BMS Virology™
Bristol-Myers Squibb Company

November 2004

Re: Important New Clinical Data
Potential Early Virologic Failure Associated with the Combination Antiretroviral Regimen of Tenofovir Disoproxil Fumarate, Didanosine, and Either Efavirenz or Nevirapine in HIV Treatment-Naïve Patients with High Baseline Viral Loads

Dear Health Care Provider,

Bristol-Myers Squibb (BMS) Company is writing to advise you of important new clinical data regarding coadministration of Viread® (tenofovir disoproxil fumarate [TDF]), Videx® EC (didanosine delayed-release capsules enteric-coated beadlets [ddI EC]), and either Sustiva® (efavirenz [EFV]) or Viramune® (nevirapine [NVP]). Data for EFV + TDF + ddI EC are derived from an open-label randomized study (virologic failure in 6/14 patients) and a retrospective database analysis (virologic failure in 5/10 patients), while data for NVP + TDF + ddI EC are derived from a retrospective database analysis (virologic failure in 2/4 patients).

- Results from two recently conducted, investigator-sponsored trials by Podzamczer et al[1] and JM Gatell (written communication, July 2004) have demonstrated a potential for early virologic failure associated with this antiretroviral regimen in treatment-naïve HIV patients with high baseline viral loads. The mechanism of early virologic failure in these patients is unclear.

- Early virologic failure appears to be limited to the specific combination of TDF + ddI EC + either EFV or NVP as there are data from registrational trials supporting the efficacy of EFV and TDF-based regimens as well as EFV and ddI EC-based regimens in treatment-naïve HIV patients.[2-4] Additionally, a recent post-hoc analysis performed in treatment-experienced HIV patients with high baseline viral loads receiving a boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs) demonstrated lower virologic failure rates in subjects receiving ddI EC and TDF than those receiving another nucleoside analogue in combination with TDF, though significance testing could not be performed due to a small number of patients (n=55).

Based on this information:

- **clinicians should use caution when coadministering TDF, ddI EC, and either EFV or NVP in treatment-naïve HIV patients with high baseline viral loads.**

- **further investigations are ongoing to better understand the clinical implications of these results.**

For further details on these studies, please refer to the following pages for study summaries.

Studies Demonstrating Early Virologic Failure in Treatment-Naïve HIV Patients with High Baseline Viral Loads

- **The ININ Study**[1] (Podzamczer et al)**:** An open-label, randomized, multicenter, pilot study with a planned enrollment of 50 treatment-naïve HIV patients designed to assess efficacy and safety of TDF 300 mg once daily + ddI EC 250 mg once daily (≤60 kg: 200 mg once daily) + EFV 600 mg once daily compared with TDF 300 mg once daily + ddI EC 250 mg once daily (≤60 kg: 200 mg once daily) + EFV 600 mg once daily + Kaletra® (lopinavir/ritonavir [LPV/RTV]) 400/100 mg twice daily. Of the 36 enrolled patients, 26 were available for follow-up at 3 months. Six of 14 patients (42.8%) in the TDF + ddI EC + EFV arm experienced protocol-defined virologic failure*, versus 0 of 12 patients in the TDF + ddI EC + EFV + LPV/RTV arm. Baseline viral load >100,000 copies/mL and advanced stage of disease (low CD4+ cell counts [<200 cells/mm^3] plus CDC stage C or B3) were seen in all six patients with virologic failure but in none of the eight patients without virologic failure. Resistance patterns that included G190E/S (n=3), L74V/I (n=4), and K65R (n=2) mutations were observed at failure.

- **JM Gatell et al** (written communication, July 2004)**:** A retrospective database analysis of 5000 treatment-naïve HIV patients in whom therapy was initiated between October 2002 - March 2004 was performed. Fourteen patients were identified as having received a regimen of ddI EC 250 mg once daily and TDF 300 mg once daily, plus either EFV 600 mg once daily (n=10) or NVP 400 mg once daily (n=4). After 12 weeks of therapy, 5/14 patients (36%) experienced suboptimal (plasma viral load drop <2 log_{10} copies/mL) response rates. Two additional patients (total 7/14, 50%) who were treatment-responders at Week 12 reached protocol-defined virologic failure at Week 24.† The seven cases of virologic failure consisted of 2/4 patients receiving NVP- and 5/10 patients receiving EFV-containing regimens. At baseline, virologic failure patients had a median log_{10} viral load of 5.8 (range, 4.7-6.0) copies/mL and a median CD4+ cell count of 126 (range, 24-281) cells/mm^3. Four of the virologic failure patients exhibited the K65R and L74V mutations and all 7 exhibited one or more of the following mutations: L100I, K103N/R/T, Y181C, and G190E/Q/S.

Studies of Treatment-Naïve HIV Patients with Combination Antiretroviral Regimens containing EFV and TDF or ddI EC

- **Gilead Study 903**[2]**:** A 144-week, Phase III, multicenter, randomized, double-blind, active-controlled trial in treatment-naïve HIV patients designed to evaluate the efficacy and safety of TDF compared to Zerit® (stavudine [d4T]) capsules, each in combination with 3TC + EFV. At 48 weeks, similar efficacy was observed between the two treatment groups: EFV + 3TC + TDF (n=299), HIV RNA <400 copies/mL = 79% and <50 copies/mL = 76%; versus d4T + 3TC + EFV (n=301), HIV RNA <400 copies/mL = 82% and <50 copies/mL = 79%, ITT analysis. At 48 weeks, Study 903 showed comparable virologic efficacy (HIV RNA <400 copies/mL) in patients with baseline viral loads above and below 100,000 copies/mL (n=600; >100,000 copies/mL = 86% in the TDF arm and 85% in the d4T arm; ≤100,000 copies/mL = 87% in the TDF arm and 89% in the d4T arm).[5] These trends continued through 144 weeks.[6]

- **Study 301A**[3,4]**:** A 48-week, double-blind, active-controlled multicenter study compared Emtriva® (emtricitabine [FTC]) 200 mg once daily administered in combination with ddI EC 400 mg once daily (patients weighing <60 kg received 250 mg) and EFV 600 mg once daily

* Virologic failure in the ININ Study was defined as (1) reduction in viral load of less than 2 log_{10} copies/mL at 3 months, (2) more than 1 log_{10} copies/mL rebound from the nadir, or (3) viral load detectable at 6 months or later.

