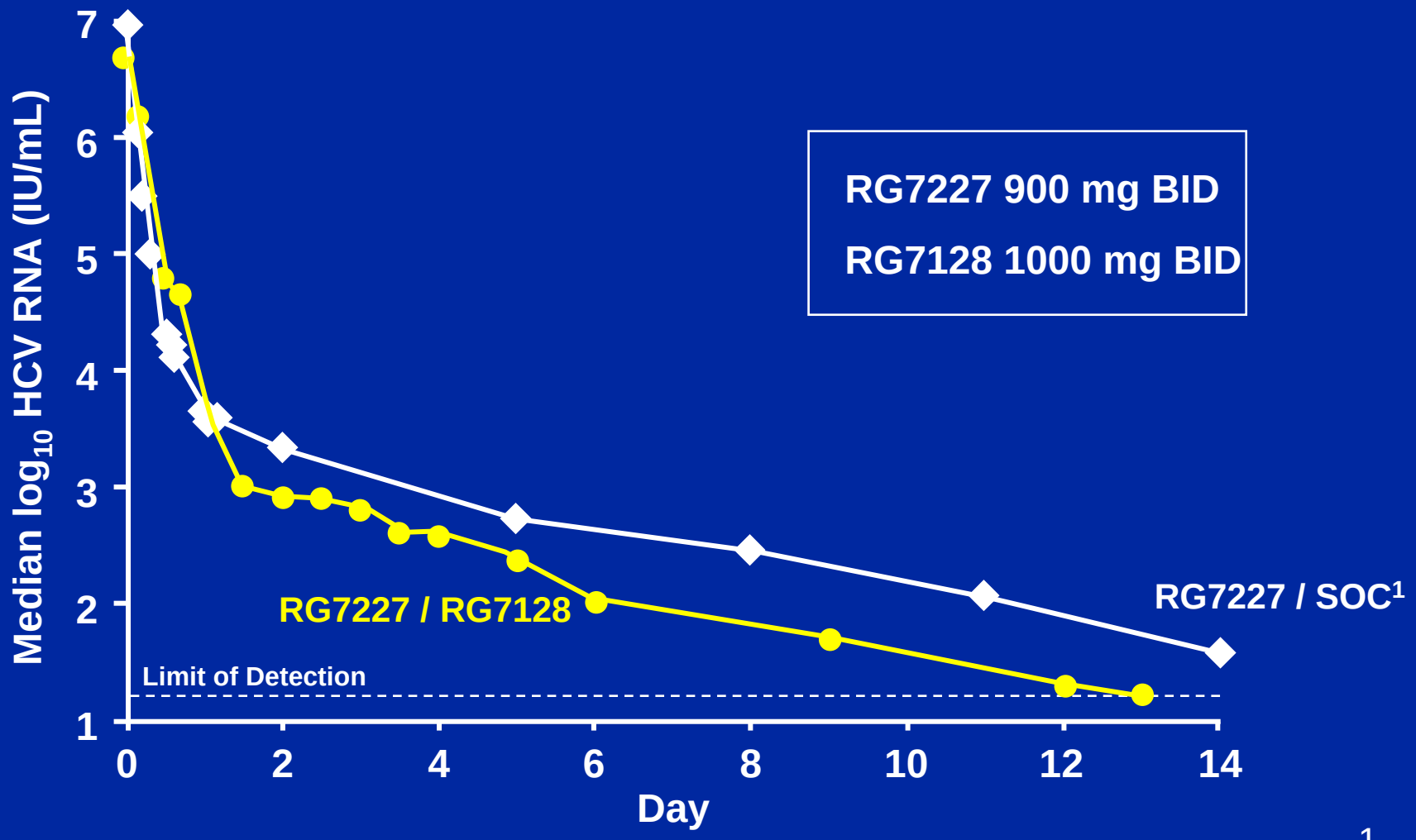
Comparison of Viral Kinetic Profiles of RG7227 plus RG7128 versus RG7227 plus SOC in G1 Naive Patients

