Switching Antiretroviral Drugs for Treatment of Metabolic Complications in HIV-1 Infection: Summary of Selected Trials

Michael S. Saag, MD, William G. Powderly, MD, Morris Schambelan, MD, Constance A. Benson, MD, Andrew Carr, MD, Judith S. Currier, MD, Michael P. Dubé, MD, John G. Gerber, MD, Steven K. Grinspoon, MD, Carl Grunfeld, MD, PhD, Donald P. Kotler, MD, and Kathleen Mulligan, PhD

Metabolic complications in HIV-1-infected patients, such as insulin resistance, lipid abnormalities, and changes in body fat distribution, are becoming more prevalent and of increasing concern to patients and clinicians. A switch in antiretroviral therapy to include classes of drugs not epidemiologically associated with metabolic complications is a potential strategy for treatment of metabolic complications. In general, treatment of the underlying HIV-1 infection should take precedence over the potential benefits of antiretroviral switching.

A number of switch studies have been conducted in which a protease inhibitor has been switched for a nonnucleoside reverse transcriptase inhibitor (NNRTI) or abacavir. It is difficult to draw conclusions from these studies because of their generally small sample size and differences in the study populations, treatment regimens, duration of follow-up, reasons for switching therapy, and methodology. Randomized clinical trials with larger numbers of patients are needed to evaluate the efficacy and safety of switch strategies in various settings. In the aggregate, however, several trends emerge:

- A switch from a protease inhibitor to nevirapine or abacavir is usually associated with an improvement in cholesterol and triglyceride levels. A switch from a protease inhibitor to efavirenz is associated with a more mixed result.
- A switch from a protease inhibitor to abacavir is associated with an improvement in insulin resistance. A switch from a protease inhibitor to nevirapine or efavirenz varies in result from no change to improvement.
- A switch from a protease inhibitor to nevirapine, efavirenz, or abacavir seems to have little impact on visceral, truncal, or other fat accumulation abnormalities.

Clinicians must take the entire treatment history (eg, prior abacavir hypersensitivity) into account before making a switch in a patient's antiretroviral therapy, and candidates for switching antiretroviral therapy should be chosen with care.

A current research question concerns the result of switching the "background" nucleoside reverse transcriptase inhibitors (nRTIs; eg, stavudine or zidovudine) in a regimen for other drugs, such as tenofovir, when the protease inhibitor remains the same. It is unclear whether such a switch would result in reversal of any metabolic abnormalities.

Selected available data on the impact of antiretroviral drug substitutions on glucose metabolism, lipid levels, and body fat distribution abnormalities are summarized in the following tables. Studies with at least 20 subjects and for whom metabolic data were collected or observations were made for at least 24 weeks are included. In cases where numerous presentations of study data were made by the same group of investigators, only the most recent data are included.

These data were compiled and used by the International AIDS Society–USA Metabolic Complications Guidelines Panel as part of its effort to develop guidelines for the diagnosis and management of metabolic complications associated with antiretroviral therapy and HIV-1 infection. These guidelines were recently submitted for publication.

Table **1.** Nevirapine Switch Studies

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + nevirapine[1]	23	24 weeks	↓	↓	↓	↓ WHR	Diet not reported.
2 nRTIs + PI → 2 nRTIs + nevirapine[2]	104	24 weeks	~↓	~↓	–	↓ WHR	Rebound in HIV-1 RNA occurred more often in PI group than nevirapine group (18% vs 4%, *P* = .015).

Chol indicates cholesterol; Glu, glucose; HDL, high-density lipoprotein; IR, insulin resistance; N, the number of subjects in switch group(s); nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TGs, triglycerides; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; ↑ or ↓, significant increase or decrease; ~↑ or ~↓, nonsignificant trend of increase or decrease.

