

Human immunodeficiency virus (HIV)

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=Abstract=

Antiviral effect and safety of triple combination therapy in human immunodeficiency virus (HIV)-infected persons

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Background : Antiretroviral combination therapy with one protease inhibitor and two reverse transcriptase inhibitors is profoundly suppressive of HIV replication. To determine the efficacy and safety of the triple combination therapy in persons with HIV infection in Korea, we analyzed the response of therapy in terms of immunity and viral load.

Methods : Ten persons with HIV infection, who were treated with triple combination therapy at least 12 months at Yonsei University College of Medicine from 1997 to 1999 were studied. The triple combination therapy regimen consisted of two reverse transcriptase inhibitors (zidovudine or didanosine, lamivudine) and one protease inhibitor (indinavir). We analyzed the levels of HIV RNA, CD4+ cell counts, γ MG, and p24Ag before and after treatment. Adverse drug reactions during therapy were described.

Results : The mean age of patients at treatment was 38.7 years. Nine patients were male, and 1 patient was female. Six patients received triple combination therapy as initial treatment, while 4 patients received it as re-treatment. The mean level of HIV RNA was 129,222 copies/mm³ before treatment. RNA level decreased to less than 500 copies/mm³ (non-detectable range) at 1 month in 7 of 10 patients, at 12 months in 9 of 10 patients. The mean CD4+ cell counts was 206/mm³ before treatment, and 376/mm³ after 12 months treatment. The γ MG decreased to 2.7 mg/L from 2.8 mg/L after 12 months of treatment. The p24Ag was positive in 3 of 10 patients and negative in all of the patients at 3 months treatment. Mild hyperbilirubinemia (5 cases) was the most frequent adverse reaction followed by flank pain (3 cases), skin rash (2 cases), abdominal discomfort (2 cases), and mild elevation of AST/ALT (1 case).

Conclusion : The triple combination therapy in HIV infection appeared to be generally well tolerated, and was able to profoundly sustain suppression of HIV replication. (Korean J Med 58:582-589, 2000)

Key Words : Human immunodeficiency virus, Antiretroviral treatment, Zidovudine, Protease inhibitor, AIDS

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Human immunodeficiency virus (HIV)
 3) .
 3 .
 . 1987 3
 HIV zidovudine 가 1 , 2
¹⁾ zidovudine HIV . HIV viral load
²⁾ zidovudine HIV RNA RT-PCR (Roche, USA)
³⁾, 1995 , CD4+
 (Becton Dickinson, USA)
 가 HIV CD4+
 HIV RNA viral load
 가 가 . 2MG p24Ag .
^{4, 5)}
 zidovudine 3 HIV 4.
⁶⁻⁸⁾ ,
^{9- 12)} 3 3
 HIV 3 .
 5.
 1. 2 1 ,
 ,
 1997 1999 4 HIV
 3 12
 HIV RNA CD4+ 가 1.
 10 가 가 9 ,
 가 1 . Zidovudine 가 6 (,
 5 , 1) didanosine 가
 2. 3 4 (1 , 3) .
 2 1 3 38.7 , HIV
 zidovudine didanosine, lamivudine, indinavir 14.9 . HIV
 12 . Zidovudine 1 200 4 , 4
 mg 3 , lamivudine 150 mg 2 , 1 ,
 indinavir 800 mg 3 , didanosine 200 mg 2 1 .
 가 5 , 가 2
 6 (zidovudine 5 , didanosine Acquired Immunodeficiency Syndrome(AIDS)
 1) , zidovudine didanosine 가 3 . 3 ,

1 , 2 , 2 , , 1 8,021 copies
Molluscum contagiosum 1 . /mm³ 1 가
3 가 12 982 copies/mm³
HIV RNA 129,222 ± 168,078 . Didanosine 4 HIV RNA
copies/mm³ , CD4+ 206.4 ± 175/mm³ 135,364 copies/mm³, 1 12,860 copies/
, 2MG 2.8 ± 1.0 mg/L , p24Ag 10 mm³, 2 500 copies/mm³ ,
3 1 3 , 4
HIV RNA가 가
2. 6 5 (zidovudine 4 ,