see Morcos et al., AASLD 2009 poster #1594

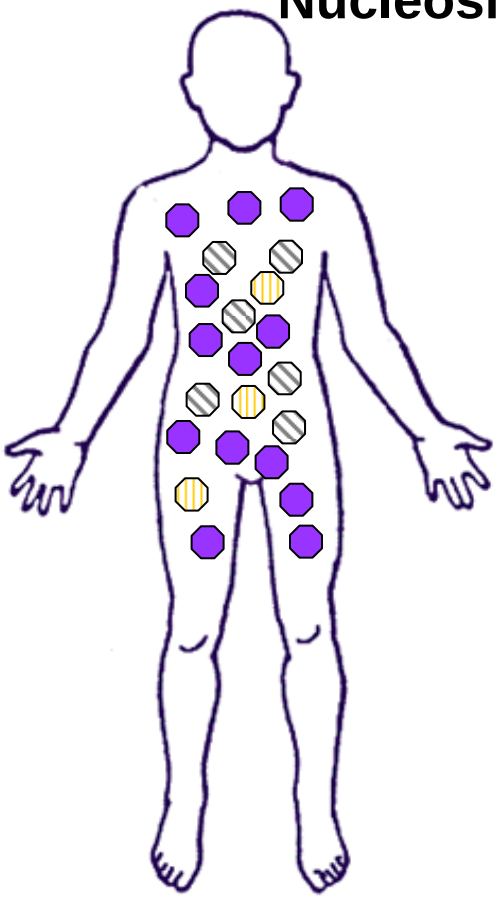


1. Forestier et al. EASL 2009; Abstract #1847

Considerations for trials with two or more DAA

- Duration of IFN-free therapy to achieve SVR is unknown
  - 12 weeks - 16 weeks - 24 weeks - ?
- Issues associated with longer term dosing of small molecules may arise
- We can look at basic principles from Infectious Diseases:
    - TB prophylaxis and treatment
    - Malaria prophylaxis
    - HIV
- Need to design DAA regimens to minimize resistance, chronic toxicities, and drug-drug interactions

Nucleoside/tide Inhibitors Have A Higher Barrier to Resistance



Treatment Naïve HCV+ Patient

***Option 1*: Treatment with Nucleoside/tide Inhibitor**

Few resistant variants within the viral swarm

***Option 2*: Treatment with a Non-Nucleoside Inhibitor**

Higher proportion of non-nucleoside-resistant variants within the swarm

***Option 3*: Treatment with a Protease Inhibitor**

Higher proportion of protease-inhibitor-resistant variants within the swarm

Viral quasispecies

- Wild-type virus
- Nucleos(t)ide-resistant variant
- Non-nucleoside-resistant variant
- Protease inhibitor-resistant variant

