Redefining Expanded Access in 2009

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Background

- Several potent antiretrovirals (ARVs) in the past 4 years have enabled many patients with multidrug-resistant (MDR) HIV to suppress their HIV viral load.

- Due to several factors, there is still a relatively small number of patients who have developed resistance or toxicity to the newer ARVs.

- To protect them from functional monotherapy, these patients are not allowed in pre-approval studies.

- Some ARVs in phase II studies may potentially help those patients, but combining them after their respective approvals will be possible in 3 or 4 years.

Background (continuation)

- Some of these patients may risk clinical decline and death if no viable ARV regimen is available for them before 2012.
- The approximate number of patients in this situation is unknown.
- A survey was performed to attempt to answer this question.

144-Week Efficacy of Raltegravir in Treatment-Experienced Patients

(J.M. Gatell et al, IDSA 2009)

P005 - Week 144 Efficacy by Prognostic Factors (OF Approach)†

	Raltegravir (all doses combined) + OBT	
Prognostic Factors	n/N	% with HIV RNA < 50 copies/mL (95% CI)
Total	55/116	47 (38, 57)
Enfuvirtide Use in OBT		
No	28/71	39 (28, 52)
Yes (enfuvirtide naïve)	20/30	67 (47, 83)
Yes (enfuvirtide experienced)	7/15	47 (21, 73)
Baseline GSS‡		
0	30/61	49 (36, 62)
1-2	22/50	44 (30, 59)
3 or more	3/5	60 (15, 95)

† In the Observed Failure (OF) approach, only discontinuations due to lack of efficacy are counted as failures afterwards; ‡ GSS was defined as total number of drugs in OBT to which a patient's viral isolate showed genotypic sensitivity. Enfuvirtide use in enfuvirtide-naïve patients was counted as one active drug and added to the GSS. n/N = (number of responders) / (number of patients) in each category group.

J.M. Gatell et al. 144-Week Efficacy & Safety of Raltegravir in Treatment-Experienced Patients . IDSA 2009- Philadelphia

HIV Drug Pipeline – 2009

Agent	Class	Sponsor	Status
Rilpirivine, TMC 278	NNRTI	Tibotec	Phase III
Vicriviroc	CCR5 antagonist	Schering	Phase III
Elvitegravir	Integrase Inh.	Gilead	Phase III
Apricitabine, ATC*	NRTI	Avexa	Phase II/III
Bevirimat *	Maturation Inh.	Myriad	Phase IIb
UK453,061*	NNRTI	Pfizer	Phase II
IDX889*	NNRTI	Idenix/GSK	Phase II
GSK1349572*	Integrase Inh.	GSK/Shionogi	Phase IIb
GSK1265744	Integrase Inh.	GSK/Shionogi	Phase IIa
PRO 140*	CCR5 antagonist	Progenics	Phase II
Ibalizumab*	CD4 antagonist	Taimed	Phase IIb
Gilead 9350	PK booster	Gilead	Phase II

