

1                                   **The Forum for Collaborative HIV Research**  
2                                   **Meeting on Drug Interaction Research in HIV Disease**  
3   **April 1, 2000**  
4   **Noordwijk, The Netherlands**  
5

6           The Forum for Collaborative HIV Research held this meeting on drug interaction  
7 research in HIV disease directly following the 1<sup>st</sup> International Workshop on Clinical  
8 Pharmacology in HIV Therapy. The meeting was held to follow up on issues raised at a  
9 workshop co-sponsored by the Forum in May 1999 entitled *The Challenges of Clinical*  
10 *Trial Design in Assessing the Effects of Anti-HIV Therapy in Heavily Pre-Treated*  
11 *Patients*, which raised issues regarding the need for and difficulties of conducting more  
12 drug interaction studies to optimally utilize HIV therapies. As will all Forum projects, this  
13 meeting on drug interaction research brought together experts from academia,  
14 government, health care provision, industry, and patient communities to exchange  
15 information, identify gaps and impediments in the research effort, and develop  
16 recommendations to fill those gaps. The participants at this meeting came up with many  
17 useful suggestions for facilitating the research effort in this area. Some of those  
18 recommendations are directed to the Forum specifically for follow-up. Those  
19 recommendations are highlighted in bold in the Summary. The Forum will begin further  
20 discussion to implement these recommendations immediately.

21  
22   The Forum would like to thank the Organizing Committee of the 1<sup>st</sup> International  
23 Workshop on Clinical Pharmacology of HIV Therapy for their support and input. We  
24 would also like to thank Terry Blaschke, Mark Becker, and Merrill Gersten for their input.  
25 Alice Plantinga at Virology Education provided invaluable assistance with the meeting  
26 logistics. The Forum staff – June Bray, Helen Nuamah and Paul Oh – make each Forum  
27 meeting possible and successful.

28  
29   David Barr – Executive Director  
30  
31  
32

33   The Forum for Collaborative HIV Research, a project of the Center for Health Services Research and  
34 Policy at the George Washington University School of Public Health and Health Services, was founded in  
35 1997. The goal of the Forum is to facilitate discussion regarding emerging issues in HIV clinical research  
36 and the transfer of research results into care. The Forum is a coalition of government agencies, clinical  
37 researchers, health care providers, pharmaceutical companies, and patient advocates. The Forum is run by  
38 an Executive Committee made up of representatives from each of the above named constituency groups.  
39 The Executive Committee determines the subject and scope of the Forum projects. The Forum brings these  
40 constituencies together to identify gaps and impediments in the understanding of the medical management of  
41 HIV disease and develops recommendations to fill those gaps. The Forum is a public/private partnership,  
42 which receives financial support from its governmental and industry members and with in-kind support from  
43 its membership within the academic research, patient care, and advocacy communities. For more  
44 information about the Forum, visit the web site at: [www.gwumc.edu/chsrp](http://www.gwumc.edu/chsrp) then click on HIV  
45 RESEARCH.

1  
2  
3

1                                   **The Forum for Collaborative HIV Research**  
2                                   **Meeting on Drug Interaction Research in HIV Disease**

3                                   **April 1, 2000**

4                                   **Noordwijk, The Netherlands**

5  
6   **Summary**

7   The Forum for Collaborative HIV Research met on April 1, 2000, in Noordwijk, The Netherlands,  
8   to consider drug interaction research in HIV disease. A preliminary presentation outlined the  
9   premises proposed by the ACTG to determine when drug interaction studies should precede or be  
10   done as part of larger clinical trials.

11           Representatives of European and U.S. regulatory agencies, the pharmaceutical industry,  
12   and the patient advocate community then reviewed the role of drug interaction studies in drug  
13   licensing from those four perspectives. The FDA calls for drug interaction studies early in drug  
14   development so that clinical implications of interactions can be assessed as fully as possible in  
15   later clinical trials. The advocacy community representative urged drug developers to share their  
16   compounds with others for interaction studies, called for post-approval monitoring of interactions  
17   to uncover interactions missed in small populations studies before approval, and recommended  
18   studies of interactions of drugs now combined in salvage mega-regimens.

19           Open discussion by the Forum panel focused on three issues:

20   1. Facilitating industry collaboration on drug interaction studies:

- 21   • Panelists agreed that collaboration on drug interaction studies between competing companies  
22   is difficult and often lacking.  
23   • The problem can be partly remedied by public funding of trials through networks such as the  
24   US AIDS Clinical Trials Group (ACTG) and the Centers for Education and Research on  
25   Therapeutics (CERT).  
26   • **The Forum will collect information on CERT and distribute it to Forum panelists.**  
27   • Studies of interactions between pharmaceuticals and “alternative or complementary” therapies,  
28   as well as “recreational” drugs are needed, but again the burden of performing these studies  
29   falls on independent investigators who do not have the funds to carry out all the studies that  
30   might be helpful.  
31   • The FDA representative encouraged feedback from the medical and advocacy communities on  
32   interaction studies it should request from drug developers.  
33   • **The Forum will consider gathering and validating drug interaction findings and**  
34   **recommendations on a single Web site. Such a project would depend on industry funding.**  
35