1. Uzgirug et al HepDart 2007
2. Kuntzen T et al Hepatology 2008;48:1769

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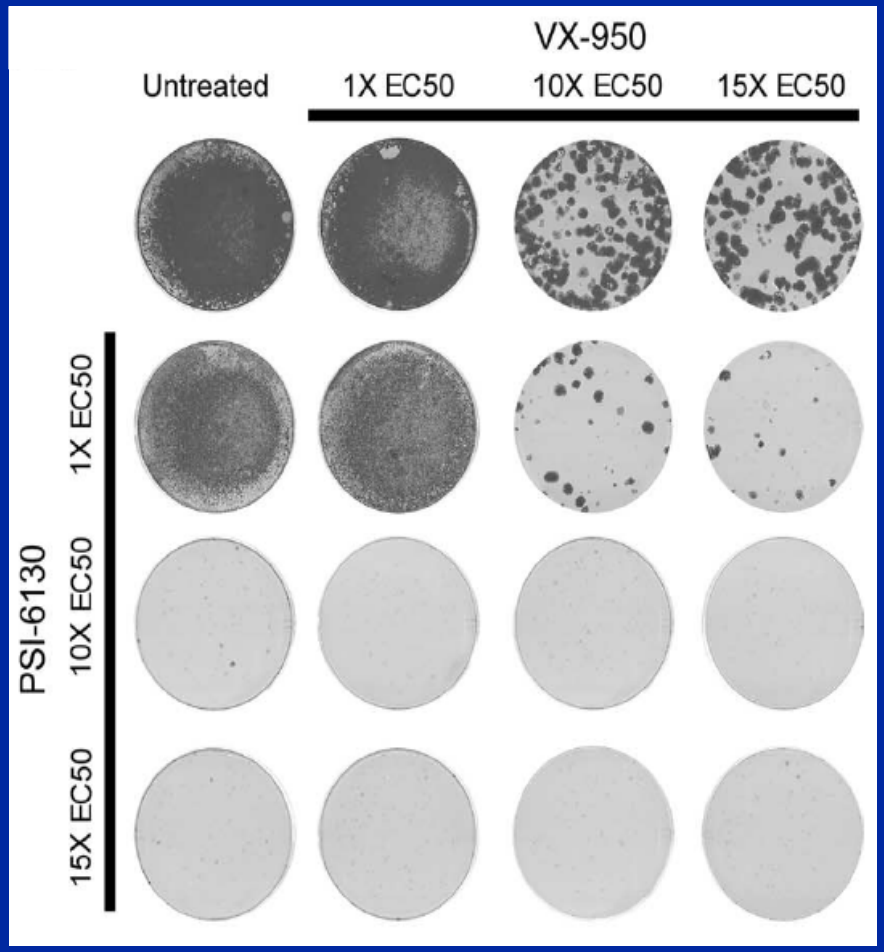
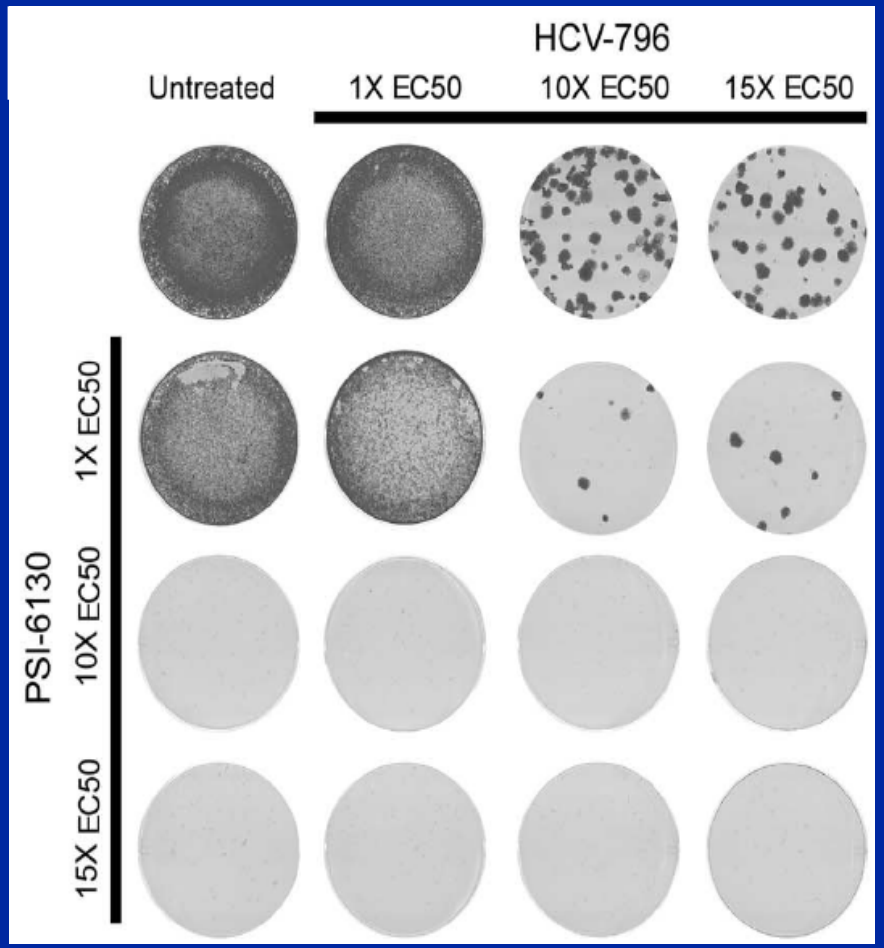
Nucleoside analogs can prevent development of resistance to protease or to non-nucleoside polymerase inhibitors





In vitro data show nucleoside analogs can suppress the emergence of resistance to VX-950 and HCV-796