***Potential activity against extensive drug resistance?**

Courtesy of Bob Huff- TAG

EMEA Guidelines for Studies on New Drugs in ART-Experienced Patients

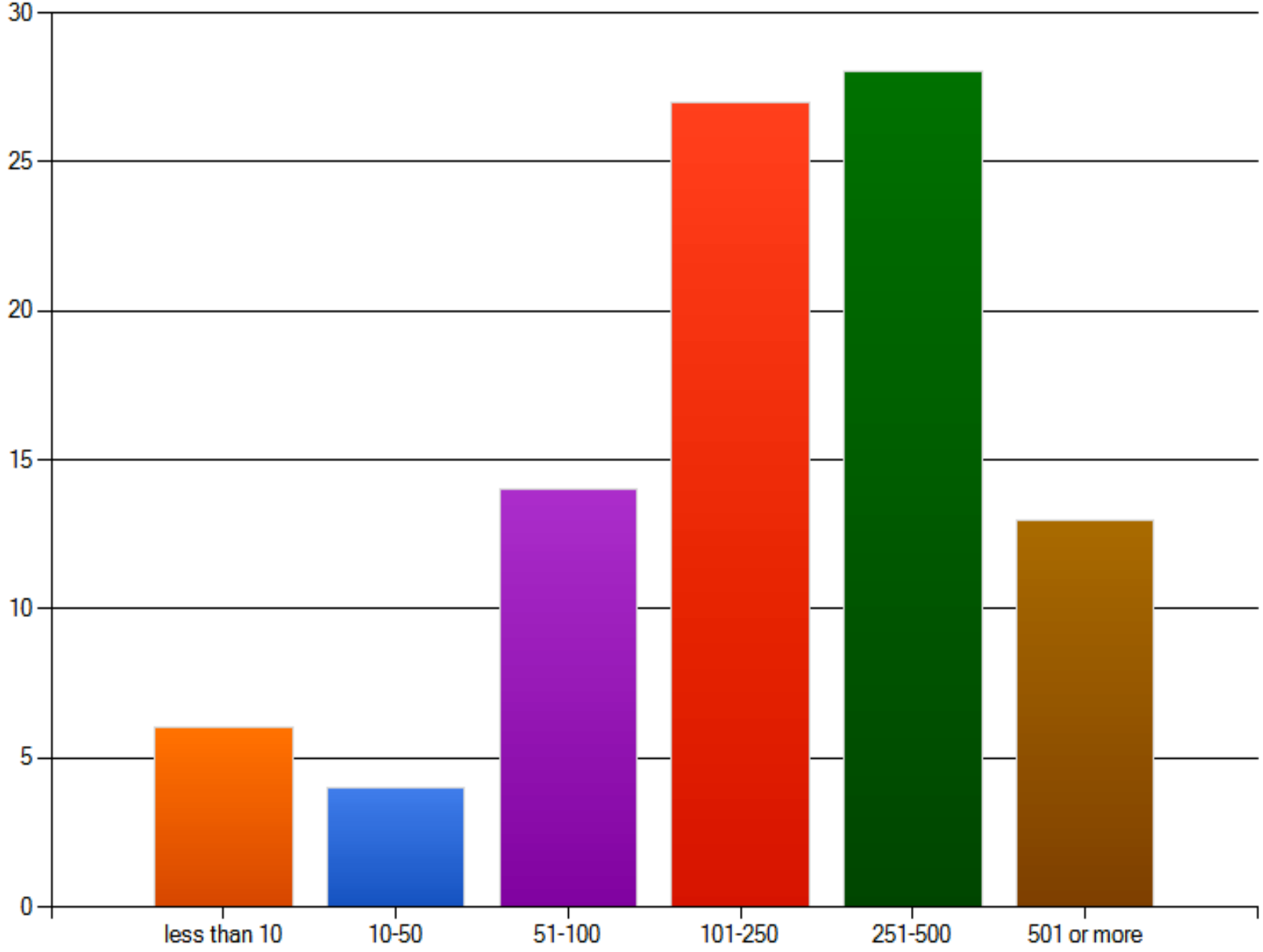
After screening for inclusion, there will be patients detected who are ineligible for randomization because they have less than two likely active licensed drugs available for use in optimized background therapy (OBT). These patients could be included in a parallel arm of the study in which they receive the novel agent plus OBT (which in some circumstances might include another experimental compound). Such patients should be followed in the same manner as those in the randomized arms of the study, with the primary aim to provide safety data. An assessment of the new agent in this manner is considered to be preferable to inclusion of these patients only in extended access programs.

Excerpted from section 4.2.3 '*Studies in ART experienced patients'* in the EMEA Guidelines on the Clinical Development of Medicinal Products for the Treatment of HIV Infection.