1) HIV RNA
HIV RNA 129,222 copies/mm³
1 5,408 copies/mm³, 2 500 copies/
mm³ (non-detectable range; 가)
12 .
HIV RNA가 가
1 7 , 4 9 1
1 가 가 4
636 copies/mm³ . Zidovudine
6 HIV RNA가 125,128
copies/mm³ 1 500 copies/mm³
1
3 , 4 5 HIV RNA가 가

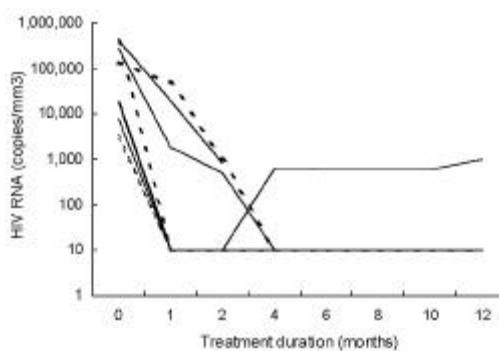


Figure 1. Change of HIV RNA after triple combination therapy. — case with zidovudine, case with didanosine.

Table 1. Change of HIV RNA after triple combination therapy

| Case | HIV RNA | | | | Time of NDT (months) |
|------|--------------------------------------|---|--|---|----------------------|
| | Before Tx. (copies/mm ³) | After 1 month Tx. (copies/mm ³) | After 4 months Tx. (copies/mm ³) | After 12 months Tx. (copies/mm ³) | |
| 1* | 277,674 | 1,820 | NDT | NDT | 4 |
| 2* | 17,959 | NDT | NDT | NDT | 1 |
| 3* | 18,751 | NDT | NDT | NDT | 1 |
| 4* | 8,021 | NDT | 636 | 982 | 1 |
| 5* | 409,565 | 816 | NDT | NDT | 4 |
| 6* | 18,800 | NDT | NDT | NDT | 1 |
| 7† | 141,000 | 51,442 | NDT | NDT | 4 |
| 8† | 2,759 | NDT | NDT | NDT | 1 |
| 9† | 394,209 | NDT | NDT | NDT | 1 |
| 10† | 3,491 | NDT | NDT | NDT | 1 |

NDT: non-detectable range (HIV RNA < 500 copies/mm³)

*; case with zidovudine, lamivudine, and indinavir
†; case with didanosine, lamivudine, and indinavir
Case 1-5, 7; case with initial treatment
Case 6, 8-10; case with retreatment.

didanosine 1) 12 HIV RNA가 127/mm³, 6 268/mm³, 12
 가 . 3 289/mm³ 1 104/mm³ 가가
 4 , 2 1 HIV RNA가 가 . 12 218/mm³
 . 1 1 CD4+ 가가 117/mm³
 가 가 4 636 가가 .
 copies/mm³ . 4 (zidovudine
 1 , didanosine 3) 1 HIV 3) 2MG
 RNA가 가 가 12 2MG 5 1 가
 (Table 1, Figure 1). 4 가 . Zidovudine 6
 2.6 mg/dL, 1 1.5 mg/dL, 2
 2.4 mg/dL, 6 1.5 mg/dL 12 2.1

2) CD4+
 CD4+ 10 9 가 .
 Didanosine 1
 CD4+ 가 399/mm³ 12
 370/mm³ (Table 2, Figure 2). 12
 206/mm³, 1
 265/mm³, 2 249/mm³, 6 351/mm³,
 12 376/mm³ 1
 170/mm³ 가 . zidovudine
 6 CD4+
 221/mm³, 1 371/mm³, 2 326/mm³, 6
 420/mm³, 12 438/mm³
 1 217/mm³ 가 , didanosine 4
 185/mm³, 1 216/mm³, 2

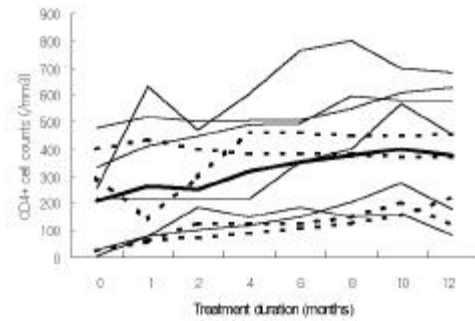


Figure 2. Change of CD4+ cell counts during 12 months triple combination therapy ; total mean counts. — ; case with zidovudine, ---- ; case with didanosine.