- 1 2. Encouraging drug developers to share compounds with independent investigators for drug-drug  
2 interaction studies.  
3
- 4 • Independent investigators have great difficulty securing investigational compounds for drug  
5 interaction studies.
  - 6 • Industry is wary of providing such agents to independent investigators because the compound  
7 may be studied in ways industry feels are not appropriate or in ways other than those originally  
8 proposed by the investigator.
  - 9 • **The Forum agreed to seek ways to facilitate the sharing of investigational agents for drug  
10 interaction studies.**
  - 11 • **One proposal called for the Forum to act as a conduit for requests to industry for such  
12 compounds, to log such requests, and then follow up to secure a response from the drug  
13 developer.**
  - 14 • Industry representatives expressed support for such an approach, stating that it would formalize  
15 and clarify the application process.
  - 16 • **The Forum will collect standard request forms already used by drug developers (Material  
17 Transfer Agreements or MTAs) and will determine the appropriate company contacts for  
18 such requests. A smaller Forum meeting may be convened to outline a formal request  
19 procedure that the Forum might oversee.**  
20
- 21 3. Encouraging evaluation of therapeutic drug monitoring (TDM):  
22
- 23 • The panel reviewed four issues: (1) uses of TDM, (2) problems with current TDM, (3) quality  
24 assurance of TDM for antiretrovirals, and (4) clinical validation of TDM for antiretrovirals.
  - 25 • The panel agreed that two key questions about TDM must be addressed: (1) What evidence is  
26 needed to determine that TDM is a standard of care? (2) What TDM studies are under way,  
27 and which studies not being done should be planned?
  - 28 • **As a first step, the Forum will gather information on the use and quality assurance of  
29 TDM for other diseases.**  
30

## Meeting Attendees

- 1
- 2
- 3 David Back, Ph.D. - University of Liverpool, United Kingdom
- 4 David Barr - Forum for Collaborative HIV Research, USA
- 5 Mark Becker, Pharm.D. - Agouron Pharmaceuticals, USA
- 6 Terrence Blaschke, M.D. - Stanford University School of Medicine, USA and Pharsight Corporation
- 7 June Bray, Ph.D. - Forum for Collaborative HIV Research, USA
- 8 David Burger, Pharm.D., Ph.D. - University Medical Centre Nijmegen, the Netherlands
- 9 William Cameron, M.D. University of Ottawa, Canada
- 10 Diane Carey, Ph.D. - University of New South Wales, Australia
- 11 Hilde Carlier, Ph.D. - Boehringer Ingelheim, Belgium
- 12 Pravin Chaturvedi, Ph.D. - Vertex Pharmaceuticals, USA
- 13 Ben Cheng - Project Inform, USA
- 14 Simon Collins – European AIDS Treatment Group, UK
- 15 Elaine Daniels, M.D., M.P.H. - DuPont Pharmaceuticals, USA
- 16 Albertus de Boer, M.D. - Leiden/Amsterdam Center for Drug Research, The Netherlands
- 17 Nikos Dedes - European AIDS Treatment Action Group, Greece
- 18 Yvette Delph, M.D. - Treatment Action Group, USA
- 19 Keith Gallicano, Ph.D. - Ottawa Hospital, Canada
- 20 John Gerber, M.D. - University of Colorado, USA
- 21 Kees Groen, M.D. - Virco, Belgium
- 22 Yasmin Halima - European AIDS Treatment Group, United Kingdom
- 23 David Hall, Ph.D. - Boehringer Ingelheim Pharmaceuticals, USA
- 24 Anna-Karin Hamberg, M.Sc. (Pharm.) - Medical Products Agency, Sweden
- 25 Mark Harrington - Treatment Action Group, USA
- 26 Ann Hsu, M.D. - Abbott Laboratories, USA
- 27 Poe Hrr Hsyu, Ph.D. - Agouron Pharmaceuticals, USA
- 28 Bradley Kerr, Pharm.D. – Agouron Pharmaceuticals, USA
- 29 Juan Lertora, M.D., Ph.D. - Tulane University, USA
- 30 Mark Mascolini, recording secretary for the April 1 meeting
- 31 Thomas Merigan, M.D. - Stanford University, USA
- 32 Edward O’Mara, M.D. - Bristol-Myers Squibb, USA
- 33 Stephen C. Piscitelli, Pharm.D. - National Institute of Allergy and Infectious Disease, USA
- 34 Kathleen Presto, Hoffman La Roche, USA
- 35 Mario B. Regazzi, Pharm.D. - Irees-Policlinico S. Matteo, Italy
- 36 Jonathan Schapiro, M.D. - Tel Aviv University, Israel
- 37 Daniel Stein, Ph.D. - Glaxo Wellcome, USA
- 38 Michael Stek, Jr., M.D. - Merck, USA
- 39 Kimberly Struble, Pharm.D. - Food and Drug Administration, USA
- 40 Ronald van der Geest, M.D. - Virco, Belgium
- 41 Mike Youle, M.D. - Royal Free Hospital, United Kingdom
- 42

1 **Agenda**  
2

3 The Forum for Collaborative HIV Research met on April 1, 2000, in Noordwijk, The Netherlands,  
4 to consider issues related to interactions between drugs used to treat HIV infection and related  
5 conditions. After introductions and a description of the Forum for Collaborative HIV Research, the  
6 Forum's Executive Director, David Barr, began the meeting by listing the following topics for  
7 consideration:

- 8 • Role of drug interaction data in HIV drug licensing
- 9 • Need for better exchange of data, drugs, and assays for drug interaction and pharmacology  
10 study
- 11 • Methods to improve sharing of data, drugs, and assays

12  
13 Barr then asked attendees to suggest other items for discussion. Mark Harrington (Treatment  
14 Action Group, USA) proposed:

- 15 • Steps necessary to validate therapeutic drug monitoring (TDM) as a clinical tool.

