Maraviroc Expanded Access Program

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Study Objectives

- To provide maraviroc to patients, who have limited approved treatment options due to resistance or lack of tolerability
- To collect safety data in a larger and more diverse patient population than participated in the Phase 2/3 clinical trials

Expanded Access Program

Goals of Program

	Program	Comments
Countries	23	▪ Countries with high unmet need in TE populations
Sites	▪ Clinical trial sites ▪ Experienced with trials ▪ Research naïve sites	▪ Broad access to patients in need, while assuring physicians are familiar with EAP safety reporting requirements ▪ Focused effort to recruit research naïve sites
Entry Criteria	▪ Patients with R5 HIV ▪ Not restrictive (based on MD perception of need)	▪ Attempt to not exclude patients in need ▪ Decision to use MVC is clinically driven
Safety	• Collect safety data on a larger population that is more representative of the population that will access MVC after approval	• Safety concerns with CCR5 class: • Hepatotoxicity • Malignancy • Emergence of X4 virus
Duration	• From Phase 2b/3 data to launch • 4 - 6 mo in US • >12 mo ROW	• Important to investigators • The earliest possible access to the drug once safety and efficacy is known

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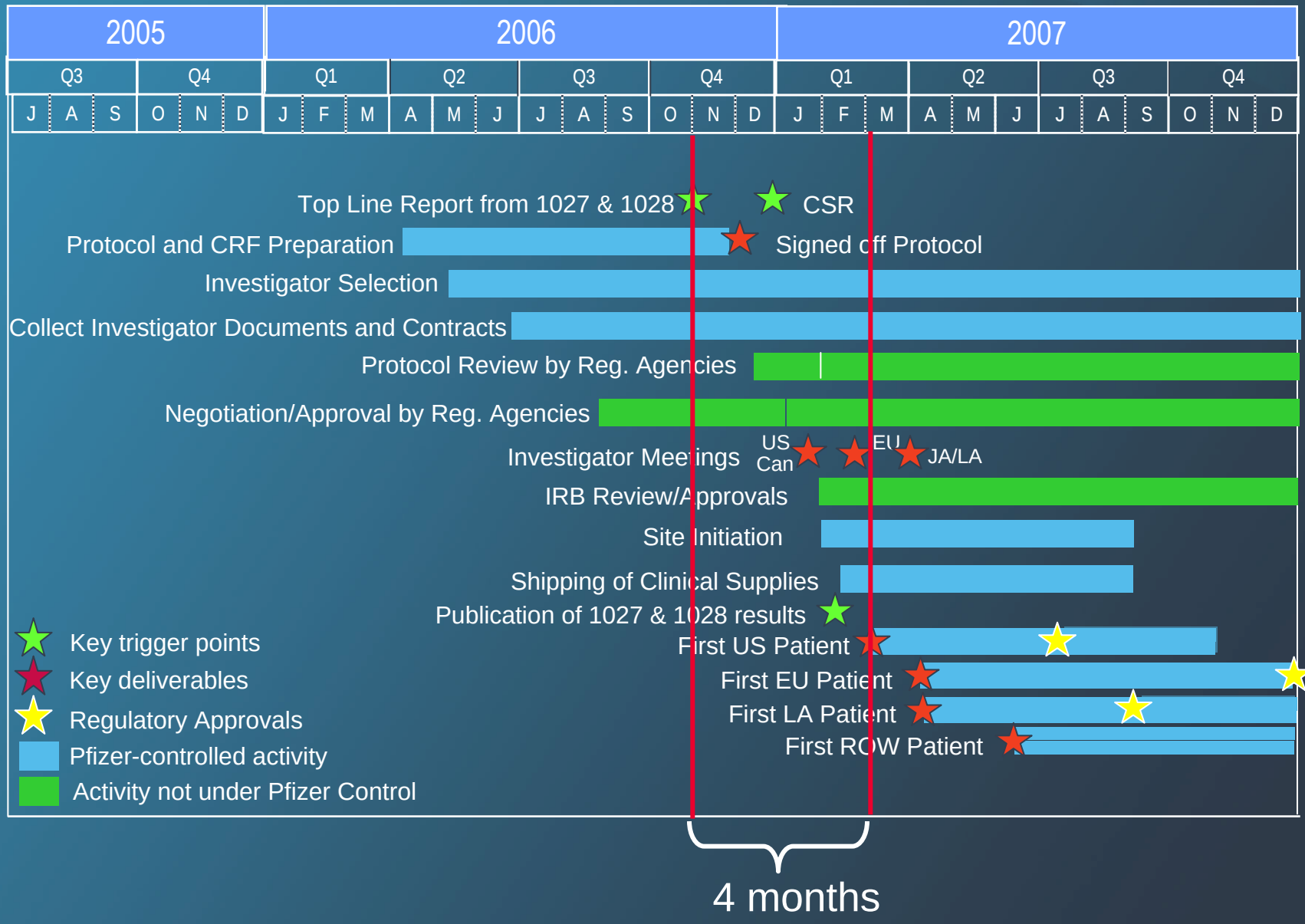
Countries that Participated in the EAP