Table 2. Change of CD4+ cell counts after triple combination therapy

| Case | CD4+ cell counts (/mm ³) | | | | |
|------|--------------------------------------|-------------------|--------------------|-------------------|---------------------|
| | Before Tx. | After 1 month Tx. | After 2 months Tx. | After 6 monthsTx. | After 12 months Tx. |
| 1* | 6 | 76 | - | 148 | 178 |
| 2* | 222 | 216 | 216 | 350 | 455 |
| 3* | 256 | 634 | 469 | 763 | 680 |
| 4* | 476 | 518 | - | 507 | 624 |
| 5* | 29 | 80 | 182 | 182 | 80 |
| 6* | 334 | 413 | - | 493 | 577 |
| 7† | 25 | 68 | - | 106 | 218 |
| 8† | 399 | 435 | - | 384 | 370 |
| 9† | 21 | 60 | 127 | 124 | 122 |
| 10† | 296 | 145 | - | 457 | 451 |

- ; not check
 * ; case with zidovudine, lamivudine, and indinavir
 † ; case with didanosine, lamivudine, and indinavir
 Case 1-5, 7 ; case with initial treatment
 Case 6, 8-10 ; case with retreatment.

mg/dL, didanosine 4 4 가
 3.1 mg/dL, 1 2.3 mg/dL, 6 12 1 .
 2.7 mg/dL 12 3.4 3 (zidovudine 2 , didanosine
 mg/dL 가 . 2.6mg 1), 2 (zidovudine 2
 /dL 12 1.4 mg/dL ,), 2 (zidovudine 1 , didanosine
 2.3 mg/dL 12 3.1 1)
 mg/dL 가 (Table 3). 1 (zidovudine 1) .

4) p24Ag ,
 p24Ag 3 3 .
 1 2 , 3 .

3. HIV HIV
 3 12 . 1987
 AIDS HIV zidovudine 가
 zidovudine 1 1¹⁾ 2).
 가 1

4. 2
 3 12 13 가 1991 zidovudine
 5 2^{13, 14)}, 1995
 1 .

Table 3. Change of β MG after triple combination therapy

| Case | β MG (mg/dL) | | | | |
|-----------------|--------------------|-------------------|--------------------|--------------------|---------------------|
| | Before Tx. | After 1 month Tx. | After 2 months Tx. | After 6 months Tx. | After 12 months Tx. |
| 1* | 3.2 | 1.7 | - | 1.7 | 2.4 |
| 2* | 2.1 | 1.2 | - | 1.4 | 1.7 |
| 3* | 1.5 | 1.2 | 1.3 | 1.3 | 1.4 |
| 4* | 1.5 | 1.5 | - | - | 1.7 |
| 5* | 4.8 | - | 3.5 | - | 3.7 |
| 6* | 2.7 | 1.8 | - | 1.4 | 1.5 |
| 7 [†] | 3.0 | 1.8 | 2.0 | 2.0 | 3.1 |
| 8 [†] | 2.2 | 1.8 | - | 1.5 | 2.2 |
| 9 [†] | 3.9 | 3.3 | 4.1 | 4.2 | 4.3 |
| 10 [†] | 3.1 | 2.1 | - | 3.2 | 3.6 |

-; not check
 *; case with zidovudine, lamivudine, and indinavir
 †; case with didanosine, lamivudine, and indinavir
 Case 1-5, 7; case with initial treatment
 Case 6, 8-10; case with retreatment.