16 The participants agreed that TDM should be discussed.  
17

18 **Summary of pharmacology issues from the May 1999 meeting on clinical trial**  
19 **design and HIV salvage therapy**  
20

21 Terrence Blaschke, M.D., summarized pharmacologic issues discussed during a 1999 meeting on  
22 clinical trial design and HIV salvage therapy co-sponsored by the Forum: (1) drug interactions, (2)  
23 therapeutic drug monitoring, (3) causes of antiretroviral failure, and (4) factors affecting  
24 individual pharmacokinetics.

25 Causes of treatment failure include (1) transmission of drug-resistant virus, (2)  
26 inadequate/inconsistent drug exposure, and (3) drug-drug interactions. Factors that affect  
27 individual pharmacokinetics are (1) genetics, (2) drug transporters and variability in transporter  
28 expression and induction, (3) diseases involving organs of drug elimination, (4) gastrointestinal  
29 disorders, and (5) drug-drug interactions.

30 Even before the emergence of highly active antiretroviral therapy (HAART), multiple  
31 drugs were being given to people with HIV infection and causing drug-drug interactions. However,  
32 only with the advent of protease inhibitors did the concept emerge that drug exposure is critical to

1 response. The following formula can be used to calculate the number of possible drug  
2 combinations (M) if n drugs are taken p at a time:

$$3 \quad M = n!/p! (n - p)!$$

4 In the pre-HAART era, if p = 2 and n = 31, then M = 465.

5 In the HAART era, if p = 3 and n = 31, M = 4495.

6

7

8 That order-of-magnitude increase in number of possible drug combinations, daunting in  
9 itself, does not even reflect complexities of dosing and other factors. Blaschke concluded that  
10 researchers cannot overcome the problem of defining all drug-drug interactions simply by doing  
11 more studies because the magnitude of the problem is so great.

12 Although all drug-drug interactions cannot be anticipated, members of the US AIDS Clinical  
13 Trials Group (ACTG) met to decide when potential interactions should be investigated in the  
14 context of a planned trial. The panel proposed the following premises:

- 15 1. If there are no human data on a particular combination to be used in a planned trial, and if it is  
16 expected that the combination may pose a risk, a small prospective drug interaction study in  
17 healthy volunteers may be recommended.
- 18 2. If human pharmacokinetic data already suggest an interaction between drugs to be used in a  
19 trial, that trial may go forward but a dose adjustment may be recommended and/or a  
20 pharmacokinetic sub-study may be conducted as part of the trial.
- 21 3. If no human interaction data are available but pharmacologic principles suggest it is unlikely  
22 that an interaction will occur between drugs in a planned trial, then population  
23 pharmacokinetic screening may be carried out as part of that trial.

24

25 The ACTG also formed a pharmacologic review panel to address specific questions and  
26 provide guidelines to carry out drug interaction studies. The pharmacologic review panel will  
27 decide whether a pharmacologic preamble study should be performed, according to the preceding  
28 premises.

29

### **Role of drug interaction data in HIV drug licensing**

30 Four speakers considered the role of drug interaction data in drug licensing from different  
31 perspectives: the European Medicines Evaluation Agency (EMA), the U.S. Food and Drug  
32 Administration (FDA), industry, and patient advocates.

33

34 **EMA perspective** - Anna-Karin Hamberg, Ph.D. (Medical Products Agency, Sweden) said that  
35 drug interactions are not yet considered at the European level, though they are in individual

1 countries. A meeting of representatives from member countries has been scheduled to discuss HIV  
2 drug interactions and to revise the Points to consider document in the Assessment of Anti-HIV  
3 medicinal products appropriate document on the EMEA Web site:

4 [www.eudra.org/humandocs/PDFs/EWP/060295en.pdf](http://www.eudra.org/humandocs/PDFs/EWP/060295en.pdf)  
5 [www.eudra.org/humandocs/PDFs/EWP/060295en.pdf](http://www.eudra.org/humandocs/PDFs/EWP/060295en.pdf)

6  
7 General guidance on the investigation of drug interactions is available online at:

8  
9 [www.eudra.org/humandocs/PDFs/EWP/056095en.pdf](http://www.eudra.org/humandocs/PDFs/EWP/056095en.pdf)  
10 [www.eudra.org/humandocs/PDFs/EWP/056095en.pdf](http://www.eudra.org/humandocs/PDFs/EWP/056095en.pdf)

11  
12 In Sweden, regulators ask for relevant pharmacokinetic data on a drug in  
13 development before large Phase II/III trials begin. The pharmacokinetic properties, including  
14 metabolic characteristics, need to be thoroughly characterized so that possible source of  
15 variability (e.g. food interactions, drug-drug interactions, age and gender effects) can be identified.  
16 Whether the pharmacokinetics is changed in these situations should be studied as well as the  
17 potential effects on the pharmacokinetics of other drugs. Preferably, these studies should be  
18 performed early to allow this information to be taken into consideration when designing the  
19 confirmatory phase III studies. An understanding of the relationship between plasma concentration  
20 and therapeutic/toxic effects is a prerequisite to be able to assess the relevance of changed  
21 exposure.