- North America
  - Canada
  - USA and Puerto Rico
  - Mexico
- Central and South America
  - Argentina
  - Chile
  - Costa Rica
  - Dominican Republic
  - Peru
- Europe
  - Austria
  - Belgium
  - France
  - Greece
  - Italy
  - Netherlands
  - Portugal
  - Romania
  - Spain
  - Switzerland
  - UK
- Asia
  - Hong Kong
  - Malaysia
  - India
- Australia

* Brazil conducted its own Open Label Safety Study

Maraviroc Expanded Access Program (EAP)

Phase 2b/3 Design Resulted in Short Execution Timeline



EAP Design

MVC + OBT*
Pts followed per local standard of care

Key selection criteria

- ≥16 yr of age
- Limited or no approved treatment options available due to resistance or intolerance
- Medically stable
- Only R5 HIV (Tropism assay requires HIV RNA >1000 c/mL)
- MVC dosing with background therapy is known

*** permitted any drug for which PK interaction is known**

Use of Other Experimental ARVs

- Subjects receiving investigational ARVs through participation in a Phase 3 or 4 clinical study are eligible to participate in this trial provided:
  - That the 2 investigational agents are required to offer the patient a regimen with 2 or 3 active antiretroviral drugs
  - Neither protocol prohibits the use of the other ARV, AND
  - The dosing of the two agents when used together is known