가¹⁷⁾, Gag, 209/mm³, 148 198/mm³ 가가 .
 Gag-Pol poly protein 3
 가 4 70%, 17 90% viral load가 가
^{18, 19)}, 2 12
 가¹²⁾, 가 1 12 HIV
 HIV RNA가 1000 copies/mm³
 , viral load HIV RNA ,
 HIV Zidovudine 1 ,
 가^{4, 5, 15)}, HIV didanosine 2 HIV
 HIV error rate HIV RNA 가 500 copies/mm³
 HIV zidovudine 가
 , zidovudine 6 3 가
^{15, 16)}, 4 가
 HIV didanosine .
 zidovudine 3
 3 (zidovudine, lamivudine, indinavir) 1996 HIV HIV RNA가 100,000 copies/mm³ ,
 1 , viral load didanosine
 가⁶⁻⁸⁾, .
 12 HIV 80% viral 3 CD4+ 가
 load 가 500 copies/mm³ Gulick¹⁰⁾
 , 52 24 86 ± 11.9/mm³ 가
 2 가 , Hammer⁹⁾ 3 40
¹⁰⁾, 가 zidovudine lamivudine rito- 12/mm³ CD4+ 가
 navir nelfinavir^{20, 21)} . 12 170/mm³
 가
 3 AIDS , didanosine
¹²⁾, 3 4 zidovudine 6 CD4+
 viral load 가가 .
 zidovudine lamivudine 2 indinavir HIV ,
 가
 , , ²³⁻²⁵⁾ .
 3
 3 AIDS 1
 3
 . 1999 Gulick²²⁾ zidovudine AIDS
 dine, lamivudine, indinavir 3 .
 HIV RNA CD4+ 3
 , HIV . Gulick¹⁰⁾
 RNA 100 78%, 148 67% 33 3 (zidovudine, lamivudine, indi-
 가 , CD4+ 100 navir) 4 , 4 ,

11 , indinavir 6 351/mm³, 12 376/mm³ .
 64 9 2MG 2.8 mg/L 12
 Carpenter 6) 3 2.7 mg/L . p24Ag 10 3
 , , 1 2 , 3
 indinavir . 13
 5 , 5 , 3 , 2
 , 3 , 2 , 1 .
 : 3 HIV 10
 HIV RNA, CD4+ , p24Ag
 2MG
 HIV 3
 HIV viral 3
 load 가

1
 HIV
 3
 가 1
 3
 1997
 1999 4 HIV 12
 3 10 . 3
 2 (zidovudine+lamivudine,
 or didanosine+lamivudine)
 1 (indinavir) . HIV RNA,
 CD4+ , 2MG, p24Ag 3

: HIV 10
 38.7 가 9 , 가 1 . 3
 6 , 4
 HIV RNA 129,222 copies/mm³
 , 1 7 , 4 9 , 12 9
 가 CD4+
 206/mm³ , 1 265/mm³,

REFERENCES

- 1) Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, Leedom JM, Groopman JE, Mildvan D, Schooley RT. *The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS related complex. N Engl J Med 317:185-191, 1987*
- 2) Larder BA, Darby G, Richman DD. *HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. Science 243:1731-1734, 1989*
- 3) Choo V. *Combination superior to zidovudine in Delta trial. Lancet 346:895, 1995*
- 4) Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, Kingsley LA, Todd JA, Saah AJ, Detels R, Phair JP, Rinaldo CR Jr. *Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 126:946-954, 1997*
- 5) Hughes MD, Johnson VA, Hirsch MS, Bremer JW, Elbeik T, Erice A, Kuritzkers DR, Scott WA, Spector SA, Baspoz N, Fischl MA, D'Aquila RT. *Monitoring plasma HIV-1 RNA level in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. Ann Intern Med 126: 929-938, 1997*
- 6) Carpenter CCJ, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JSG, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG, Volberding PA. *Antiretroviral therapy for HIV infection in 1996: Recommendations of the international AIDS society- USA panel. JAMA 276:146-154, 1997*
- 7) Carpenter CCJ, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JSG,

- Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG, Volberding PA. *Antiretroviral therapy for HIV infection in 1997: Updated recommendations of the international AIDS society-USA panel.* JAMA 277:1962-1969, 1997
- 8) Carpenter CCJ, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JS, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG, Volberding PA. *Antiretroviral therapy for HIV infection in 1998: Updated recommendation of the international AIDS society-USA panel.* JAMA 280(1):78-86, 1998
- 9) Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, Eron JJ. Jr, Feinberg JE, Balfour HH. Jr, Deyton LR, Chodakewitz JA, Fischl MA, Phair JP, Spreen W, Pedneault L, Nguyen BY, Cook JC. *A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4+ cell counts of 200 per cubic millimeter or less.* N Engl J Med 337:725-733, 1997
- 10) Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, Richman DD, Valentine FT, Jonas L, Meibohm A, Emini EA, Chodakewitz JA, Deutch P, Holder D, Schlieff WA, Condra JH. *Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy.* N Engl J Med 337:734-739, 1997
- 11) Ullum H, Katzenstein T, Alladin H, Nielsen C, Sondergaard SR, Gerstoft J, Skinh J, Pedersen BK. *Immunological changes in human immunodeficiency virus (HIV)-infected individuals during HIV-specific protease inhibitor treatment.* Scandinavian J of Immunology 49:539-547, 1999
- 12) Hogg RS, Health KV, Yip B, Craib KJ, O'Shaughnessy MV, Schechter MT, Montaner JS. *Improved survival among HIV-infected individuals following initiation of antiretroviral therapy.* JAMA 279:450-454, 1998
- 13) Delta Coordinating Committee. *Delta: a randomized double blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV infected individuals.* Lancet 348:283-291, 1996
- 14) Caesar Coordinating Committee. *Randomized trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial.* Lancet 349:1413-1421, 1997
- 15) Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. *HIV-1 dynamics in vivo: viron clearance rate, infected cell life-span, and viral generation time.* Science 271:1582-1586, 1996
- 16) Coffin JM. *Population dynamics in vivo: implications for genetic variation, pathogenesis and therapy.* Science 267:483-489, 1995
- 17) Markowitz M, Saag M, Powderly WG, Hurley AM, Hsu A, Valdes JM, Henry D, Sattle F, La Marca A, Leonard JM. *A preliminary study of ritonavir, an inhibitor of HIV-1 protease, to treat HIV-1 infection.* N Engl J Med 333:1534-1539, 1995
- 18) Kohl NE, Emini EA, Schlieff WA. *Active human immunodeficiency virus protease is required for viral infectivity.* Proc Natl Acad Sci USA 85:4686-4690, 1988
- 19) Peng C, Ho BK, Chang TW, Chang NT. *Role of human immunodeficiency virus type 1-specific protease in core protein maturation and viral infectivity.* J Virol 63:2550-2556, 1989
- 20) Powderly WG, Sension M, Conant M, Stein A, Clendeninn N. *The efficacy of Viracept (nefnavir mesylate, NFV) in pivotal phase I/II double-blind randomized controlled trials as monotherapy and in combination with d4T or AZT/3TC(Abst).* In: Program and abstracts of the Fourth Conference on Retroviruses and Opportunistic Infections. Washington DC. January 22-27, 1997(Abst 370)
- 21) Markowitz M, Cao Y, Vesanen M. *Recent HIV infection treated with AZT, 3TC, and a potent protease inhibitor(Abst LB8).* In: Program and abstracts of the Fourth Conference on Retroviruses and Opportunistic Infections. Washington DC. January 22-27, 1997
- 22) Gulick R, Mellors J, Havlir D, Eron J, Valentine F, McMahon D, Gonzalez C, Jonas L, Meibohm A, Chodakewitz JA, Isaacs R, Richman D. *Treatment with indinavir (IDV), zidovudine (ZDV), and lamivudine (3TC): Three-year follow-up(Abst 388).* 6th Conference on Retroviruses and Opportunistic Infection. Chicago, IL. 1999
- 23) . HIV -
- 24) . 27:1-10, 1995
- 25) . 30:507-515, 1998
- 25) . Human immunodeficiency virus(HIV) p. 90, 1998