Demo Slide Project – References and Notes
Sara Lou O'Connor

References:

Andrejak M, Genes N, Vaur L, et al. Electronic pill-boxes in the evaluation of antihypertensive treatment compliance: comparison of once daily versus twice daily regimen. *Am J Hypertens* 2000, 13:184-190.

Slide 1: Andrejak, et al, p. 185
Slide 8: Andrejak, et al, p. 190
Slide 13: Andrejak, et al, p. 189

Note: This study presents some impressive figures for comparison between compliance results for once-daily and twice-daily dosing. The differences were not statistically significant for measures of disease control or efficacy. With so many dissimilarities between hypertension management and HIV management, we must be careful when comparing the two:

Adverse event profiles: Much worse with HIV treatment.

Ability to ignore disease symptoms: Much easier to be in denial with HIV, because symptoms develop over weeks or months, compared with those of hypertension that can be rapidly incapacitating.

Beliefs about the diseases: hypertension can be controlled and is a "normal" illness; HIV cannot be controlled and is a frightening "terminal" illness.

Despite the results shown on p. 189, Table 4, a between-groups difference in percentage of patients who achieved blood pressure normalization of 40.9% and 24.4% was not statistically significant. This points out the problem with statistics, and perhaps we should be willing to say what the authors were not: despite the lack of statistical significance, this was (was it not?) a substantial difference in clinical results.

Cardiello PG, van Heeswijk RP, Hassink EA, et al. Simplifying protease inhibitor therapy with once-daily dosing of saquinavir soft-gelatin capsules/ritonavir (1600/100 mg): HIVNAT 001.3 study. *J Acquir Immune Def Syndr* 2002,29:464-470.

Slide 8: Cardiello, et al, p. 464, 469
Slide 9: Cardiello, et al, p.465, 468-469
Slide 10: Cardiello, et al, p. 469

Note: The form of drug (saquinavir soft-gel capsule) used in this study was later withdrawn from the market. Historically, 2000-2002 was a time of testing the older products in different combinations and regimens. As far as this study goes, at the time, 2002, saquinavir looked like a contender for once-daily dosing regimens of HAART when "boosted" with ritonavir.

While companies do need to distinguish the pros and cons of their products, the companies supporting educational programs about HIV and HAART have created a tradition of never talking about only one drug. HIV education programs for HIV practitioners consistently convey information on all drugs. Even for conferences supported by only one company, the company sponsors and the participating faculty agreed that it was crucial to educate practitioners about all the options. Combinations often used products from different companies; saquinavir and ritonavir were produced by two different pharmaceutical companies.

Although only one drug study was included in the research materials provided, saquinavir as an example of once-daily dosing, I would not advise a client to format an educational program on such limited information. Even if the study were of a new drug with remarkable results, HIV therapy involves many agents used together. Educational programs on HIV therapy will, I hope, continue to follow the comprehensive model that produced many benefits. By explaining advances in therapeutic understanding, makers of an educational program gain access to information from leading practitioners, and genuine cooperation between sponsoring clients and medical/scientific faculty.

Another advantage of creating programs that include comprehensive reviews of treatment is that should one product be identified as a problem, the entire educational program need not be thrown out and can be revised to introduce the important change in the knowledge base. Knowing that three years after this study was reported, the product (saquinavir soft-gel capsules) was withdrawn from the market emphasizes the advantages of "sticking together" with other products and not positioning oneself apart from the recognized field of approved antiretroviral drugs.

Historically, what this study presented was the possibility of reducing the dosing frequency of PIs to a once-daily regimen. The advantages of this would be to simplify the treatment regimen, reduce the number of pills taken daily, reduce the number of doses to once-daily, and hopefully to increase adherence.

Ritonavir inhibits first-pass metabolism. By combining saquinavir with ritonavir, the plasma level of saquinavir is greatly increased over what is achieved even with a higher dose of saquinavir alone.