Table **1.** Nevirapine Switch Studies *(continued)*

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + nevirapine[3]	60	36 weeks	↓	↓	NC	NC	Randomized study. Virologic failure: 4 with nevirapine; 3 with PI.
2 nRTIs + PI → 2 nRTIs + nevirapine + adefovir + hydroxyurea[4]	49	48 weeks	↓	↓	NC	↓ VAT ↓ WHR ↑ lipoatrophy	Randomized (2:3) study. No difference in HDL chol. Weight and CD4+ cell count decreased. Virologic failure: 3 (6%) in experienced patients; 6 (19%) with PI. Intolerance in 15 experienced patients.
2 nRTIs + PI → 2 nRTIs + nevirapine[5]	40	48 weeks	↓	NC	↓	NC	Severe rash in 6 patients; therapy changed to efavirenz. One patient with virologic failure.
2 nRTIs + PI → 2 nRTIs + nevirapine[6]	26	52 weeks	↓	↓	–	NC	Randomized to nevirapine, efavirenz, or control. Only 1 patient had rebound in plasma HIV-1 RNA level in nevirapine group.
2 nRTIs + PI → 2 nRTIs + nevirapine[7]	73	52 weeks	↓	NC	–	NC	Nonrandomized; 10 patients on efavirenz, 63 nevirapine. Infrequent virologic failure.
2 nRTIs + PI → 2 nRTIs + nevirapine[8]	68	24 weeks	~↓	NC	–	–	Virologic failure in 4 cases.
2 nRTIs + PI → 2 nRTIs + nevirapine, abacavir, or efavirenz[9]	81	24 weeks	↓	NC	↓	–	Randomized substudy of[10]. Glu/IR same in all 3 groups. Nevirapine and efavirenz arms had increase in HDL; abacavir arm had decrease in HDL.
2 nRTIs + PI → 2 nRTIs + nevirapine, abacavir, or efavirenz[10]	460	48 weeks	↓	NC/ ↑ HDL	↓	–	Abacavir arm had greater decrease in TGs; there was a greater decrease in total chol with abacavir, but HDL increased only in the nevirapine and efavirenz arms.

Table **2.** Efavirenz Switch Studies

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + efavirenz[11]	33	40 weeks	NC	NC	NC	NC	Subset analysis of a cohort of 624 patients evaluated for body fat, lipid, and glucose abnormalities.
2 nRTIs + PI → 2 nRTIs + efavirenz[12]	39	24 weeks	~↑	NC	NC	NC	Virologic control maintained. Modest increase in HDL chol.
2 nRTIs + PI → 2 nRTIs + efavirenz[13]	43	24 weeks	~↑	NC	–	NC	HIV-1 RNA remained <50 copies/mL in all patients. HDL chol was unchanged.
2 nRTIs + PI → 2 nRTIs + efavirenz[14]	20	24 weeks	↓	NC	↓	↓ WHR ↓ VAT	HIV-1 RNA became detectable in 1 patient.
2 nRTIs + PI → 2 nRTIs + efavirenz[6]	25	24 weeks	~↓	NC	–	NC	Randomized to nevirapine, efavirenz, or control. Only 1 patient had HIV-1 RNA rebound in the nevirapine group vs 2 in the efavirenz group and 1 in the PI group.
2 nRTIs + PI → 2 nRTIs + efavirenz[15]	25	24 weeks	~↑	~↑	↓	~↓ VAT	HIV-1 RNA remained <500 copies/mL for all patients.
2 nRTIs + PI→ 2 nRTIs + efavirenz[16]	164	24 weeks	–	NC	–	–	Improvement in HDL chol in efavirenz group.

Chol indicates cholesterol; Glu, glucose; HDL, high-density lipoprotein; IR, insulin resistance; N, the number of subjects in switch group(s); NC, no change; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TGs, triglycerides; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; ↑ or ↓, significant increase or decrease; ~↑ or ~↓, nonsignificant trend of increase or decrease.