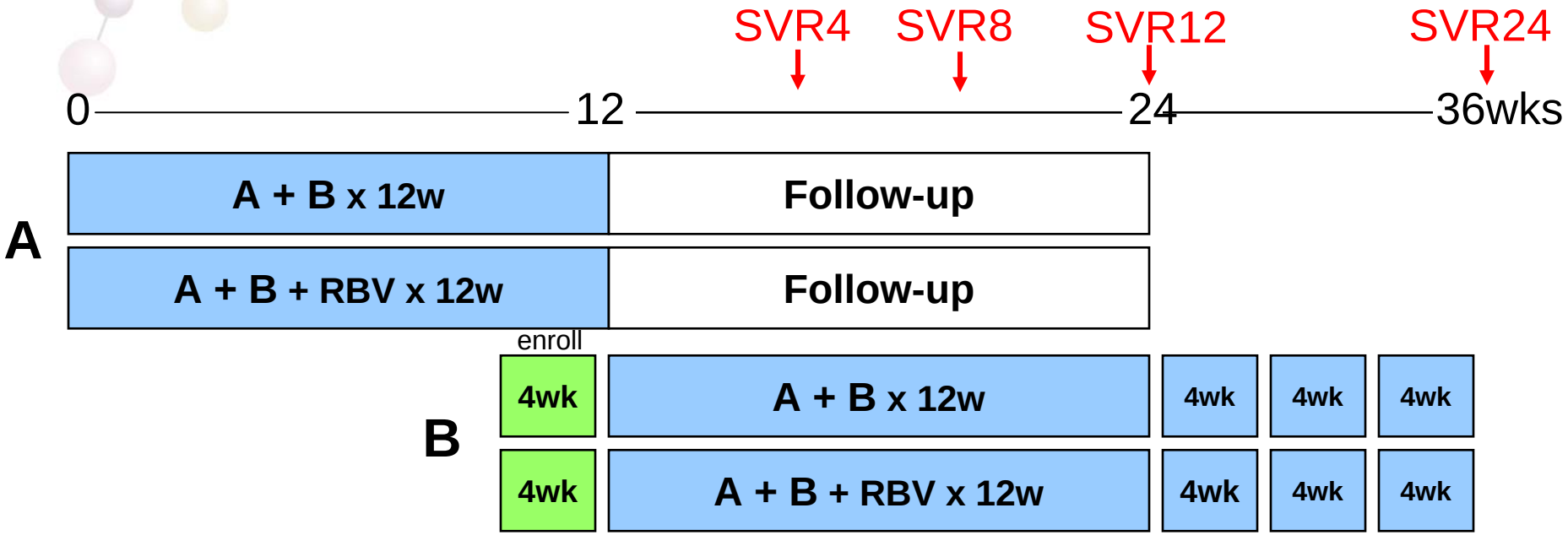
McCown *et al*, (2008) Antimicrob Agents Chemother, *2008*

Mechanisms to Avoid Resistance

- **Raise the “barrier” to viral escape**
  - **Combination therapies with complementary profiles**
- **Maximally reduce virus replication**
  - **Use highly potent antivirals**
  - **Optimal early viral suppression**
- **Raise the “pharmacologic barrier” to viral escape**
  - **High trough levels for compounds that are Cmin dependent**
  - **Tissue distribution that includes sanctuaries, e.g. liver**
  - **Maximize patient adherence**