22 Swedish regulators adopt the stance that drug interactions must be taken into account when  
23 considering a candidate drug's risk-benefit ratio. Hamberg cited an example of how this  
24 conservative approach to drug approval led Swedish regulators not to approve a non-HIV agent  
25 that was licensed, and later withdrawn, in other countries.

26  
27 **FDA perspective** - Kimberly Struble, M.D., a regulatory review officer for the FDA, offered that  
28 agency's perspective on the role of drug interaction data in licensing HIV therapies. The FDA  
29 believes developers of new drugs should explore whether an investigational drug is likely to have  
30 a significant impact on metabolic elimination of drugs already on the market and whether drugs on  
31 the market are similarly likely to affect the investigational drug. Potential interactions should be  
32 assessed early in drug development so that clinical implications of interactions can be assessed as  
33 fully as possible in later clinical studies. Developers should determine whether any identified



1 interactions necessitate a dose adjustment of the candidate drug or of drugs it will be used with, or  
2 if anticipated interactions require additional therapeutic monitoring.

3 Struble outlined two steps in the study of drug-drug interactions during drug development:

- 4 • *Step 1.* Drug-drug interaction studies should be performed based on knowledge about (1)  
5 elimination, and (2) potential effects on the pharmacokinetics of other drugs. Information on  
6 these topics is available online at <http://www.fda.gov/cder/guidance/clin3.pdf>, and  
7 <http://www.fda.gov/cder/guidance/2635fnl.pdf>.
- 8 • *Step 2.* After information is gathered on how an agent is metabolized or what pathways may be  
9 affected, developers should design drug interaction studies involving the candidate drug and  
10 commonly used medications that may interact with it.

11  
12 Among important considerations for HIV drug developers are determining when multiple-dose  
13 versus single-dose studies are appropriate and characterizing an agent's inhibition and/or  
14 induction of the cytochrome P450 (CYP) metabolic system. Before studies begin in large cohorts  
15 of HIV-positive persons, drug-drug interaction studies should be done in healthy volunteers or in a  
16 small cohort of HIV-positive individuals. If such studies are done in an HIV-positive group, data  
17 should be analyzed in real time and dose adjustments should be made accordingly. Before  
18 approval of an agent, ideally the FDA would like to review appropriate drug-drug interaction  
19 dosing information for all antiretroviral agents.

20 Struble listed three instances in which antiretroviral drug interactions are likely to be complex:

- 21 1. Dual protease inhibitor or dual nonnucleoside combinations
- 22 2. Combinations involving three or more agents metabolized by or affecting the same pathway
- 23 3. Two-way interactions

24  
25 Not all drug-drug interactions require a change in the drug regimen, Struble noted. Spacing  
26 doses of different drugs appropriately may be all that is required to avoid the interaction.

27 Taking a drug with food or on an empty stomach can increase or decrease bioavailability. The  
28 FDA considers it important to understand food effects before phase III trials so that a candidate  
29 drug's activity can be considered in these trials under optimal conditions. Information on this issue  
30 is available at <http://www.fda.gov/cder/guidance/1719dft.pdf>.

31  
32 **Industry perspective** - Mark Becker, Pharm.D., (Agouron Pharmaceuticals, USA) summarized the  
33 pharmaceutical industry's perspective on drug interactions in the developmental process. He listed  
34 three reasons for conducting drug interaction studies:

- 35 1. To understand pharmacokinetic interactions between the candidate drug and other agents

- 1 2. To confirm in vitro and suspected interactions (absorption, distribution, metabolism,  
2 elimination)
- 3 3. To address concerns about safety (drug side effects and interactions that may adversely effect  
4 individuals with unstable medical conditions)

5  
6 Becker then outlined factors that influence the type of interaction studies during new drug  
7 development trials:

- 8 1. How a new agent is positioned, either as a first line agent or as a salvage drug, which will  
9 determine which type of interaction studies to do;
- 10 2. Frequently used concomitant medications, including antiretroviral agents and other drugs  
11 commonly prescribed for HIV-positive people;
- 12 3. The sub-population where the new agent will be used, including infants and children.

13  
14 Drug developers typically consider six factors when planning trials:

- 15 1. Clinical issues
- 16 2. Timing: When in the development process should certain studies be conducted?
- 17 3. Resources: Availability of drug, funds, personnel and other key resources;
- 18 4. Safety: What are the potential interactions or side effects when the candidate agent is  
19 coadministered with other drugs or in individuals with certain medical conditions?
- 20 5. Dose: Does the dose of the candidate drug or a coadministered drug have to be changed?
- 21 6. Positioning: When during the course of the disease is the drug used? This will help to  
22 determine the priority and the types of interaction studies that need to be evaluated.

23  
24 Other factors developers consider when planning trials are the appropriate study participants  
25 (healthy individuals, HIV-positive persons, or certain HIV-positive subpopulations), and whether  
26 trials should be conducted internally, by independent investigators, or in clinical trial networks.

27

28 **Patient advocate perspective** - Yvette Delph, M.D. (Treatment Action Group, USA) summarized  
29 issues that the HIV-positive community believes are critical in the study of drug-drug interactions.

- 30 • Pharmaceutical companies should be willing to supply each other with drugs needed for  
31 interaction studies.
- 32 • In addition to infants and children, subpopulations in drug interaction studies should include  
33 individuals with kidney or liver disease, and the elderly.
- 34 • Because most persons taking an antiretroviral regimen take at least three antiretrovirals,  
35 ongoing post-approval monitoring is crucial. Pharmacokinetic studies typically involve small  
36 groups of study participants, so those studies may not anticipate the wide range of individual  
37 characteristics that may influence drug interactions.
- 38 • Interactions between individual components of so-called mega-HAART combinations are  
39 poorly understood.