In this study, patients who had been taking saquinavir twice daily, switched to the combination of saquinavir + ritonavir for 24 weeks. The dosage levels (p. 465) were:

> saquinavir 1400 mg twice-daily (requiring 7 pills each dose or 14 daily)
>
> switching to:
>
> saquinavir 1600 mg once-daily (8 pills) + ritonavir 100 mg once-daily (1 pill) = 9 pills daily

All patients also took twice-daily combinations of NRTIs.

Results were solidly positive and supportive of doing further study of once-daily dosing of PIs:

> All patients who started the once-daily plus NRTI regimen had HIV plasma concentrations <50 copies/mL. At the end of 24 weeks, 93% were still at that level, and all patients had virus levels <300 copies/mL. (p. 467)
>
> The level of saquinavir plasma concentration varied greatly, but all patients had a minimum level (trough) that was above the inhibitory concentration. (p. 467-468)
>
> No patients had to stop the treatment because of adverse effects or toxicity.
>
> CD4 cell counts (now called CD4+ T cell counts) increased over the 24 week period, with a median increase of 123/µL. The probability that this difference was beyond the range expected of a chance occurrence was significant at the $p<.001$ level. (p. 468)

Dezii CM, Kawabata H, Tran M. Effects of once-daily and twice-daily dosing on adherence with prescribed glipizide oral therapy for type 2 diabetes. *South Med J* 2002, 95:68-71.

> Slide 5: Dezii, et al, p. 70
> Slide 8: Dezii, et al, p. 68
> Slide 14: Dezii, et al, p. 68

Note: This was a retrospective study and did not look at any measures of disease control. Only a review of prescription renewals provided the information used to indicate adherence with the two regimens being compared. The authors

state that aside from the limited associations they make with age and dosing frequency, there is little information to support the role of various patient characteristics on adherence. (p. 70) Yet this work was done after that of Gifford, et al, 2000, which included massive amounts of information about patient characteristics and cites many others.

I am not sure why this paper is included as a reference. I would look for something with more to contribute.

Frank I. Once-daily HAART: toward a new treatment paradigm. *J Acquir Immune Def Syndr* 2002, 31: Suppl 1,S10-S15.

Slide 2: Frank, p. S10, citing Paterson, et al, 2000
Slide 4: Frank, p. S10, citing Paterson, et al, 2000
Slide 6: Frank, p. S11
Slide 6: Frank, p. S11, citing Paterson, et al, 2000; Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents [GUARVA 2002]; Gebo, Keruly, Moore, 2001
Slide 7: Frank, p. S11
Slide 7: Frank, p. S11, citing, Bartlett, et al, 2001; Cahn, 2000
Slide 8: Frank, p. S10
Slide 8: Frank, p. S11, citing, Bartlett, et al, 2001; Cahn, 2000
Slide 9: Frank, p. S11
Slide 9: Frank, p. S12-S14
Slide 9: Frank, p. S11, citing Paterson, et al, 2000
Slide 10: Frank, p. S11
Slide 11: Frank, p. S11
Slide 11: Frank, p. S12-13
Slide 13: Frank, p. S11
Slide 13: Frank, p. S13, reviewing studies and specific drugs
Slide 14: Frank, p. S11, citing Mannerheimer [sic, check spelling], et al, 2000

Note: Frank reviews the case for once-daily dosing. In addition to providing many patient characteristics that have been correlated with adherence rates, he gives practical advice for the practitioner who wants to help patients achieve better adherence.

The dosing study review explains several aspects of adherence, including number of drugs, methods of assuring adherence, number of pills, and overall “fatigue” of adherence. The author reports pill count as being inversely related and simpler regimens as being positively related to adherence.

Frank reports studies that showed equivalence of therapeutic response for once-daily dosing, which was certainly a concern until analyses revealed the potential for improving response with once-daily regimens.

At the time, Frank reported seven studies that compared once-daily dosing of at least part of the regimen, plus another two studies that put together true once-daily combinations. The researchers hoped to find effective once-daily regimens.