Table 2. Efavirenz Switch Studies *(continued)*

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
2 nRTIs + PI → 2 nRTIs + abacavir + efavirenz[17]	27	36 weeks	~↓	~↓	~↓	NC	Some overall fat loss by BIA (2.5 kg), but no change in symptoms of fat redistribution. Virologic failure in 1 patient.
2 nRTIs + PI → 2 nRTIs + efavirenz[18]	56	24 weeks	↓	↑ HDL	–	NC	No virologic failure. Some increase in lipoatrophy (5 patients).
2 nRTIs + PI → 2 nRTIs + efavirenz[19]	45	48 weeks	↓	~↓	–	–	Virologic failure in 2 patients.
2 nRTIs + PI → 2 nRTIs + efavirenz[20]	20	24 weeks	NC	NC	NC	NC	No virologic failures. Subjective improvement in morphologic appearance but no change in anthropometric studies.
2 nRTIs + PI → 2 nRTIs + efavirenz[21]	46	52 weeks	↓	NC	↓	↓ WHR ↓ VAT	Moderate increase in HDL chol with efavirenz; no difference in HIV-1 RNA outcome or SAT loss.
2 nRTIs + PI → 2 nRTIs + efavirenz[22]	41	52 weeks	–	–	NC	–	Patients with lipodystrophy syndrome; only IR and Glu tolerance evaluated.
2 nRTIs + PI → 2 nRTIs + efavirenz or nevirapine[23]	100	52 weeks	↓	↓	NC	NC	HIV-1 RNA suppression maintained in 80%; no difference between efavirenz and nevirapine groups.
2 nRTIs + PI → 2 nRTIs + efavirenz[24]	226	48 weeks	~↑	NC	–	–	Virologic failure in 7% of switch group vs 15% of controls (*P*=.024). TGs increased in both groups. Significant increase in HDL in switch group.

Table 3. Nucleoside Reverse Transcriptase Inhibitor Switch Studies

Regimen	N	Follow-up	TGs	Chol	Glu/IR	Body Change	Comments
Stavudine → zidovudine or abacavir[25]	59	36 weeks	↓	NC	NC	↑ SAT NC in VAT	Some patients (n=18) on dual nRTIs; remainder (n=41) on PI/nRTI; lactate declined significantly.
2 nRTIs + PI → 2 nRTIs + abacavir[26]	211	24 weeks	~↓	↓	↓	–	Randomized to continue PI or not. Virologic failures: abacavir (9; 3 virologic); PI (14; 2 virologic).
2 nRTIs + PI → 2 nRTIs + abacavir[27]	84	52 weeks	↓	↓	–	–	Randomized to continue PI or not. Virologic failures: abacavir, 11; PI, 5.
2 nRTIs + PI → 2 nRTIs + abacavir[28]	105	45 weeks	~↓	~↓	–	–	Randomized to continue PI (106) or not (105). Virologic failures: abacavir, 4; PI, 2.
Stavudine + nRTI + PI → zidovudine + lamivudine + abacavir[29]	40	48 weeks	–	~↓	–	↑ SAT	Randomized trial. No virologic failure in switch group.
Stavudine → abacavir or zidovudine[30]	86	24 weeks	–	–	–	~↑ SAT	Increase in SAT was detected by DEXA scan. 11% - 26% subjective improvement in lipoatrophy reported. No loss of virologic control.
Stavudine or zidovudine → abacavir[31]	55	24 weeks	NC	NC	NC	↑ SAT NC in VAT	Randomized to continue current therapy or switch. No virologic failure in switch group. Increase in SAT detected by DEXA and CT.

BIA indicates bioelectrical impedance analysis; Chol, cholesterol; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; Glu, glucose; HDL, high-density lipoprotein; IR, insulin resistance; N, the number of subjects in switch group(s); NC, no change; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SAT, subcutaneous adipose tissue; TGs, triglycerides; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; ↑ or ↓, significant increase or decrease; ~↑ or ~↓, nonsignificant trend of increase or decrease.

References

1. Martinez E, Conget I, Lozano L, Casamitjana R, Gatell JM. Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. AIDS. 1999;13:805-810.

2. Barreiro P, Soriano V, Blanco F, Casimiro C, de la Cruz JJ, Gonzalez-Lahoz J. Risks and benefits of replacing protease inhibitors by nevirapine in HIV-infected subjects under long-term successful triple combination therapy. AIDS. 2000;14:807-812.

3. Ruiz L, Negredo E, Domingo P, et al. Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with HIV-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. *J Acquir Immune Defic Syndr.* 2001;27:229-236.

4. Carr A, Hudson J, Chuah J, et al. HIV protease inhibitor substitution in patients with lipodystrophy: a randomized, controlled, open-label, multicentre study. AIDS. 2001;15:1811-1822.

5. Tebas P, Yarasheski K, Henry K, et al. Evolution of multiple metabolic parameters after the switch of protease inhibitors to nevirapine. [Abstract ThPpB1485.] XIII International AIDS Conference. July 9-14, 2000; Durban, South Africa.