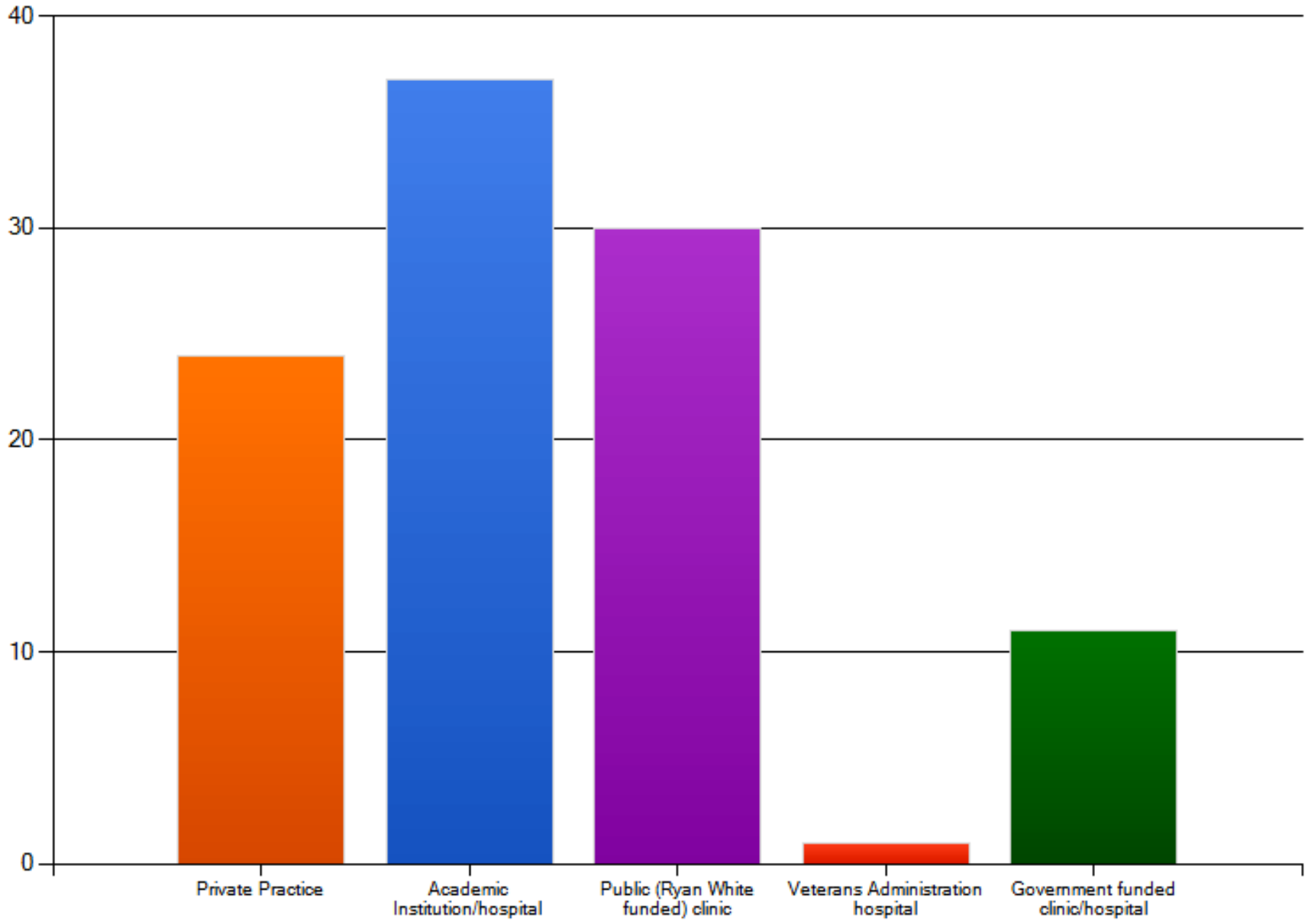
Physician Survey

- **Goal:** To determine how many physicians in the U.S. have patients with genotypic score (GSS) < 2 and their views/interest about access to investigational agents
- **Review team**: Steven Deeks, MD, Jay Lalezari, MD, Richard Loftus, MD, Bob Huff, Lynda Dee, Matt Sharp, Nelson Vergel
- 94 physicians participated
- Survey distribution was assisted by:
  - HIV Medicine Association
  - TheBody PRO
  - American Academy of HIV Medicine
  - National AIDS Treatment Advocacy Project (NATAP)
  - The Forum for Collaborative HIV Research
- Survey limitations: We may not have reached all physicians treating patients with GSS < 2. We did not ask how many of these patients are in clinical decline.

Number of HIV Patients in Care



Where Physicians Practice



How many patients in your practice have only one or zero fully active, commercially available antiretroviral agents?

Answer Options	Response Percent	Response Count
None	31.3%	26
One	19.3%	16
Two	25.3%	21
Three	13.3%	11
Four	10.8%	9
More than four? *(please specify)**		12
Answered question		83
Skipped question		11

