HIV Forum: Emerging Issues in HIV Clinical Trials

Experiences from S/GSK1349572 development programme:
A Shionogi & ViiV Healthcare joint venture

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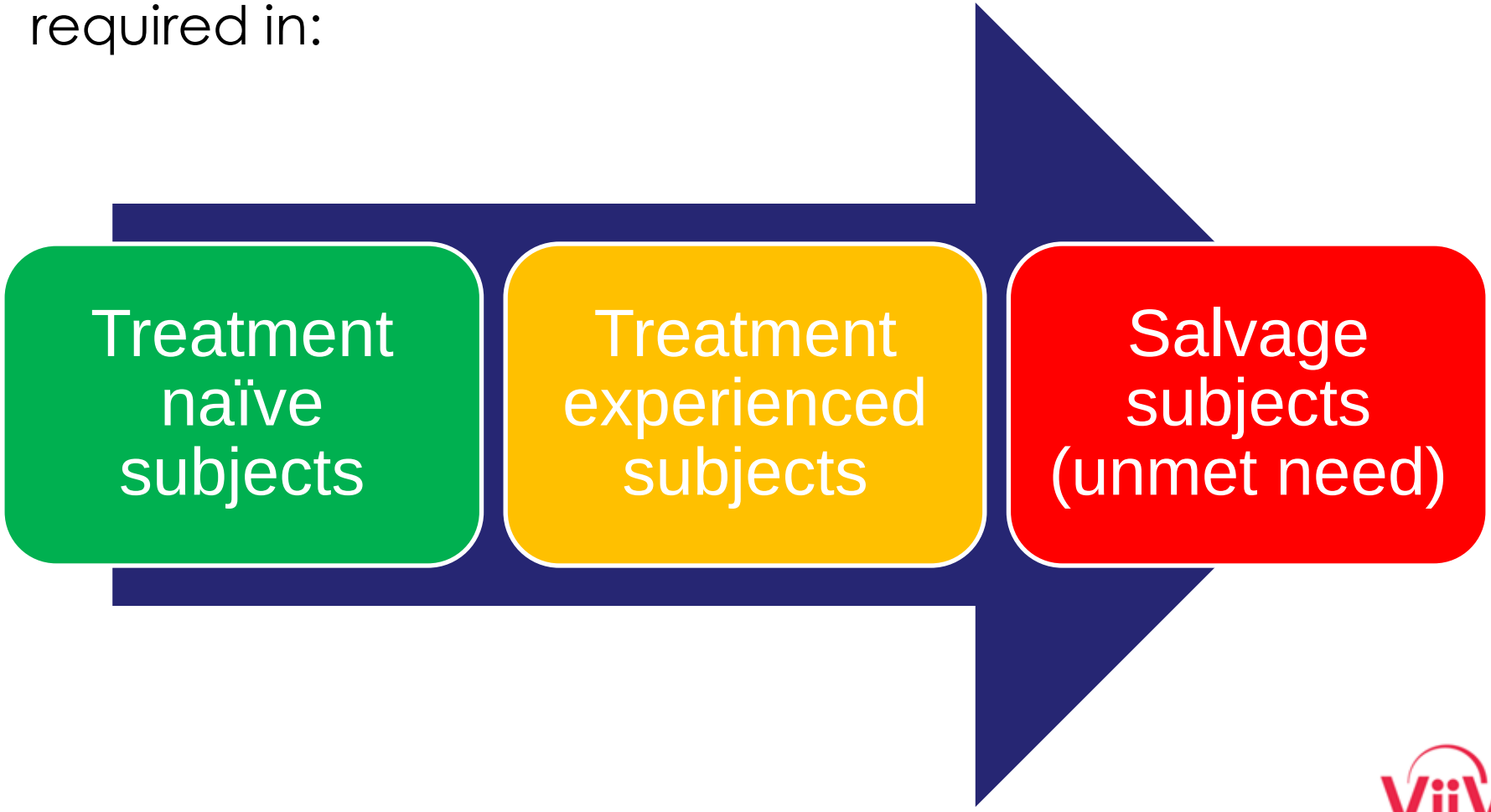
Current Drug Development Paradigm

For a license which covers the full spectrum of HIV patients requiring treatment, Phase III studies currently required in:



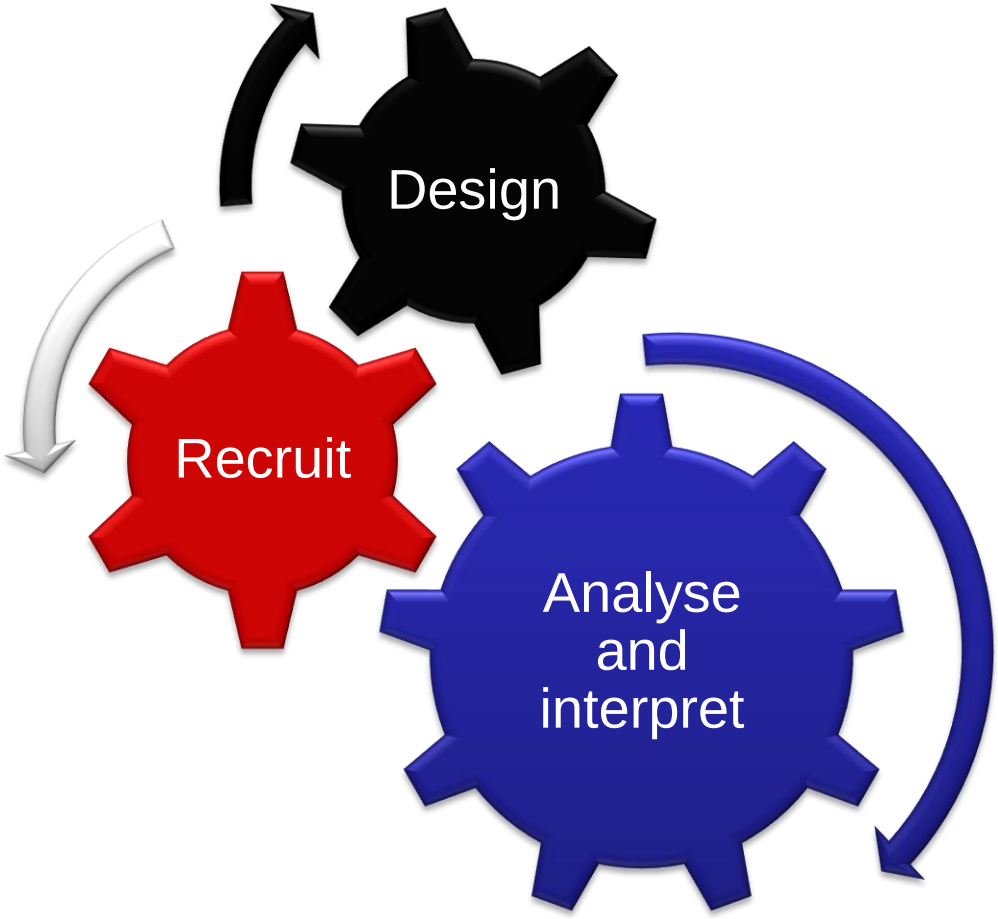
‘572 Phase III Programme

Treatment-experienced study:

- Randomised, double-blind, 48-week, non-inferiority study
- ‘572 vs raltegravir with *background drugs*
- N≈690 HIV+ therapy-experienced, integrase-inhibitor-naïve adult subjects
- *Two-class drug resistance required at entry*
- Non-inferiority margin: 12%
- Primary endpoint: %<50cp/mL at 48 weeks (snapshot)

‘572 Experience: Treatment Experienced Considerations

Experienced studies incredibly challenging to:



‘572 Experience: TE Design Considerations - OBR

- Two trial types continue to be used:
  - placebo-controlled superiority trials (ie ‘add-on’ to OBR) – most relevant for first-in-class drugs
  - non-inferiority trials (ie new drug vs alternative plus OBR)

- For both trial types, one MAJOR issue is potency of OBR - OBR is getting ‘too good’
  - Implication for superiority trials is failure to demonstrate superiority (vicriviroc)
  - Implication for non-inferiority trials is tendency to declare non-inferiority even if new drug ineffective

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Assay Sensitivity

- Critical to consider for non-inferiority trials:
  - **Assay sensitivity = *if test drug inferior, is the trial capable of demonstrating that inferiority?***

- Assay sensitivity concerns for '572 (& others):
  - several new, potent drugs available even for patients with many-years treatment experience and multi-drug resistance
  - OBR, if unrestricted, can contain ≥3 active drugs
  - 63% subjects in VICTOR had ≥ 3 active drugs in OBR
  - With OBR ≥3 active drugs, assay sensitivity is lost – OBR alone gives good response rate