40

1 Delph proposed that expanded access programs afford a good opportunity to conduct drug  
2 interaction studies in larger populations.

### 4 **Group discussion: Facilitating industry collaboration on drug interaction studies**

6 Several Forum panelists expressed the strong opinion that poor cooperation between  
7 pharmaceutical companies hampers clinical understanding of the best way to combine certain  
8 agents. One physician offered the example of ritonavir plus saquinavir. After years of study,  
9 clinicians still do not understand which dose of each protease inhibitor to use in different  
10 situations. Divergent information on combining protease inhibitors was characterized as “a huge  
11 problem” that can be traced to a financial incentive: Companies are eager that *their* protease  
12 inhibitor be given at a higher dose to increase sales.

13 An advocate noted that when he calls two companies to encourage them to collaborate in a  
14 trial, both companies are apt to blame the other for failing to cooperate. Industry representatives  
15 confirmed that cooperation is often lacking; Glaxo and Abbott each had to purchase the other’s  
16 protease inhibitor for dual-PI studies. Even when companies do agree to collaborate, lengthy  
17 contract negotiations can slow progress.

18 It was proposed that the collaboration problem could be solved if greater control and  
19 funding is given to non-industry investigators. For example, the US AIDS Clinical Trials Group  
20 (ACTG) is an independent trial network supported by public funds, but it can be “hamstrung by  
21 proprietary interests.” Health economists can justify spending \$100,000 or more to purchase drugs  
22 for such studies. The money spent is more than made up in savings on improperly prescribed  
23 medications. Purchasing the drug outright also has the advantage of freeing investigators from  
24 obligations spelled out by a company when it donates drug for study.

25 It was noted that the ACTG has shouldered the responsibility of doing some drug  
26 interaction studies. One example cited was a ritonavir/indinavir study. But such trials can be  
27 “incredibly expensive” if the ACTG must purchase the drugs and run the trial. A physician  
28 maintained that publicly funded trials, such as the above mentioned ACTG study, do not happen  
29 often enough because public funds are not inexhaustible. One question raised was how forceful the  
30 US Food and Drug Administration (FDA) can be in requiring specific drug interaction studies  
31 before approving an agent.

1 Dr. Struble responded that the agency cannot force a company to do specific drug  
2 interaction studies, but that it can “strongly recommend” such studies toward the end of phase II in  
3 drug development. She noted that triglyceride elevations found when Abbott’s investigational  
4 protease inhibitor ABT-378 is combined with low-dose ritonavir led the FDA to ask Abbott to  
5 study interactions of that combination with lipid-lowering agents. Abbott complied. Struble added  
6 that the FDA keeps an open ear to requests for certain types of interaction studies by community  
7 members and independent investigators. The agency responded, for example, to calls for  
8 interaction studies between protease inhibitors and methadone, and between protease inhibitors  
9 and oral contraceptives.

10 It was noted that other non-industry groups conduct drug interaction studies, such as the  
11 Centers for Education and Research on Therapeutics (CERT). The ACTG, he said, is not the only  
12 mechanism for independently funded and operated drug interaction studies. David Barr said the  
13 Forum would gather information on CERT and distribute it to meeting participants.

14 An industry representative maintained that industry has a decided incentive to conduct its  
15 own drug interaction studies because independent investigators can have study goals not shared by  
16 industry. Other participants concurred that independent researchers can have their own agenda  
17 when doing drug interaction studies. Investigators were encouraged to avoid pushing their own  
18 research goals in such studies.

19 Confidence in results of interaction studies by independent investigators depends on  
20 standards for cross-validation between laboratories. Such standards do not have to be regulated,  
21 but some guidelines are essential. Industry has to feel comfortable that independent studies are  
22 reliable.

23 Industry does not always need prodding by regulatory agencies to conduct drug interaction  
24 studies. Companies react to “free-market dynamics,” one speaker noted. When a speaker at a  
25 plenary session of an important meeting notes a lack of data on a critical interaction, industry  
26 “jumps.” But another participant disagreed, maintaining that industry does not jump often enough.

27 One investigator worried that some of the drug interaction findings that get listed in product  
28 information are based on findings in only a handful of study subjects. Clinicians who adjust doses  
29 based on limited data may be unjustly confident in how well those findings apply to different  
30 individuals. But industry representatives argued that drug interaction studies by their companies

1 have involved sufficient numbers of subjects, though it was acknowledged that dropouts can limit  
2 study population size.

3 Patient advocates called for more intense study of interactions between pharmaceuticals  
4 and “natural remedies” and between pharmaceuticals and “street drugs.” Stephen Piscitelli, who  
5 recently reported one such study involving a protease inhibitor and St. John’s Wort (Piscitelli SC,  
6 Burstein AH, Chaitt D, et al. Indinavir concentrations and St John's Wort. *Lancet* 2000;355:547-  
7 548), said that NIAID has a small program to do other similar studies. But he added that a great  
8 number of such studies will not get done because industry will not pay for them.

9 An industry representative maintained that a problem with such studies is that the  
10 formulation of natural remedies and recreational drugs varies so much from batch to batch that a  
11 study of a pharmaceutical with one specific version of a remedy or street drug could be  
12 meaningless. But, a patient advocate disagreed, calling that argument a “red herring” because such  
13 studies are not looking for subtle interactions, but for large effects like those Stephen Piscitelli  
14 identified between St. John’s Wort and indinavir.