Backup Slides

Considerations for trials with 2+ DAA: Duration



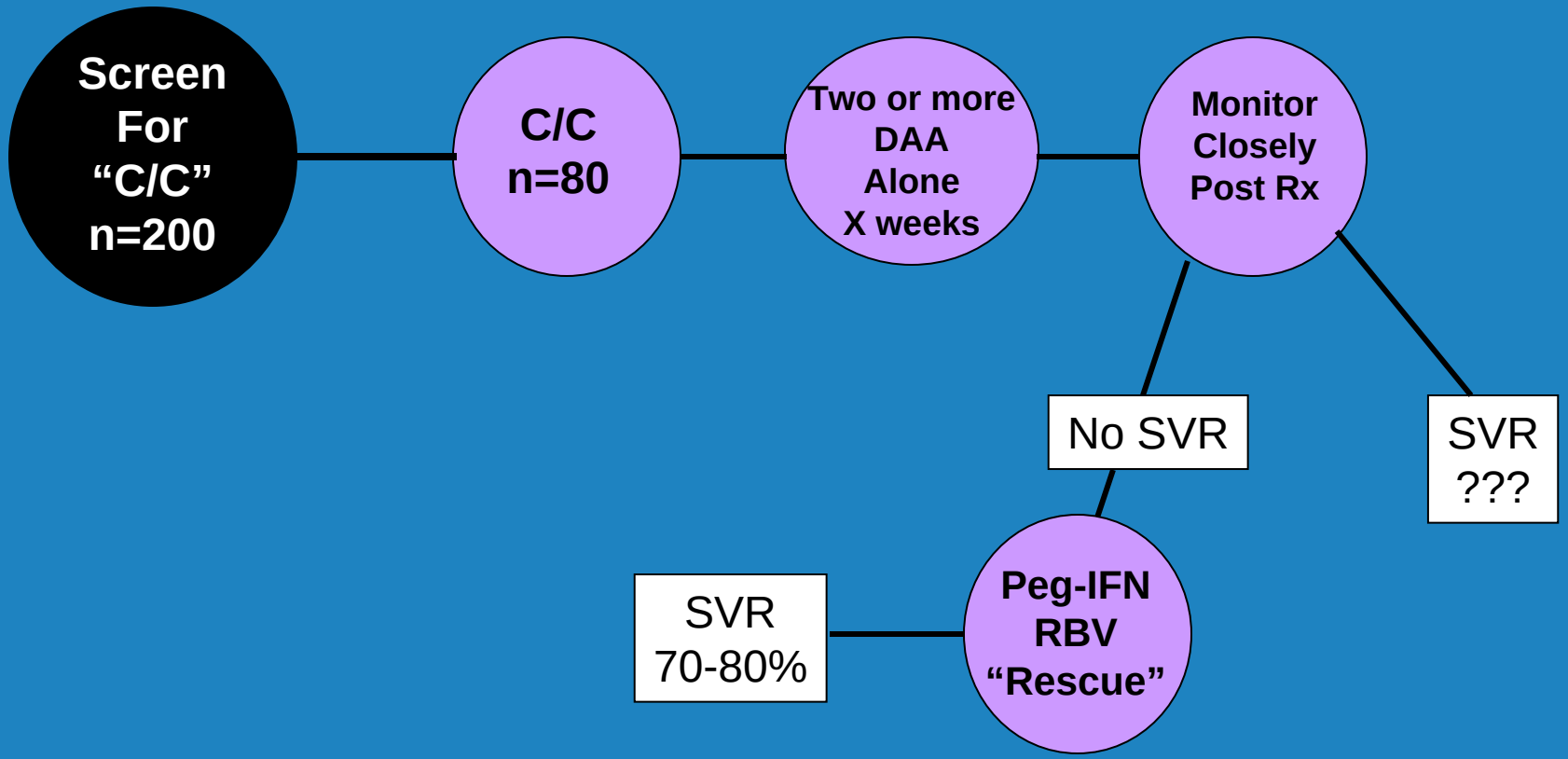
- Enroll Cohort A
- When Cohort A completes 12 weeks LPLD, enroll pre-screened patients for Cohort B over 4 wks
- As SVR data are available for Cohort A, extend Cohort B dosing by Rules:
  - If Cohort A Wk 4 SVR <X%, extend Cohort B dosing 4wks to 16wks
  - If Cohort A Wk 8 SVR <X%, extend Cohort B dosing 4wks to 20wks
  - If Cohort A Wk 12 SVR <X%, extend Cohort B dosing 4wks to 24wks

Considerations for trials with 2+ DAA: Population

- Which are the appropriate populations to assess IFN-free DAA regimens?
  - Treatment-naïve “CC” patients = easy to rescue
  - IFN-intolerant
  - Prior IFN/RBV failures
  - Traditionally “difficult to treat” and low SVR patients
  - IFN-contraindicated
  - IFN “unwilling”
- What SVR would be acceptable?
  - to move forward into longer duration studies?
  - Into other populations? (e.g., from “IFN-contraindicated” into “unwilling” but treatment-naïve)