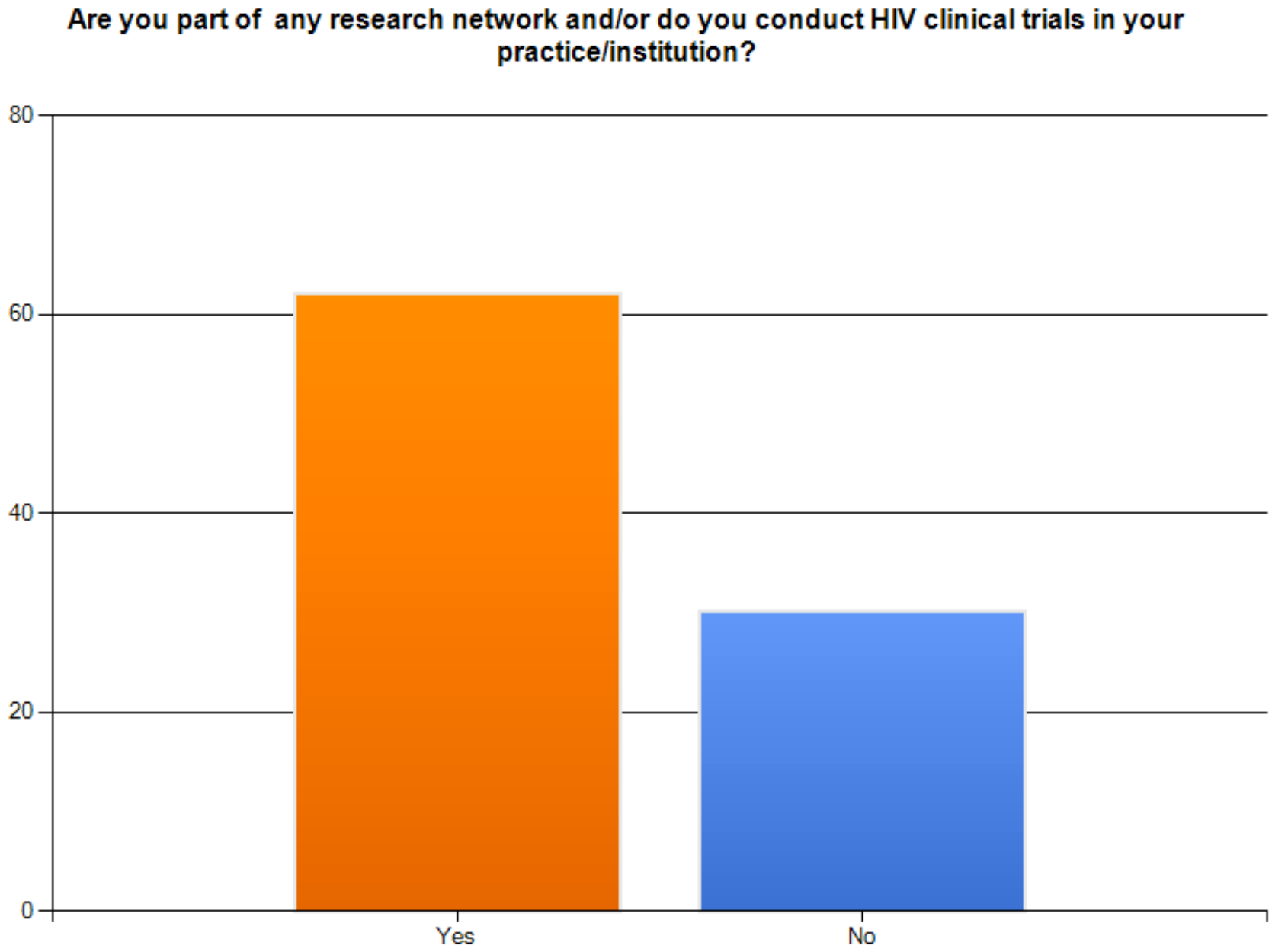
* There were 12 physicians who wrote “more than four,” comprising 123 patients.