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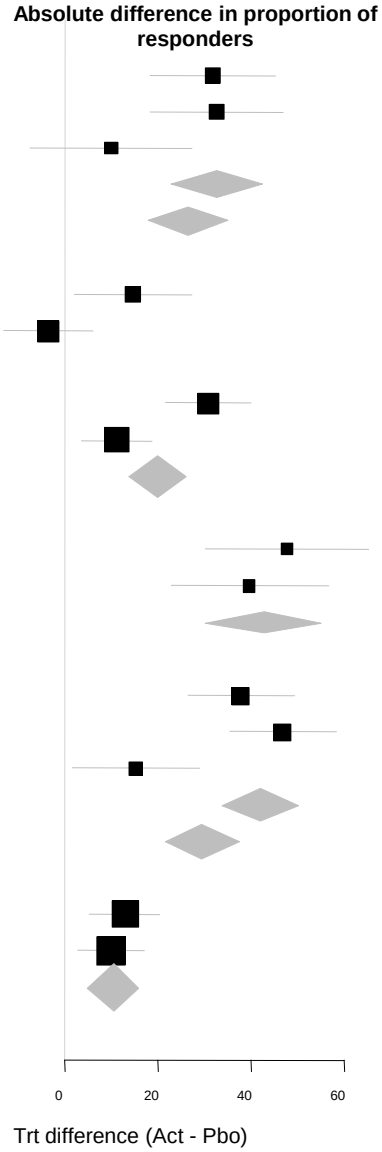
Recent Experienced Trials

Study	PSS	Active	Placebo
BENCHMRK [1]	1	83/137 (61%)	20/ 69 (29%)
	2	99/139 (71%)	24/ 62 (39%)
	3+	58/ 82 (71%)	28/ 46 (61%)
	1,2	**182/276 (66%)**	**44/131 (34%)**
	1,2,3+	**240/358 (67%)**	**72/177 (41%)**
VICTOR [2]	0,1,2	123/176 (70%)	47/ 85 (55%)
	3+	179/293 (61%)	94/145 (65%)
DUET [3]	1	125/200 (63%)	64/201 (32%)
	2+	197/252 (78%)	169/252 (67%)
	1,2+	**322/452 (71%)**	**233/453 (51%)**
POWER [4]	1	17/ 34 (50%)	1/ 40 (3%)
	2+	27/ 48 (56%)	10/ 60 (17%)
	1,2+	**44/ 82 (54%)**	**11/100 (11%)**
MOTIVATE [5]	1	49/114 (43%)	2/ 38 (5%)
	2	57/106 (54%)	4/ 57 (7%)
	3+	84/146 (58%)	33/ 78 (42%)
	1,2	**106/220 (48%)**	**6/ 95 (6%)**
	1,2,3+	**190/366 (52%)**	**39/173 (23%)**
TORO [6]	1	28/162 (17%)	3/ 68 (4%)
	2+	70/291 (24%)	23/163 (14%)
	1,2+	**98/453 (22%)**	**26/231 (11%)**



'572 Experience:
TE Design Considerations – Indirect Placebo

- One quality marker for non-inferiority studies requires reproducing study conditions as similar as possible to studies of control drug *versus* placebo
  - For '572, relevant trial conditions to reproduce are BENCHMRK (raltegravir *vs* placebo)
  - BENCHMRK required subjects with at least 3-class resistance

- Due to increasing use of raltegravir and thus low prevalence of 3-class resistant, INI näive subjects, BENCHMRK-like subjects are very difficult to find
  - Strategy: expand entry criteria to 2-class resistance but incorporate design elements to bring study population closer to that of BENCHMRK (eg restricting OBR to ≤2 drugs)

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'572 Experience: TE Design Considerations - OBR

- Strategy for assay sensitivity
  - Restrict total number of background drugs to 1-2 (ie ensures 'effective PSS' of 1-2)
    - Ethical acceptability of this approach?
  - Consequence: effective PSS ≤2 different population to actual PSS ≤2

- Additional assay sensitivity challenge - not all background drugs viewed as equally potent (esp. darunavir/r)
  - Strategy: cap recruitment of PI-susceptible subjects using DRV/r to allow subgroup analysis excluding these subjects to have relatively high power
    - Challenging to implement operationally
    - Increases study timelines

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‘572 Experience: TE Recruitment Challenges

Summary of recruitment feasibility feedback from treating physicians:

- Very few virological failures now observed:
  - Failure with multiple mutations also less common now
  - If failure does occur, often due to non-compliance – poor candidates for clinical trials
  - Patients with multi-drug resistance have already been treated with raltegravir – thus ineligible for ‘572 trial
    - 3-class resistant & eligible not feasible; 2-class resistant challenging
- Some concerns re restricting OBR to ≤2 drugs
- Capping subjects with DRV/r limiting for some countries
- Preference for tolerability switch studies in experienced subjects

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‘572 Experience: TE Recruitment Challenges

Recent recruitment – best estimates from publicly available information:

	# subjects	# countries	# sites	Recruitment period	**Recruit Rate Pt/site/mth**
BENCHMRK-1 (3-class resistant)	350	12	61	~ 5 mths (2006)	**1.15**
VICTOR E-3, E-4 (2-class resistant or ≥6 month exp.)	857	NA, EU, LatinA, SAF	>160	~12 mths (2007/8)	**0.45**
Elvitegravir (resistance or ≥6 month exp. of 2 classes)	700	14	183	~14 mths (2008/9)	**0.27**
Lersivirine Ph2 (NNRTI resistance; pre-protocol amendment)	189	11	55	~8 mths pre-amendment (2009/10)	**0.02**
ING111762	***688***	***18-20***	***226 +***	***?***	***?***

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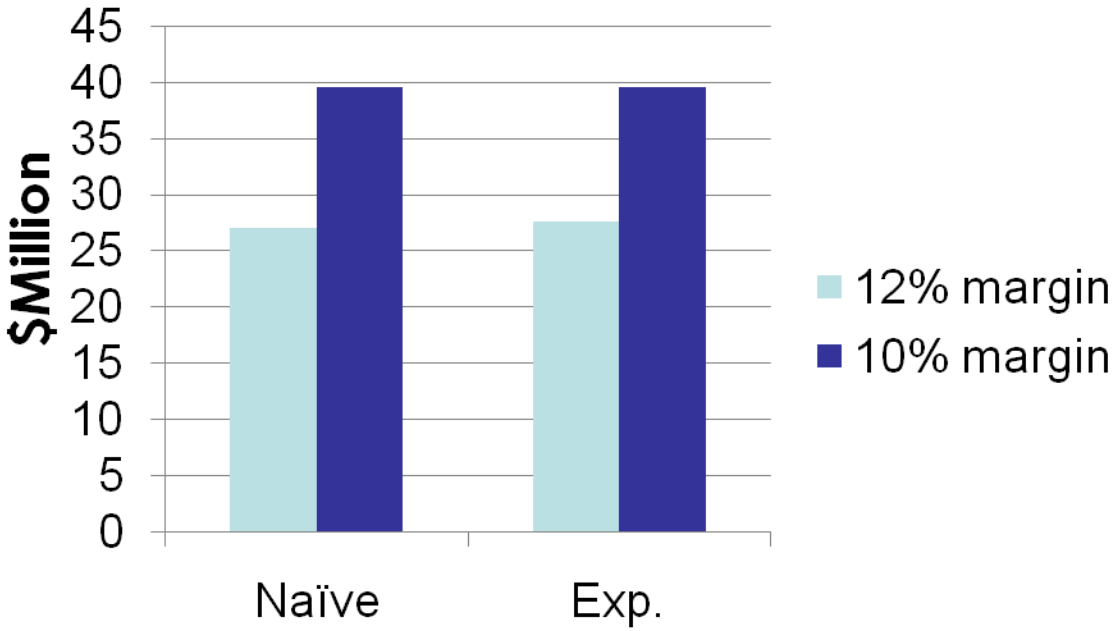
‘572 Experience:
TE Non-inferiority Margin Selection

- Unlike naïve situation, still possible to justify margin based on control *vs* placebo data – as per FDA draft guidance
- Despite ability to justify 12% NI margin this way, *some* regulatory preference for a margin <12%
- Impact of 10% vs 12% margin:



10 vs 12% margin:

Naïve: 250 additional subjects

Experienced: 300 additional subjects; ++ months additional recruitment

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‘572 Experience: Treatment Experienced Summary

- The ‘572 PhIII experienced study design is, by necessity, a compromise between an ideal scientific assessment of non-inferiority and the trial that prevailing conditions allow:
  - Feasibility of mirroring conditions of control vs placebo study
  - Stage of treatment where control drug is most often used
  - Number of available drugs and drug potency of OBR
  - Recruitment challenges (against a backdrop of regulatory desire to tighten non-inferiority margins due to assay sensitivity concerns with consequent increase in sample size)

- Question: are these likely temporary problems due to recent arrival of several new, potent drugs? Or not?
  - Tentative answer: belief that these issues are likely to remain at least mid-term

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Future Drug Development Paradigms?