15 It was suggested that drug-drug interaction studies be grouped by disease category.  
16 Clinicians are not eager to infer from discrete drug-drug interaction findings. For example, a study  
17 of the interaction between a protease inhibitor and rifampin is not enough because it doesn’t tell  
18 clinicians how to treat HIV infection and tuberculosis in the same patient. He emphasized the need  
19 no just to say what drugs to avoid, but what can/should be used to treat a particular comorbidity.

20 A physician proposed that the Forum should investigate what drug interaction studies are  
21 being done and what important interaction questions remain to be answered. Sildenafil (Viagra),  
22 for example, deserves study because of its high use by sexually active HIV-positive people. Other  
23 participants supported this suggestion and encouraged the Forum to push for greater dissemination  
24 of drug-drug interaction findings. Too often, interest in publication of drug interaction studies is  
25 limited because they are regarded as “mundane” and not “cutting edge science.”

26 David Barr acknowledged the importance of disseminating information, but cautioned that  
27 doing so is not simple. He noted that the Forum is revamping its Web site in a way that could  
28 accommodate easier access to drug-drug interaction data. Barr said it is important for the Forum  
29 Executive Committee to hear that panel members see this as a priority deserving resources that  
30 might otherwise be directed elsewhere.

1 Terrence Blaschke proposed that the Forum coordinate information from different Web  
2 sites that address interactions between HIV drugs. He said the Forum could encourage industry to  
3 support a single reliable source for drug interaction findings and advice. Nikos Dedes urged that  
4 such a site should consider its audience as international.

5 Stephen Piscitelli noted the importance of having a “gatekeeper” who assures the  
6 reliability of information on such a site. Mark Becker seconded Piscitelli’s call for quality control  
7 and added that the site should not just list findings, but should offer “salient recommendations.”  
8

### 9 **Encouraging drug developers to share compounds with independent investigators** 10 **for drug-drug interaction studies** 11

12 One researcher broached the problem of obtaining investigational compounds from developers for  
13 drug interaction studies. Once a drug is licensed, he said, it can always be purchased if the  
14 manufacturer chooses not to provide it for studies. But there’s no way to get an unlicensed  
15 compound without the manufacturer’s cooperation. Another added that independent investigators  
16 often do not ask for large quantities of a compound when establishing assays needed for carrying  
17 out drug interaction studies. Shortage of a compound in development is not a good argument for  
18 turning down requests for small amounts of pure compound for analytical purposes interaction  
19 studies. Shortage of a compound in development is not a good argument for turning down requests  
20 for small amounts. “Maybe I need only 10 mg,” he said. “It fits in an envelope.” The problem in  
21 obtaining investigational agents for study, he continued, is not cost, but control. Industry has  
22 legitimate concerns that any compound it provides to independent investigators must be used only  
23 for the stated purpose.

24 An industry representative confirmed the investigator’s point that control is a concern when  
25 providing a new agent for studies outside the company. If the new compound winds up getting used  
26 in a mouse study, he noted, “and a mouse dies,” that death is a “reportable event.” Even after a  
27 drug is licensed, anything that happens in studies not involving the manufacturer can have a  
28 substantial impact on the future of that drug.

29 Another researcher reiterated the point that researchers are routinely frustrated in attempts  
30 to secure an investigational compound for study. He proposed that improving the flow of such  
31 agents should be a “major issue” addressed by the Forum.

1 An industry representative noted that an early hurdle to securing new compounds for  
2 interaction studies is simply reaching the appropriate contact person at the company developing the  
3 drug. David Barr said that coordinating contact information is a task that the Forum can undertake.  
4 Another industry representative argued that reaching the right contact is not the primary problem in  
5 getting drug for study. Whether such requests are accommodated, and how quickly, depends on  
6 where the decision is made, and the decision maker may change from request to request. But David  
7 Barr said that, still, the right contact has to be reached to “start the wheels turning.”

8 It was proposed that the Forum contact all companies in the HIV field and ask them to  
9 provide the appropriate contact information for such requests. It was further suggested that the  
10 Forum itself might act as a conduit, logging all requests for compounds and following up until a  
11 decision is made. The Forum could draft a standard request form, called a Materials Transfer  
12 Agreement or MTA.

13 Industry representatives agreed that a formal request procedure like the one outlined above  
14 would improve the quality of requests. Some requests are unclear in stating exactly what  
15 applicants want and why they want it. One representative noted that the “typical” request for an  
16 investigational compound asks not only for the compound, but also for a grant to study it. He  
17 believes that is the reason many requests get turned down.

18 It was suggested that requests made through the Forum should specify that the compound  
19 will be used only in drug interaction studies. Researchers requesting an agent should realize, said  
20 an industry representative, that they have a “slim chance” of getting the compound during phase II  
21 testing. He proposed that such requests be made during the expanded access phase of development.

22 David Barr said the Forum would collect standard investigational agent request forms  
23 already used by drug developers, as well as appropriate contact names. He proposed that a  
24 smaller Forum meeting should be convened to determine the steps in the request procedure. As a  
25 first goal, documenting what requests are made and how developers respond will itself clarify the  
26 process.