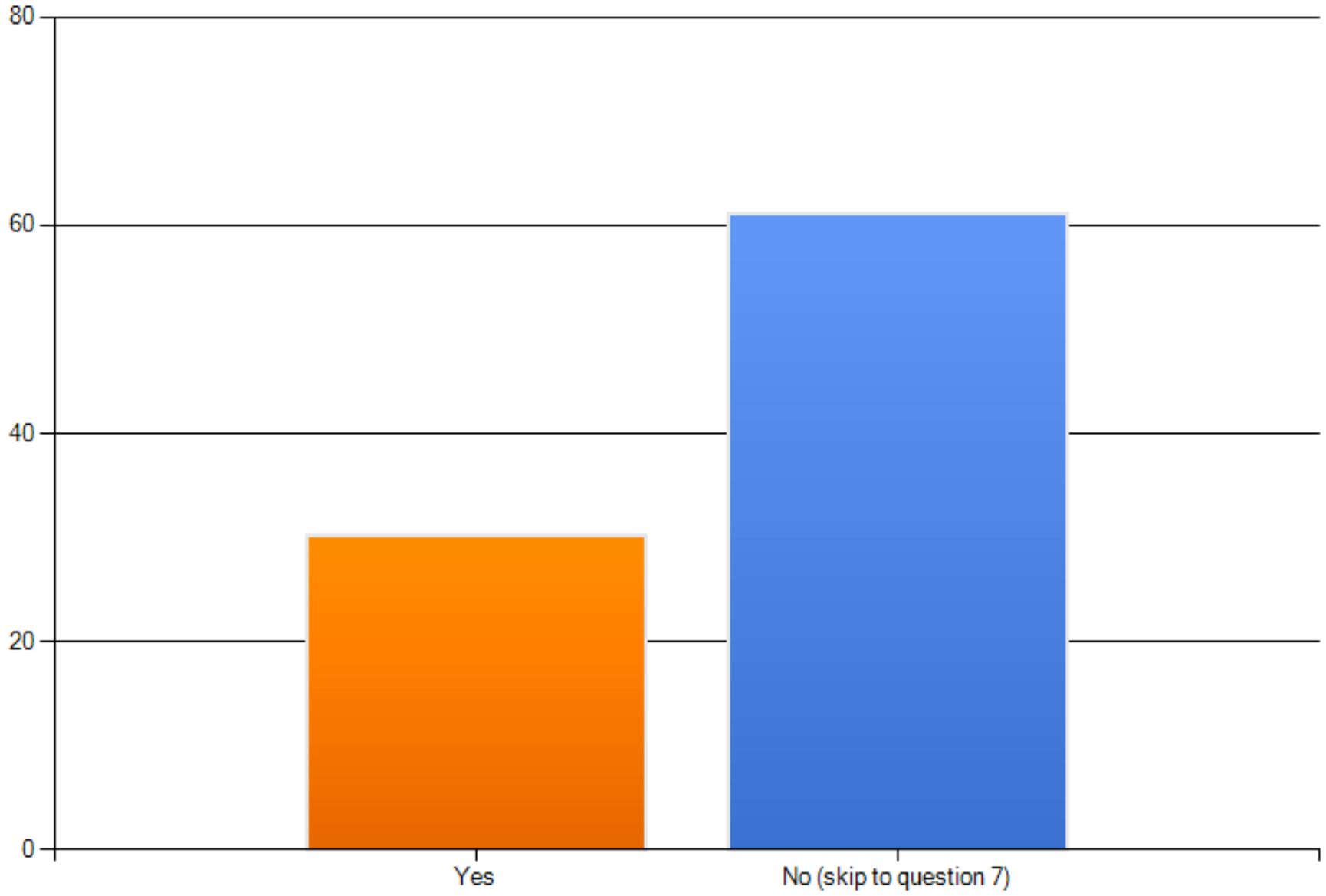
Total # of patients = 252

Geographical Distribution

City, State	No. of Physicians	Patients with GSS<2
Los Angles Area, CA	**5**	**54**
Seattle, WA	5	9
Philadelphia, PA	4	5
Houston, TX	**4**	**13**
New York Area ,NY	**4**	**17**
Chicago, IL	3	5
Milwaukee, WI	3	4
San Francisco, CA	**2**	**38**
Aurora, CO	2	4
Wistom-Salem- NC	1	4
New Haven, CT	2	4
Minneapolis, MN	2	3
Madison, WI	**1**	**15**
Cincinnati, OH	1	5
Wichita, KS	1	4

There was response from 47 cities. Listed above are cities where physicians reported more than 2 patients with GGS < 2


Are you part of any research network and/or do you conduct HIV clinical trials in your practice/institution?
80
60
40
20
0
Yes
No


Have you ever tried to apply for pre-approval access of investigational agents outside clinical studies or regular expanded access programs for individual MDR patients via the current FDA emergency treatment IND process?
80
60
40
20
0
Yes
No (skip to question 7)

Physician Request for a Single Patient IND for Compassionate or Emergency Use

When a physician would like to request an Investigational New Drug (IND) application to use an unapproved drug or other product for a single patient, the first step is to obtain permission from the manufacturer. **Without the consent of the manufacturer, the unapproved product will not be available to the patient.**

Source: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm163982.htm

Physician Request for a Single Patient IND for Compassionate or Emergency Use

Statement that the request is for an individual patient IND for treatment use (specifying whether it is an emergency IND or individual patient IND)

Brief Clinical History and Proposed Treatment Plan (Reference a published protocol or journal article if appropriate.)