Has the treatment of HIV changed sufficiently in the past 5-7 years so that the drug development paradigm should also change?

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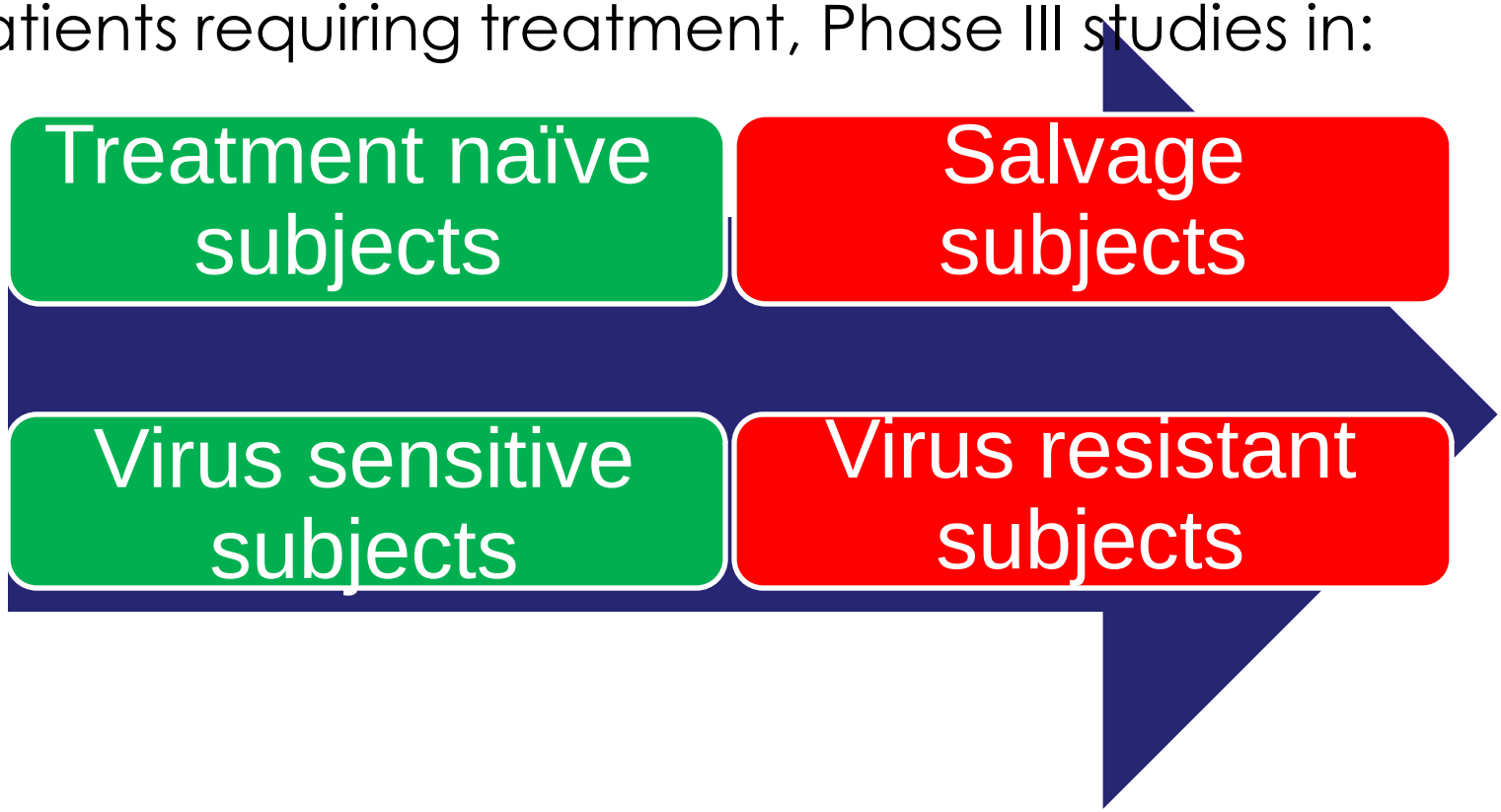

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