Should all the data Frank reports be included in this slide presentation? In writing a slide presentation, some researchers and practitioners attempt to present collections of data, such as listings of studies from the Frank report, into a slide. Others report specific results of a clinical trial in a slide. Neither of these collections of data are well represented by the slide format, but would be better presented in a written summary. If a researcher wants to make a live-presentation, then an exhibit with a take-home brochure would be a better way to present such lists and details.

Slides are regularly used to provide notes to people attending a lecture, and there is no reason the description and data from a study or collection of studies cannot be duplicated or re-presented on a slide format. What does not work well is showing such data during a speaking presentation, if the purpose is to involve the audience or to assure they are listening and remembering the points made in the discussion. If all the important points are given in a slide series, then the audio presentation is really a waste of air-time. This type of presentation developed in classrooms, with inexperienced instructors who had no speaking or teaching talent, but who were happy to engage their students in looking at their laptops for an hour.

Gifford AL, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *J Acquir Immune Def Syndr* 2000, 23:386-395.

Slide 3: Gifford, et al, p. 387, citing, Havlir, et al, 1998; Pialoux, et al, 1998; Reijers, et al, 1998; Montaner, et al, 1998; Hecht, et al, 1998; Shafer, et al, 1998
Slide 4: Gifford, et al, p. 389
Slide 5: Gifford, et al, p. 388
Slide 5: Gifford, et al, p. 389
Slide 5: Gifford, et al, p. 390
Slide 6: Gifford, et al, p. 387, citing Morse, et al, 1991; Samet, et al, 1992; Muma, et al, 1995; Singh, et al, 1999; Kalichman, et al, 1999
Slide 6: Gifford, et al, p. 389
Slide 7: Gifford, et al, p. 388

Slide 7: Gifford, et al, p. 389-390
Slide 7: Gifford, et al, p. 387, citing Haubrich, et al, 1999; Chesney, et al, 2000; Roca, Gomez, Amedo, 1999; Gordilla, et al, 1999
Slide 10: Gifford, et al, p. 387-388, 392, 393-394
Slide 11: Gifford, et al, p. 392
Slide 13: Gifford, et al, p. 388-389
Slide 13: Gifford, et al, p. 393
Slide 15: Gifford, et al, p. 392-393

Note: This is an excellent study of adherence to HAART, but there are some elements not examined. None of the patients were on once-daily regimens, so that aspect of adherence has to be taken from other studies. This study did not look at adherence over time, but only at a specific point in time.

In an ideal world, the next big study would use the same techniques to compare once-daily and twice-daily regimens. And the study after that would compare patients following the best regimen who receive specific training to enhance adherence with patients who receive no specific instruction beyond what is usual.

Howard AA, Arnsten JH, Lo Y, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS* 2002, 16:2175-2182.

Slide 3: Howard et al, p. 2176, citing Wainberg and Friedland, 1998
Slide 4: Howard, et al, p. 2180
Slide 5: Howard, et al, p. 2179
Slide 7: Howard, et al, p. 2179
Slide 8: Howard, et al, p. 2179
Slide 11: Howard, et al, p. 2181
Slide 12: Howard, et al, p. 2180
Slide 15: Howard, et al, p. 2176, citing Liu, et al, 2001; Carrieri, et al, 2001; Mannheimer [sic, check spelling], et al, 2002

Note: Excellent study of adherence and characteristics affecting adherence that does include the factor of time. When adherence rates over the time period studied were compared, the differences were statistically significant, indicating that time was most likely to be related negatively to adherence. (p. 2175) Because this study was limited to women with HIV, some of the indicators may not be directly applicable to the population of people with HIV.

I also used the following as an additional resource for basic information, (GUARVA).

Guidelines for the Use of Antiretroviral Agents (GUARVA) in HIV-1-Infected Adults and Adolescents October 10, 2006. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC).

Note: while this is the 2006 version, previous versions were available in 2002-2004, and were cited by authors of the primary references.