† Virologic failure in the Gatell et al study was defined as (1) plasma viral load drop of less than 2 log_{10} copies/mL at 3 months or (2) viral load rebound less than 200 copies/mL for 2 consecutive measurements separated by at least one week, after an initial drop below 200 copies/mL.

versus d4T + ddI EC + EFV in 571 treatment-naïve patients. Thirty-eight percent of patients had baseline viral loads >100,000 copies/mL. In the FTC + ddI EC + EFV arm (n=286), 81% of patients had HIV RNA <400 copies/mL and 78% had <50 copies/mL at Week 48. In the d4T + ddI EC + EFV arm (n=285), 68% of patients had HIV RNA <400 copies/mL and 59% had <50 copies/mL at Week 48.

Study of Treatment-Experienced HIV Patients with a Combination Antiretroviral Regimen Containing a RTV-Boosted PI, TDF and ddI EC or another NRTI

- **BMS Study AI424-045**[7]**:** A Phase III, open-label trial in which 358 treatment-experienced patients with multiple virologic failures were randomized to one of three boosted PIs (shown below) each in combination with TDF and one other NRTI (approximately half on ddI EC):
  - Reyataz® (atazanavir sulfate [ATV]) 300 mg + RTV 100 mg once daily or
  - LPV/RTV 400/100 mg twice daily or
  - ATV 400 mg+saquinavir (SQV) 1200 mg once daily.

  The ATV + SQV arm had statistically inferior results to those in the ATV + RTV and LPV/RTV arms, and will not be discussed. Interaction studies of ddI EC + TDF demonstrated increased ddI exposure when ddI EC 400 mg was administered one to two hours before TDF 300 mg and a light meal. Consequently, a protocol amendment specified ddI EC dose reduction to 250 mg (adults weighing ≥60 kg with creatinine clearance ≥60 mL/min) or 200 mg (adults weighing <60 kg with creatinine clearance ≥60 mL/min) once daily. By Week 24, approximately 2/3 of ddI EC subjects had reduced dosage to 250 mg. Forty-eight week results were stratified according to baseline viral load and assessed for differences between ddI- and non-ddI-containing regimens. A post-hoc analysis using these data was performed on the subset of treatment-experienced patients with a baseline viral load ≥100,000 copies/mL.[‡] The two combined arms of ATV + RTV and LPV/RTV demonstrated a 33% (8/24) virologic failure rate[§] through Week 48 in the ddI-treated group compared to 52% (16/31) in the non-ddI-treated group.

Please refer to the enclosed full prescribing information for Videx® EC (didanosine) Delayed Release Capsules Enteric Coated Beadlets and Sustiva® (efavirenz) Capsules and Tablets.

BMS is committed to providing you with current product information for the management of your patients with HIV infection. If you have any questions about this new information or require additional medical information, please contact the Virology Medical Services Department at Bristol-Myers Squibb Company at 1-800-426-7644 (select Option 3).

Sincerely,

Sally L. Hodder

Sally L. Hodder, MD
Vice President, Virology Medical Affairs
Bristol-Myers Squibb Company

Enclosures: Videx® EC (didanosine) and Sustiva® (efavirenz) Package Inserts

[‡] Median baseline HIV RNA: ATV/RTV arm=4.44 $\log_{10}$ copies/mL, LPV/RTV arm=4.47 $\log_{10}$ copies/mL.
[§] Virologic failure rates measured by TLOVR (time to loss of virologic response) analysis.

REFERENCES

1. Podzamczer D, Ferrer E, Gatell JM, et al. Early virologic failure with a combination of tenofovir, didanosine and efavirenz. *Antiviral Therapy* 2004 9:S172, Poster 156 presented at the 13th International HIV Drug Resistance Workshop; June 2004; Tenerife Sur, Spain.
2. Viread® (tenofovir disoproxil fumarate) Prescribing Information. Gilead Sciences, Inc., June 2004.
3. Emtriva™ (emtricitabine) Prescribing Information. Gilead Sciences, Inc., July 2003.
4. Saag M, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA*. 2004; 292:180-189.
5. Staszewski S, Gallant J, Pozniak A, et al. Efficacy and safety of tenofovir disoproxil fumarate (TDF) versus stavudine (d4T) when used in combination with lamivudine (3TC) and efavirenz (EFV) in HIV-1 infected patients naïve to antiretroviral therapy (ART): 48-week interim results. XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Oral Presentation LbOr17.
6. Gallant JE, Staszewski S, Pozniak A, et al. Long-term efficacy and safety of tenofovir DF (TDF): A 144 week comparison versus stavudine (d4T) in antiretroviral-naïve patients. XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Poster 4538.
7. Data on file, Bristol-Myers Squibb Company, Princeton, New Jersey.