PMPA: first human data

In April 1997, at the 10th International Conference on Antiviral Research in Atlanta, Gilead Sciences reported data from the first human study of PMPA after 8 days of treatment. Both PMPA and Bis Pom PMEA (see accompanying report) are nucleotide analogues being developed by Gilead. This class of reverse transcriptase inhibitors have a different mechanism of action than a nucleoside RTI (AZT, d4T, etc). Gilead Sciences, the developer of both PMPA and PMEA, say that unlike nucleoside analogues, nucleotide analogues are already activated; they can enter uninfected cells and form a reservoir of drug that pre-arms the cell against the virus; which may be why the drug may be more potent; in contrast, AZT and drugs in its class work only in cells that have the machinery to activate the drug.

Up until now the only data available for PMPA has been from animal studies and the laboratory. Previously it was reported that PMPA has a long intracellular 1/2 life of 35 hours in monkeys and 30 hours in human cells in vitro. It is hoped that this long half-life will allow for relatively less frequent dosing than with the administration of currently used antiretrovirals.

Animal data. Data was published in Science November 1995 from a study of PMPA given (in two different doses) subcutaneously to 25 macaque monkeys either before or after exposing the monkeys to S.I.V. The monkeys received once daily injections of PMPA for 4 weeks, beginning either 48 hours before, four hours after or 24 hours after inoculating the monkey with SIV. The monkeys were followed regularly for 56 weeks, but no evidence was found of SIV, SIV DNA, or SIV-specific antibodies in the plasma or peripheral blood mononuclear cells (PBMC). From three weeks post-exposure onward, all 10 placebo-treated monkeys became infected with SIV. Each monkey also had a groin lymph node biopsied 16 to 26 weeks after SIV exposure. None of the treated monkeys, but all that received placebo, showed evidence of SIV infection in the biopsied tissues. Gilead reported there were no adverse side effects caused by PMPA.

The results of this study imply application of PMPA to post-exposure HIV prevention (such as from an accidental needle stick), and may have implications for use in preventing maternal transmission of HIV to a newborn.

At the Ninth International Conference on Antiviral Research in Fukushima, Japan during May of 1996, Gilead presented data on two additional applications of PMPA in monkeys infected with SIV.

In one study, ten monkeys that had been infected with SIV for at least 19 weeks were treated with once-daily injections of PMPA for four weeks. After 2 or fewer weeks of treatment, PMPA (30 or 75 mg/kg/day) reduced SIV levels by more than 99% or approximately 2 to 3 logs; some levels decreased below the limit of detection. In the two control monkeys who did not receive PMPA, SIV viral load did not decrease. After the 4

weeks of PMPA treatment ended the SIV viral load rebounded within two weeks back to their baseline levels. It was reported that PMPA was well tolerated in the 30 mg/kg/day dose group. In the 75 mg/kg/day dose group, no clinical toxicities or side effects were observed but chemical changes in blood markers were seen (red blood cell, phosphate and hemoglobin counts went down but these effects were reversible).

In the other study, PMPA was administered in a topical gel intravaginally, and prevented the transmission of SIV to female monkeys exposed intravaginally to the virus. All of the PMPA treated monkeys showed no signs of SIV transmission or infection throughout an eight-week follow-up period. The control monkeys who did not receive PMPA showed signs of SIV transmission and infection within two weeks of exposure to the virus.

New Human Data. Twenty study participants (16 received PMPA and 4 placebo) were treated with a single intravenous dose of PMPA on day 1 followed by a 7 day washout period and then 7 consecutive days of once daily intravenous doses. Two dose levels (1.0 and 3.0 mg/kg/day) were evaluated. The median baseline CD4 counts and HIV-RNA (viral load) were 496 cells and about 50,000 copies/ml (4.7 log) for the low dose group, 239 cells and about 126,000 copies/ml for the higher dose group. For the 4 persons receiving placebo, the baseline CD4 and HIV-RNA were 804 cells and about 20,000 copies/ml (4.3 log).

After completion of 8 days of dosing (single IV dose on day one followed by 7 consecutive days off drug, and then followed by 7 consecutive days of dosing), the median change in HIV RNA from baseline was -1.1 log (n=8) for the higher dose, -0.6 log for the lower dose (n=8), and +0.1 log for the placebo (n=4). Following the initial single dose on day 1, the HIV-RNA was reduced from baseline by -0.2 log on day 3, and by -0.4 log on day 7. The CD4 count increases were about 40 cells for those receiving PMPA after day 14, and for those receiving placebo the CD4 counts decreased about 10 cells.

David Ho's widely accepted theory of HIV kinetics, based on his research and that of others, is that there is a two day half life of productively infected cells, which means that every two days there can be a 2-fold (50%) decrease in HIV in blood as a result of effective antiviral therapy. Based on the mathematics of this theory, the -1.1 log reduction achieved by PMPA in the study reported was the maximum that could be achieved in 8 days.

During PMPA treatment, viral load decreased continuously until completion of dosing. After 8 days of dosing, when treatment was stopped, the viral load decrease of -1.1 log for the higher dose was sustained for another 7 days, whereupon it started to rebound and approached baseline within about 1 week. The viral load reduction of -0.6 log achieved for the lower dose group was not sustained following stopping of drug, but immediately started rebounding after drug was stopped. This combined with the potential toxicities or side effects, which PMPA might have, could be an important factor in selecting adequate dosing. Gilead reported that the potential maximum dose has not yet been reached, and that PMPA is cleared renally (kidney) and not through the P450 liver enzyme system. Protease inhibitors and NNRTIs (non-nucleoside reverse transcriptase inhibitors) are metabolized by the P450 liver enzyme system which often is associated with difficult to

deal with drug interactions.

Safety. Gilead reported that there were no lab test abnormalities, but side effects were reported: of the 16 persons who received PMPA-- headache (5), dizziness (5), fatigue (4), protein in urine (1), neutropenia (0). The 4 persons receiving placebo experienced: headache (2), dizziness (1), fatigue (0), protein in urine (1), neutropenia (1). Gilead characterized PMPA as safe and well-tolerated. It is important to remember that PMPA is still in very early stages of development. As human trials proceed and more individuals gain experience using PMPA, unforeseen toxicities or side effects can emerge. Therefore, high expectations should be constrained.

Resistance. In previous research in SIV infected monkeys on treatment with PMPA, over 1 year resistance to PMPA was not detected, whereas AZT resistance in monkeys has been detected. In vitro, AZT resistant virus was sensitive to PMPA. Generally, animal and in vitro resistance data is preliminary and may not apply to humans. In vitro, the only identified resistance mutation found associated with PMPA is the K65R which caused a 3-fold reduction in sensitivity. In vitro, this same mutant caused a 10-fold reduction in sensitivity in to PMEA. However, a K65R mutation was introduced to SIV and a monkey infected with that mutant SIV; that monkey had a full antiviral response to subsequent PMPA therapy.

Gilead has an orally administered pro-drug for PMPA called Bis Poc PMPA which it is expected can be taken with or without food. Future human studies are planned to begin using the oral PMPA tablets within several months. Initially once a day dosing will be explored. It could be expected that a pro-drug may be more potent than an intravenous formulation. The first study will be continuous dosing for one month, and for safety sake drug administration will stop at that point. It is not expected that resistance associated with PMPA would be an issue for a one-month course of treatment based on its mechanism of action and what we know so far about resistance associated with PMPA. Brief dose escalation studies will follow to attempt to reach a maximum dose considering safety and tolerability. It is expected that by the end of 1997 a dose should be selected and large scale studies will begin. Current plans are to explore PMPA alone and in combination with other anti-HIV drugs.