## 27 28 **Encouraging evaluation of therapeutic drug monitoring (TDM)**

29 Therapeutic drug monitoring (TDM) of antiretroviral drugs (specifically, protease inhibitors) has  
30 gained wide interest since research demonstrated that drug concentrations in plasma correlate with  
31 virologic effect. Investigators have suggested that clinical use of TDM can help physicians identify

1 subtherapeutic drug levels and correct them to prevent therapeutic failure. But nearly everyone  
2 who addresses this issue agrees that several hurdles lie between the current knowledge of TDM  
3 and its efficient use as a clinical tool.

#### 4 5 **Uses of TDM**

6 Among the most basic questions about TDM, said one researcher, is exactly what to measure.  
7 Proposals include trough levels, trough plus peak levels, area under the concentration-time curve  
8 (AUC), and 50% or 90% inhibitory concentration (IC<sub>50</sub> or IC<sub>90</sub>). It was suggested that picking an  
9 optimal variable to measure may be less problematic than it seems since all these measures are  
10 interdependent.

11 Another fundamental question is exactly how TDM should be used. Proposals include  
12 using it to maximize therapeutic response, to avoid toxicity, and to detect poor adherence with the  
13 prescribed regimen.

14 However, a researcher maintained that TDM is not a reliable way to measure adherence,  
15 because an isolated drug level will tell you only if a person took the drug the day before. But not  
16 every one agreed, observing that, although a discrete drug level does not confirm *good* adherence  
17 (because a poor adherence may have taken a drug only for one or two days before the drug  
18 concentration is measured), TDM can be a reliable clue to *poor* adherence.

19 It was argued that promoting good adherence may be a more effective way to ensure a  
20 durable therapeutic response than worrying about low drug levels. One study referenced showed  
21 that everyone taking a first-line three- or four-drug regimen by directly observed therapy (DOT) in  
22 a Florida prison had a viral load below 400 copies/mL after 48 weeks, compared with only 68%  
23 taking a first-line regimen without DOT (Fischl M, Rodriguez A, Scerpella E, et al. Impact of  
24 directly observed therapy on outcome in HIV clinical trials. 7<sup>th</sup> Conference on Retroviruses and  
25 Opportunistic Infections. January-February 2000. San Francisco. Abstract 71). It was suggested  
26 that more research attention should be focused on determining the causes of poor adherence and  
27 remedying them.

28 One physician agreed that strategies that may improve adherence are known—once-daily  
29 dosing, electronic dispensing, DOT—but that clinicians “haven’t applied the resources that are  
30 available.” He observed that TDM should ideally be done along with tests for adherence and viral  
31 susceptibility (resistance) to drugs being given. Because therapeutic failure may result from



1 inadequate drug levels, poor adherence, or resistance, measuring one in isolation from the others  
2 will not give a complete picture of a person's response to a regimen.

3 Others concurred with the point that poor adherence is the primary cause of therapeutic  
4 failure. But he estimated that 10% to 20% of failures can be attributed to inadequate drug  
5 concentrations. Inter-individual variations in drug concentrations are a factor in therapeutic failure,  
6 but such variations are less predictable than drug interactions.

7 One researcher suggested that TDM be used primarily to prevent therapeutic failure. To fill that  
8 role, he noted, TDM should be used soon after a new regimen begins, not later, when other  
9 markers are already suggesting therapeutic failure.

10 It was said clinicians can take two approaches to ensuring adequate blood levels of  
11 protease inhibitors. They can use TDM early, or they can simply give a protease inhibitor with 100  
12 or 200 mg of ritonavir. Because this physician believes few clinicians are using single protease  
13 inhibitors any more, he suspects TDM may be more valuable in preventing toxicity due to  
14 excessive protease inhibitor concentrations.

15

16

17

### 18 **Problems with current TDM**

19 A researcher noted that protease inhibitor binding to plasma proteins confounds interpretation of  
20 some drug level studies. As done now, TDM almost always measures total concentration, not  
21 unbound concentration, and thus the true impact of plasma drug levels will vary depending on how  
22 avidly a given protease inhibitor binds to plasma protein, and whether the elimination of the drug  
23 is correlated with total or free concentrations.

24 According to one of the industry representatives, accurate protein binding studies depend  
25 on large-volume samples. Such studies might best be done by the ACTG or other research  
26 networks willing to tackle this problem, she said.

27 Assay turnaround time is another problem with TDM. A four-week turnaround is too slow.  
28 Resistant virus can evolve during that span, and there is little clinical value to identifying a  
29 subtherapeutic drug concentration after resistance has emerged.

30 Interpreting TDM results is more complicated than it may seem, said one researcher,  
31 because protease inhibitors are not given as monotherapy. Ideally, clinicians would want to know

1 the levels of all drugs being given. Nucleoside or non-nucleoside reverse transcriptase inhibitor  
2 levels, and not levels of protease inhibitors, may be too low. But plasma nucleoside  
3 concentrations are meaningless, because they do not correlate with intracellular levels of  
4 triphosphorylated nucleosides, and for nucleosides it's the intracellular triphosphate level that  
5 matters.

6 Another participant added that nucleoside-associated resistance mutations can emerge  
7 before protease inhibitor mutations when drugs from those classes are given together. As a result,  
8 he agreed that the value of TDM is diminished by the inability to measure intracellular nucleoside  
9 levels efficiently in the clinic.