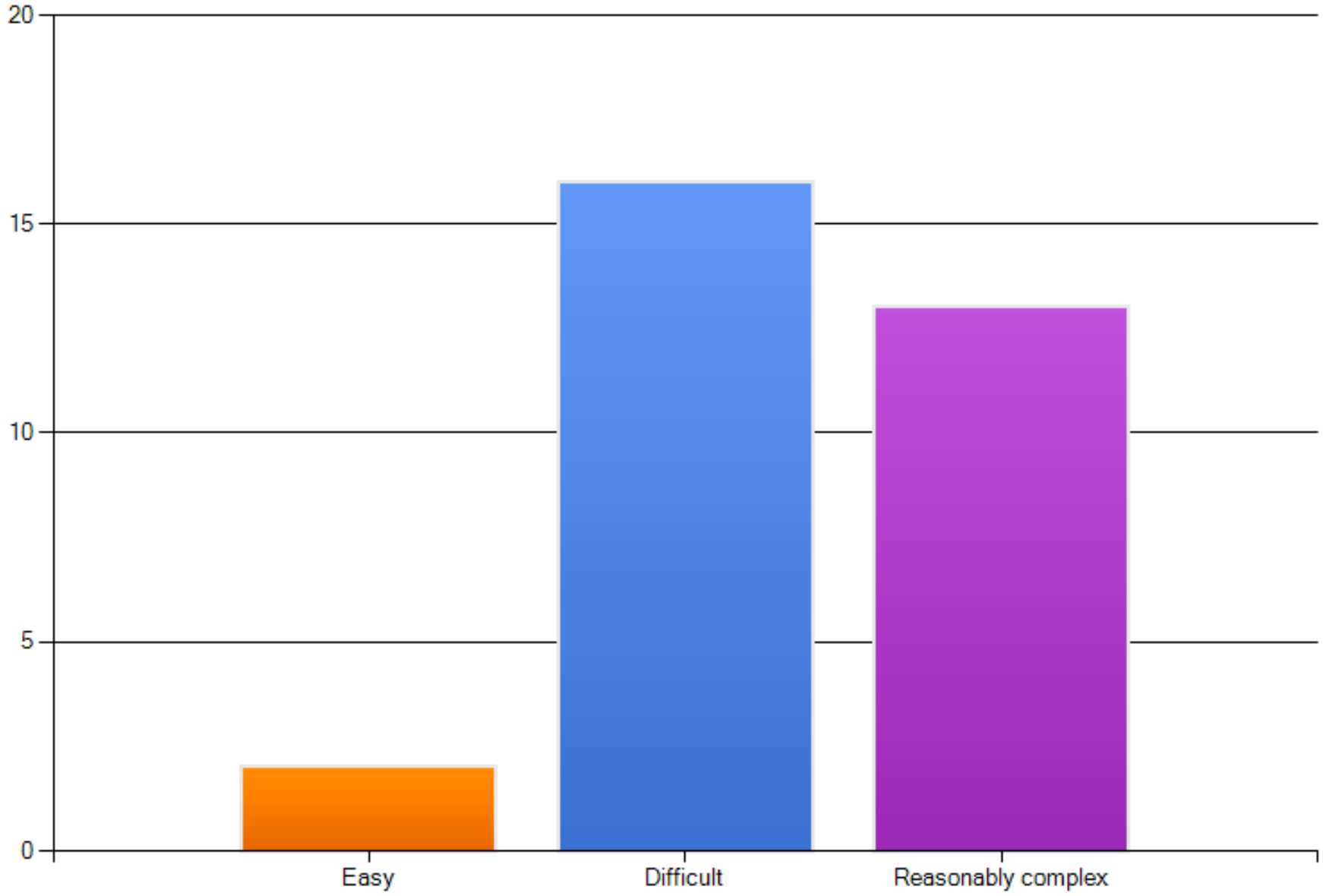
Drug Supply Reference Statement - name the supplier or manufacturer and a statement that a Letter of Authorization to cross reference an appropriate IND of the supplier or Drug Master File (DMF) of the manufacturer is included. The treating physician must contact the supplier or manufacturer for such a statement.

Informed Consent Statement and Institutional Review Board (IRB) approval prior to initiating treatment. There are some IRBs that have specific procedures for approving emergency requests.