6. Negredo E, Cruz L, Paredes R, et al. Virological, immunological, and clinical impact of switching from protease inhibitiors to nevirapine or to efavirenz in patients with human immunodeficiency virus infection and long-lasting viral suppression. *Clin Infect Dis.* 2002;34:504-510.

7. Raffi F, Bonnet B, Ferre V, et al. Substitution of a nonnucleoside reverse transcriptase inhibitor for a protease inhibitor in the treatment of patients with undetectable plasma human immunodeficiency virus type 1 RNA. *Clin Infect Dis.* 2000;31:1274-1278.

8. Buisson M, Grappin M, Piroth L, Duong M, Portier H, Chavanet P. Simplified maintenance therapy with NNRTI (nevirapine) in patients with long-term suppression of HIV-1 RNA: first results of a cohort study. [Abstract 1541.] 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000; Toronto, Canada.

9. Fisac C, Fumero E, Crespo M, et al. A randomized trial of metabolic and body composition changes in patients switching from PI-containing regimens to abacavir (ABC), efavirenz (EFV), or nevirapine (NVP). [Abstract 699-T.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

10. Martinez E, Podzamczer D, Ribera E, et al. Switching protease inhibitors to nevirapine (NEV), efavirenz (EFA), or abacavir (ABA): a randomized, multicenter, open-label, simplification trial. [Abstract LB17.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

11. Gharakhanian S, Salhi Y, Adda N, Vigouroux C, Capeau J, Rozenbaum W. Identification of fat redistribution/metabolic anomalies in a cohort treated by 2 NRTIs + 1 PI, and absence of significant modification following PI substitution. [Abstract 46.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

12. Viciana P, Alarcon A, Martin D, et al. Partial improvement of lipodystrophy after switching from HIV-1 protease inhibitors (PI) to efavirenz (EFV). [Abstract 48.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

13. Bonnet E, Lepec R, Bluteau M, et al. Evolution of lipodystrophy syndrome and lipidic profile in HIV patients after switching from protease inhibitors to efavirenz. [Abstract 49.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

14. Martinez E, Garcia-Viejo MA, Blanco JL, et al. Impact of switching from human immunodeficiency virus type 1 protease inhibitors to efavirenz in successfully treated adults with lipodystrophy. *Clin Infect Dis.* 2000;31:1266-1273.

15. Moyle GJ, Baldwin C, Dent N, Cometis S, Gazzard BG. Management of protease inhibitor (PI)-associated lipodystrophy by substitution with efavirenz (EFV) in virologically controlled HIV-infected persons. [Abstract 2064.] 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 26-29, 1999; San Francisco, Calif.

16. Katlama C. Successful substitution of protease inhibitors with Sustiva (efavirenz) in patients with undetectable plasma HIV-1 RNA levels: results of a prospective, randomized, multicenter, open-label study (DMP 266-027). [Abstract LbPeB7044.] XIII International AIDS Conference. July 9-14, 2000; Durban, South Africa.

17. Bickel M, Rickerts V, Klauke S, et al. The Protra study: switch from PI to abacavir (ABC) and efavirenz (EFV) in HIV-1 infected adults previously treated with 2 NRTIs and a PI with undetectable HIV-RNA levels (vRNA). [Abstract 1531.] 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000; Toronto, Canada.

18. Knechten H, Sturner KH, Hohn C, Braun P. 24 week follow-up of patients switching from a protease inhibitor (PI) containing regimen with lamivudine (3TC) and stavudine (d4T) or zidovudine (AZT) to an efavirenz (EFV) based therapy. [Abstract 1532.] 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000; Toronto, Canada.

19. Maggiolo F, Migliorino M, Pravettoni G, Rizzi M, Caprioli S, Suter F. Management of PI-associated metabolic changes by substitution with efavirenz in virologically controlled HIV+ persons. [Abstract 1533.] 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000; Toronto, Canada.

20. Lafon E, Bani Sadr F, Chandemerle C, et al. LIPSTOP study: evolution of clinical lipodystrophy (LD), blood lipids, visceral (VAT) and subcutaneous (SAT) adipose tissue after switching from protease inhibitor (PI) to efavirenz (EFV) in HIV-1 infected patients. [Abstract 1535.] 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000; Toronto, Canada.