EAP Design

Data Collected

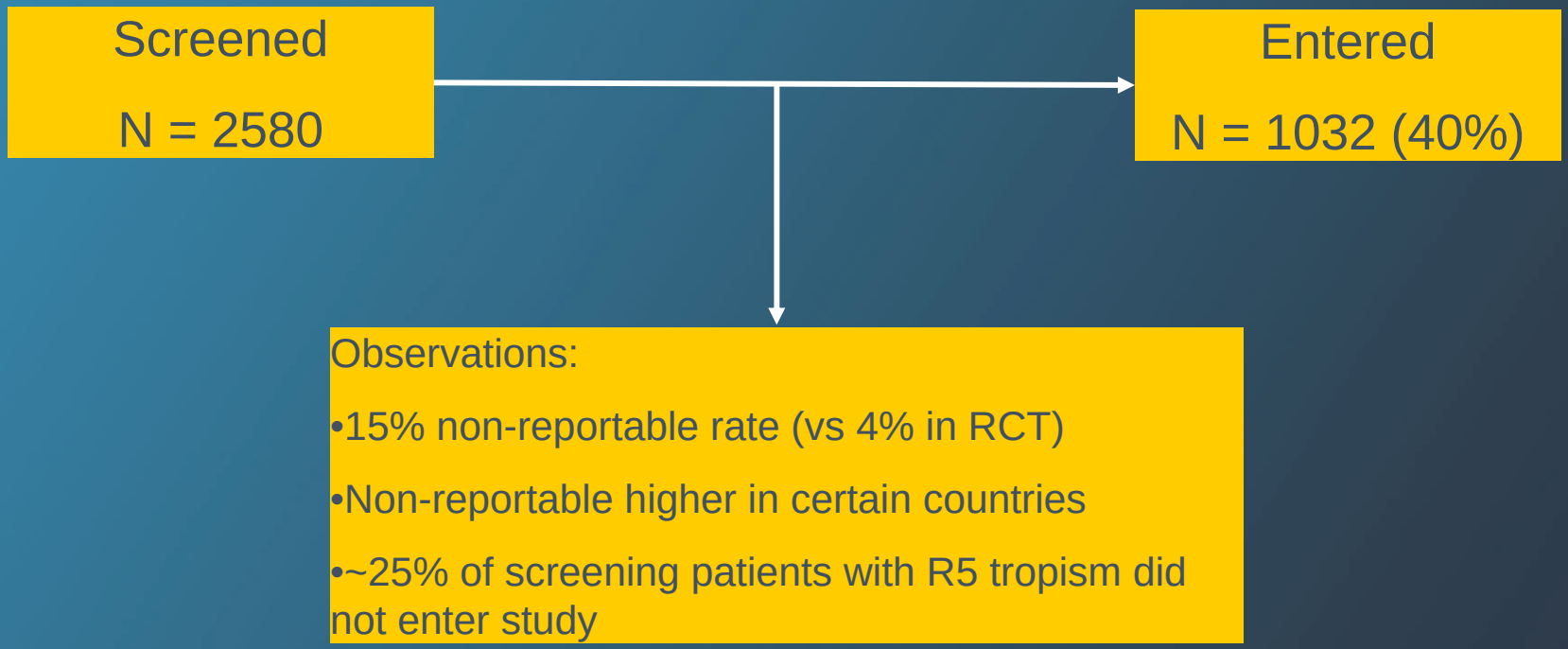
- Past medical history, prior ARV use, vital signs and physical examination
- Adequate data to accurately assess AEs and SAEs
  - Concomitant meds
  - CBC and Chemistry at Screening and BL visits, and every time HIV RNA or CD4 is done thereafter
  - Hep B and C serology at BL visit
  - Pregnancy test at Screening and as needed for females
  - Tropism at screening and time of virologic failure
- Efficacy (HIV RNA and CD4 and resistance) according to local practice. Not provided by study
- Samples to be stored for alternate tropism assays, resistance testing, HCV RNA, HBV VL, and pharmacogenomics (where permitted by regulatory agencies and IRBs – second signature required)

End of Patient Participation

- In each country will occur at the time the drug is approved and drug is available commercially
- Patients will receive maraviroc for up to 90 days after last visit on the EAP if the patients does not have reimbursement plan available
- Patients will be encouraged to participate in the maraviroc safety registry