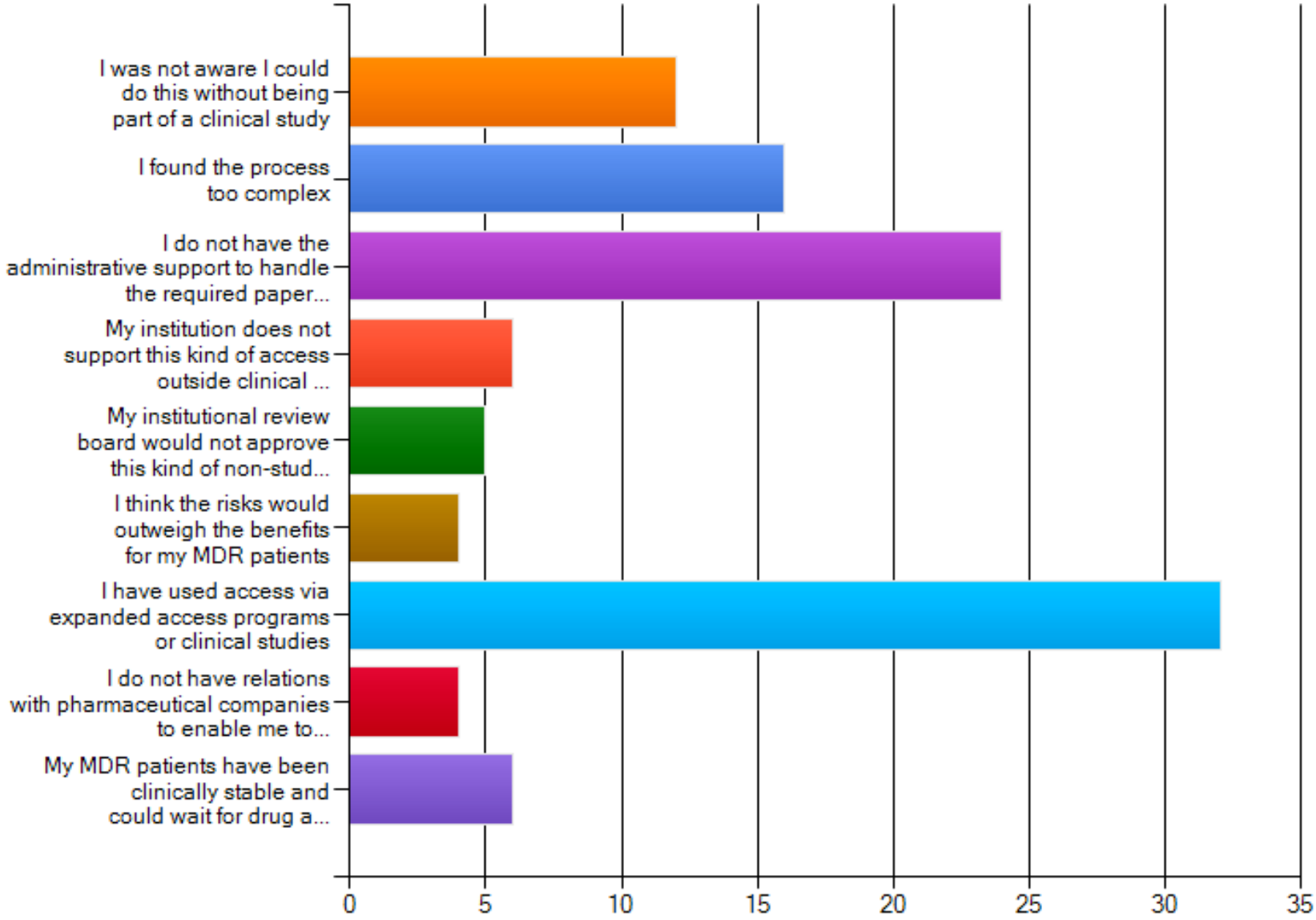
Investigator Qualification Statement - The first two pages of a Curriculum Vitae typically contain this information and are usually sufficient.

FDA Form 1571 completed with the treating physician listed as the sponsor.