IL28B

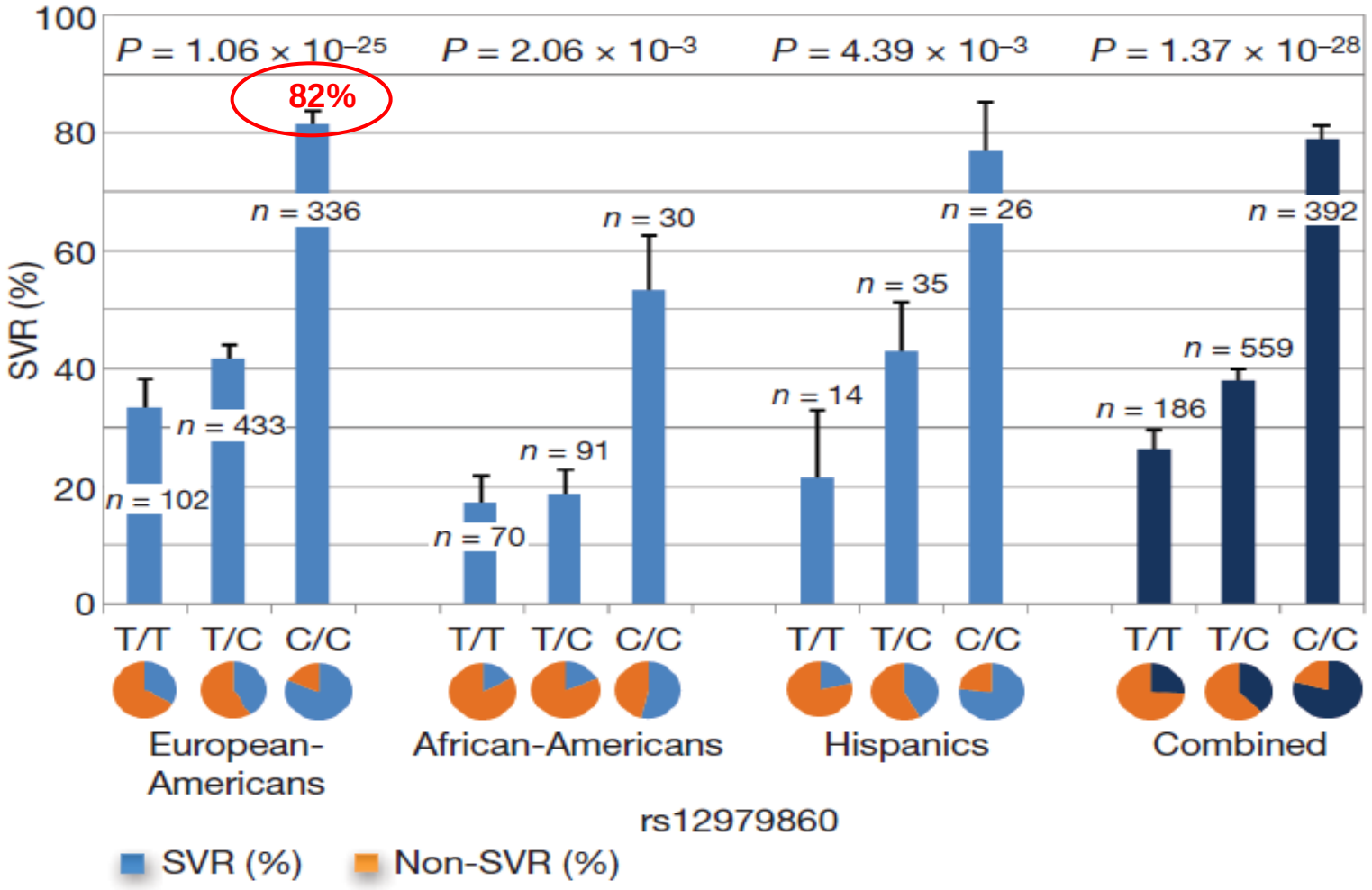
Future Direct Antiviral "Alone" Trials



Ge et al *Nature* 2009

Slide courtesy of JG McHutchison

SOC "Rescue Net": Percent SVR by IL28B genotype



Ge et al *Nature* 2009

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