10

### 11 **Quality assurance for TDM**

12

13 It was noted that TDM results vary substantially from laboratory to laboratory. A study presented  
14 at an international meeting held immediately before the Forum roundtable detected unsettling  
15 variation in the ability of different labs to measure drug concentrations correctly in blinded  
16 samples (Aarnoutse RE, Burger DM, Verweij-van Wissen CPWGM, et al. International laboratory  
17 quality control (QC) program for therapeutic drug monitoring (TDM) in HIV-infection: first  
18 results. First International Workshop on Clinical Pharmacology of HIV Therapy. March 2000.  
19 Noordwijk, The Netherlands. Abstract 1.4). It was proposed that the Forum support a quality  
20 assurance program for TDM.

21 Other participants agreed that the Forum should address quality assurance guidelines.  
22 Spending money up front to verify the accuracy of laboratories will ultimately save money that may  
23 be wasted by acting (or not acting) on inaccurate TDM reports.

24 An industry representative agreed that quality assurance must be addressed, but cautioned  
25 that the results of a single quality assurance study offer only a snapshot of quality control in  
26 different laboratories, and that the reliability of labs can be expected to improve.

27 Other participants counseled that the Forum doesn't have "to reinvent the wheel" in  
28 drafting a quality assurance program for TDM. Successful programs that already exist for other  
29 assays can be adapted to antiretroviral TDM. Standards used to certify labs for other work can be  
30 used as a blueprint for quality assurance guidelines for antiretroviral TDM. It was suggested that  
31 published quality assurance program should be consulted. International collaboration is essential  
32 for successful quality assurance. Although sending samples across borders requires more

1 paperwork, individual labs can verify the accuracy of their performance only by comparing it with  
2 that of labs in other countries.

#### 3 4 **Clinical validation of TDM**

5 Many participants feel that TDM for antiretrovirals cannot be considered a standard of care  
6 because it has not been clinically validated. As with TDM for other agents, it will be difficult to  
7 prove that antiretroviral TDM is clinically beneficial. One researcher predicted that TDM of  
8 antiretrovirals will probably benefit only a few individuals. Everyone should realize, he said, that  
9 clinicians may wind up ordering 100 drug concentration assays to benefit five patients.

10         However, a patient advocate maintained that, even at that rate, TDM could be considered a  
11 “huge benefit.” And the 95% of patients in whom TDM confirms an adequate drug concentration  
12 will have a baseline value to compare against future results.

13         One participant reminded colleagues that the medical community spent “millions” on TDM  
14 for vancomycin, only to find that strategy worthless. He cautioned against repeating that mistake  
15 with antiretroviral TDM. Validation should be sought before TDM becomes a standard of care for  
16 HIV infection.

17         A clinician warned that strategies such as TDM can take on a life of their own. “If industry  
18 isn’t interested,” he explained, “you can’t do it. When industry gets interested, you can’t stop it.”  
19 Since industry still has not sold TDM to clinicians as a standard of care, he said, now is the time  
20 to work on validating its clinical merit. He added that he and other clinicians have no idea how  
21 they might use TDM. But he echoed the suggestion of that TDM probably has to be done early in  
22 the course of a new protease inhibitor regimen to be worthwhile.

23         An investigator argued that randomized controlled trials are needed to validate TDM for  
24 HIV infection. But he noted that such a trial had been rejected by the UK’s Medical Research  
25 Council after 16 months of “fast track” consideration. A randomized trial of TDM is proceeding in  
26 The Netherlands as part of the ATHENA study.

#### 27 28 **Conclusions and recommendations regarding TDM**

29 One of the patient advocates at the meeting summarized the panel’s discussion of TDM. He asked  
30 the following questions:

- 31 • Can TDM help optimize therapy, increase efficacy, reduce resistance and delay treatment  
32 failure? If so, how many/what proportion of patients will benefit, and at what cost

- 1 (incremental extra cost) offset against what benefit (saved regimens, reduced toxicity, etc.)?  
2 Are there other means of obtaining the same result?
- 3 • If TDM can be beneficial, when and how should it be used, for which drugs, and in which  
4 patients? Specifically, should TDM be used when starting ART, or within 2 – 4 weeks (once  
5 steady-state is reached)? For early treatment failure/adherence assessment? When starting 2<sup>nd</sup>  
6 line/salvage regimens? In conjunction with resistance testing for early virologic failure to  
7 consider raising doses? For toxicity to consider lowering doses?
  - 8 • How much and what kind of evidence is needed to determine whether TDM should be  
9 integrated into standards of care? What retrospective studies can help? What prospective  
10 studies are underway (e.g. ATHENA)?
  - 11 • How should TDM assays be standardized and validated for clinical use? What sort of QA/QC  
12 should be used? Which parameters should be measured? How will they be interpreted  
13 clinically (C<sub>max</sub> for toxicity, C<sub>min</sub> for efficacy, AUC for population PK, others)?

14  
15 He repeated the suggestion of two researchers that it may make sense to focus on TDM for  
16 protease inhibitors during the first weeks that a protease inhibitor regimen is given. It is not clear  
17 that nonnucleosides are a good candidate for TDM, and all agree that nucleosides are not.  
18 Recalling the point made by one of the physicians, he said that TDM should probably be integrated  
19 with tests for resistance and adherence.

20 The group agreed that two overarching questions that should be addressed:

- 21 1. What evidence is needed to determine that TDM is a standard of care?
- 22 2. What TDM studies are under way, and which studies not being done should be planned?

23  
24 David Barr concluded the session by saying that the Forum can take a first step by  
25 gathering information on the use and quality assurance of TDM for other diseases.