What Did We Learn

Maraviroc EAP:
Patient participation

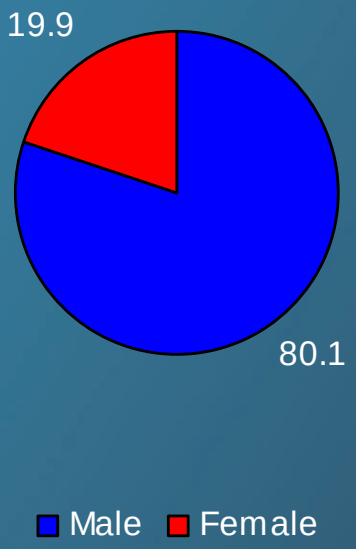


EAP Demographics

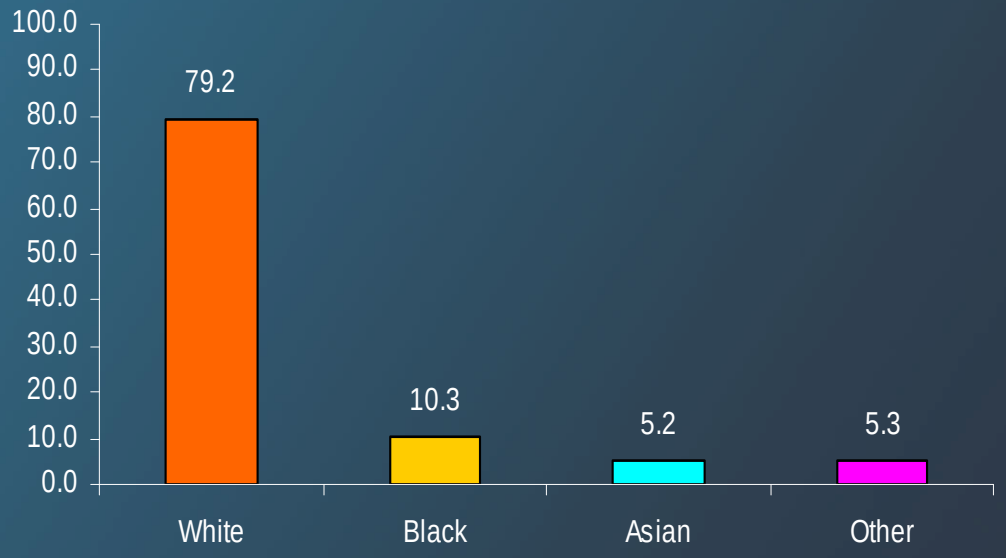
More diverse than 2b/3 Program, but not ideal

- Mean age: 46
- Median CD4: 260 cells/μL
- Median viral load: 4.3 $\log_{10}$ copies/mL
- Median follow-up: 176 days