21. Martinez E, Romeu J, Garcia-Viejo MA, et al. An open randomized study on the replacement of HIV-1 protease inhibitors by efavirenz in chronically suppressed HIV-1-infected patients with lipodystrophy. [Abstract 668.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

22. Estrada V, De Villar NGP, Martinez-Larrad T, Tellez MJ, Serrano-Rios M. Switching to efavirenz from protease inhibitor-based therapy does not improve insulin resistance after one year in HIV patients with lipodystrophy syndrome. [Abstract 671.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

23. Casado JL, Arrizabalaga J, Antela A, et al. Long-term efficacy and tolerance of switching the protease inhibitor for non-nucleoside reverse transcriptase inhibitors: a 52-week, multicenter, prospective study. [Abstract 673.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

24. Becker S, Rachlis A, Gill J, et al. Successful substitution of protease inhibitors with efavirenz (EFV) in patients with undetectable viral loads—a prospective, randomized, multicenter, open-label study (DMP 049). [Abstract 20.] Presented at: 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

25. Saint-Marc T, Partisani M, Poizot-Martin I, Touraine JL. Reversibility of peripheral fat wasting (lipoatrophy) on stopping stavudine therapy. [Abstract 52.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

26. Walli RK, Michl GM, Bogner JR, Goebel FD. Improvement of HAART-associated insulin resistance and dyslipidemia after replacement

of protease inhibitors with abacavir. *Eur J Med Res.* 2001;6:413-421.

27. Opravil M, Hirschel B, Lazzarin A, et al. Simplified maintenance therapy with abacavir + lamivudine + zidovudine in patients with HAART-induced long-term suppression of HIV-1 RNA: final results. [Abstract 476.] 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000; Toronto, Canada.

28. Montaner JSG. A novel use of abacavir to simplify therapy and reduce toxicity in PI experienced patients successfully treated with HAART: 48-week results (CNA30017). [Abstract 477.] 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2000; Toronto, Canada.

29. John M, James I, McKinnon E, et al. A randomised, controlled, open-label study of revision of antiretroviral regimens containing stavudine (d4T) and/or a protease inhibitor (PI) to zidovudine (ZDV)/lamivudine (3TC)/abacavir (ABC) to prevent or reverse lipoatrophy: 48-week data. [Abstract 700-T.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

30. McComsey G, Lonergan T, Fisher R, et al. Improvements in lipoatrophy (LA) are observed after 24 weeks when stavudine (d4T) is replaced by either abacavir (ABC) or zidovudine (ZDV). [Abstract 701-T.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

31. Carr A, Smith D, Workman C, et al. Switching stavudine or zidovudine to abacavir for HIV lipoatrophy: a randomised, controlled, open-label, multicentre, 24-week study. [Abstract 32.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

Author Affiliations: Dr Saag, The University of Alabama at Birmingham, Birmingham, Ala, and International AIDS Society–USA, San Francisco, Calif; Dr Powderly, Washington University School of Medicine, St. Louis, Mo; Dr Schambelan (Panel Chair), University of California San Francisco, San Francisco, Calif; Dr Benson (Panel Co-Chair), University of Colorado Health Sciences Center, Denver, Colo, and International AIDS Society–USA, San Francisco, Calif; Dr Carr, St. Vincent's Hospital, Sydney, Australia; Dr Currier, University of California Los Angeles, Los Angeles, Calif; Dr Dubé, Indiana University School of Medicine, Indianapolis, Ind; Dr Gerber, University of Colorado Health Sciences Center, Denver, Colo; Dr Grinspoon, Harvard Medical School, Massachusetts General Hospital, Boston, Mass; Dr Grunfeld, University of California San Francisco and San Francisco Veterans Affairs Medical Center, San Francisco, Calif; Dr Kotler, St. Luke's-Roosevelt Hospital, Columbia University, New York, NY; Dr Mulligan, University of California San Francisco and San Francisco General Hospital, San Francisco, Calif.

Financial Disclosure: All authors were consultants, and/or scientific advisors, and/or speakers, and/or had research grants involving one or more of the following: Abbott, Agouron, Bayer, Biochem Pharma, Biotechnology General, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chiron, DuPont, the European Medicines Evaluation Agency, Gilead, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Merck, Merck Sharp and Dohme, Ortho Biotech, Pfizer, Pharmacia and Upjohn, Roche, Schering, Serono, Triangle, and Trimeris.