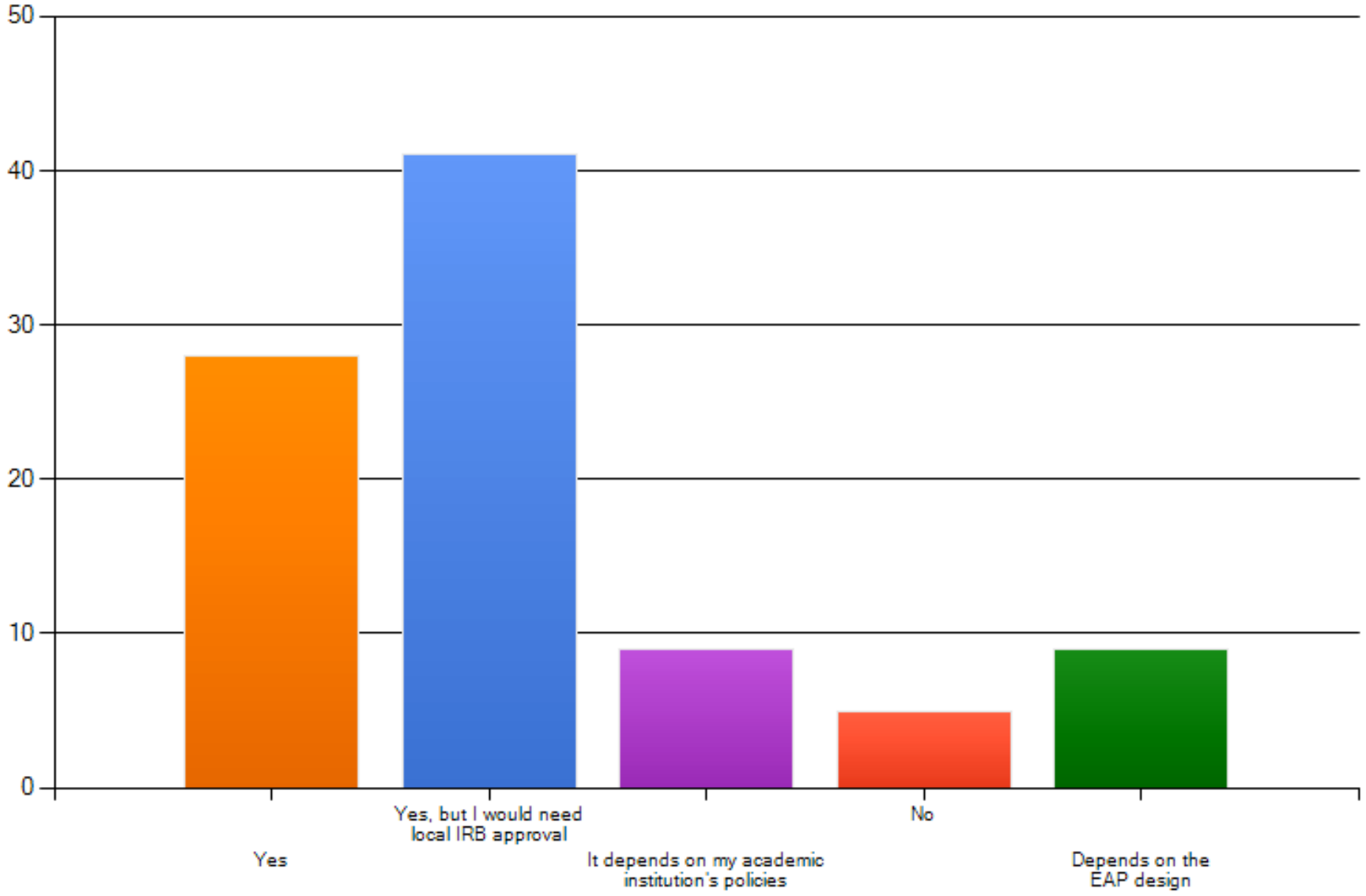
If you have applied for investigational drug access for your patients in the past, have you found the current FDA process easy or difficult to perform?



If you have not applied for early access of investigational agents for your MDR patients with limited to no options in the past, what were the main barriers to do so? (check all that apply)



If you were to be provided administrative support, would you be interested in participating in an expanded access program (EAP) of three investigational HIV medications for your patients with limited treatment options?



Summary

There are still some patients who have failed all available options. It is uncertain if this population will increase.

Access to a viable regimen may not be possible for these patients during the next 3 to 4 years.

94 physicians from 47 cities reported a total of 252 of these patients. The total number of these patients in the U.S. is unknown

Traditional single-drug expanded access programs (EAPs) will not help these patients.

Physicians report difficulties with the current single patient access process due to several factors.

A new approach that removes barriers for a multi-drug EAP in a centralized manner could help patients at risk of death before 2012, regardless of where in the U.S. they live.