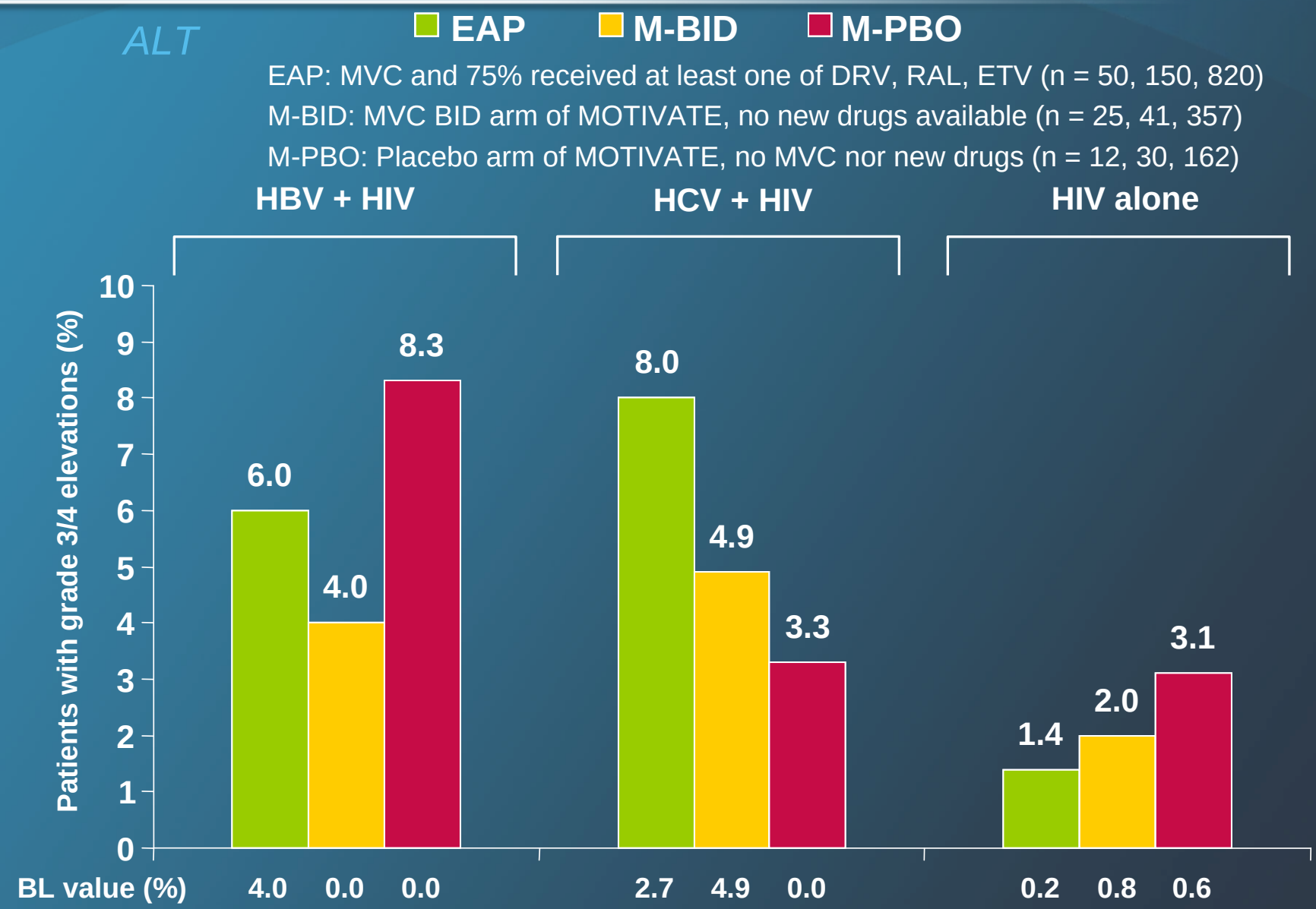
Gender



Race



Safety of Maraviroc with New Agents Could Be Explored



Lazzarin EACS 2009

The SensiTrop Assay can Fail to Detect CXCR4-using Virus

- Stored screening samples (N=100) from HIV-infected, treatment-experienced patients in the MVC EAP were retested for tropism using the SensiTrop assay and results were compared to results of the Trofile assay

Screening Trofile (n) DM or X4	Screening SensiTrop (n)
39	19 R5
	14 DM
	6 NP

SensiTrop	
Sensitivity	42.5% 95% CI: 25.6-59.3
Specificity TBC	92.5% 95% CI: 84.3-100.7
+ve Predictive Value	82.2%
-ve Predictive Value	66.4%

- These results show that the SensiTrop assay had poor sensitivity to detect DM/X4 virus in this set of clinical samples
- Use of the SensiTrop assay with these samples would have resulted in patients harboring D/M or X4 HIV-1 being inappropriately dosed with MVC
- Failure of the SensiTrop assay to detect D/M or X4 HIV-1 did not appear to be a function of the viral load of the sample

Tressler R, *et al. CROI* 2008; Poster 920a

Prospective Observational Epidemiologic Study of Maraviroc's Safety (POEM)

- Majority of MVC safety data based on clinical trial experience
  - Experimental, controlled setting
  - Limited number of patients
  - Limited duration of observation
- Safety of MVC in "real-world" clinical setting over longer term use has not been assessed
- Pfizer has committed to the US FDA and EU CHMP to conduct a prospective safety study of MVC

Population:

- 2000 MVC-exposed subjects
- 1000 MVC unexposed subjects
- Follow-up: 5 years

Endpoints:

- Deaths
- AIDS, malignancies, viral encephalitis
- Liver failure, myocardial infarction, rhabdomyolysis

- CRFs used for POEM not used in EAP
- Most patients completed EAP before POEM opened

Maraviroc EAP

- Treatment –experienced population exposed to MVC was broadened
  - More women
  - Use of newer antiretroviral agents
  - Safety in non-trial situations can be better ascertained
    - *Since it is likely that long-term safety will be a key question for newer antiretrovirals, more intensive and targeted safety data collection may need to be incorporated. This may help safety registry recruitment, if required by agencies*
- Drug assay combination
  - Anticipate problems in real clinical use:
    - High rate of non-reportable assays: clade, inadequate specimen preparation, low viral load
    - Asynchronous availability of resistance and tropism resulted in patients who could have benefited from MVC not using it
  - Extensive repository of samples to test new assays