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Research Article

Effects of Korean Red Ginseng combination therapy on HIV-infected patients treated with integrase strand transfer inhibitors

Young-Keol Cho [a,*], Jinny Lee [a], Jung-Eun Kim [b], Heungsup Sung [b]

[a] Department of Microbiology, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background: Korean Red Ginseng (KRG) combined with antiretroviral therapy (ART) has shown benefits in the treatment of HIV-1-infected patients. Current guidelines recommend regimens containing integrase strand transfer inhibitors (INSTIs) as first-line treatment for these patients. The present study assessed the duration of effectiveness of ginseng combination therapy (GCT) in patients receiving INSTIs.

Methods: This study included 58 HIV-1-infected patients previously untreated with monotherapy or two-drug combination therapy. Patients in the GCT (n = 26) group received ART plus KRG for 164 ± 64 months, whereas patients in the control (n = 32) group received ART alone for 128 ± 49 months. Subsequently, patients in these two groups received INSTI for 81 ± 36 months and 68 ± 26 months, respectively.

Results: Before INSTI treatment, only one drug resistance mutation (DRM) was observed in the GCT group, compared with an overall resistance rate of 44.4 % in the control group ($P < 0.001$). The overall resistance rate was higher in the control than in the GCT group (9.5 % vs. 0.12 %, $P < 0.001$). During INSTI treatment, the resistance rate in the GCT group remained 0 % for over 5 years, but gradually decreased in the control group from 18.3 % to 13.9 % over 6 years, indicating that the between-group difference in resistance rate gradually decreased during INSTI treatment.

Conclusion: The beneficial effects of KRG were well maintained for more than 20 years, including the INSTI treatment period.

1. Introduction

Although zidovudine (ZDV) monotherapy and two-drug combinations, such as ZDV plus lamivudine or didanosine, were shown beneficial in patients infected with human immunodeficiency virus-1 (HIV-1), these benefits did not last long due to the rapid development of ZDV resistance mutations in the viral reverse transcriptase (RT) gene [1–4]. By contrast, the combination of ZDV and Korean Red Ginseng (KRG) significantly delayed the development of mutations resistant to ZDV [5,6].

The subsequent introduction of antiretroviral therapies (ART) that included protease (PRO) inhibitors (PI) significantly reduced mortality and morbidity in HIV-1-infected patients [7]. The combination of KRG and ART, or ginseng combination therapy (GCT) was also shown beneficial in these patients [8]. KRG not only suppressed viral replication in HIV-1-infected patients [9,10], but also induced nonspecific genetic defects in HIV-1 [11–13], ultimately reducing immune activation and extending patient lifespan [14–18].

All major HIV treatment guidelines recommend integrase (IN) strand transfer inhibitor (INSTI)-based regimens as first-line therapy in patients infected with HIV-1 [19–22]. Despite the relatively high genetic barrier to resistance, virologic failure due to resistance to INSTI has been consistently observed in Korean patients [23,24]. Resistance to INSTI is associated most commonly with incomplete adherence to treatment [25,26], as well as with resistance to other types of antiretroviral drugs and delay after diagnosis [27]. Despite the introduction of INSTI in Korea, more than 100 HIV-1 infected patients have died each year since 2006 [28]. Therefore, more effort is needed to increase compliance with treatment, as well as to develop novel treatment regimens.

INSTI-based regimens have been used to treat HIV-1 infected patients in Korea since 2014 [23,24]. In particular, second generation INSTIs were found to be more powerful than conventional treatments as the former inhibit the viruses harboring drug resistance mutations (DRM) [29]. The present study investigated the synergy between GCT

* Corresponding author. Department of Microbiology, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Republic of Korea.
E-mail address: ykcho2@amc.seoul.kr (Y.-K. Cho).

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and INSTI treatment, by assessing the duration of benefits of GCT in patients receiving INSTI treatment. Patients were treated with GCT or ART alone, followed by subsequent INSTI treatment, with data analyzed before and during INSTI treatment. DRMs were not consistently observed in the GCT group before INSTI treatment, the virus in with all eight patients in the GCT group not treated with INSTI having wild-type virus after >16 years and one remaining well without an INSTI regimen. By contrast, the DRM rate in the control group after <2 years of INSTI treatment was 18.3 %, but this rate gradually declined to 10.8 % after 6 years of INSTI treatment. The beneficial effects of KRG persisted even after >20 years of treatment without INSTI. Our data show that the KRG combination therapy is still beneficial in the era of INSTI regimen.

2. Materials and methods

2.1. Ethics statement

This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Review Board of Asan Medical Center (Code 2012-0390). All subjects provided written informed consent before inclusion in this study.

2.2. Patients

The study consisted of 58 patients divided into two groups: a GCT group, consisting of 26 patients who had been treated with KRG and ART for 213 ± 70 months (range, 65–298 months) and did not harbor DRMs; and an ART-only control group, consisting of 32 patients who had been treated with ART for 184 ± 58 months (range, 78–295 months) (Table 1). The 26 patients in the GCT group had been treated with a combination of three antiretroviral drugs (plus KRG), but had not received previous ZDV monotherapy or two-drug combination therapy. Patients were included in this study if they 1) had not received previous monotherapy or two-drug combination therapy, 2) lacked DRMs at baseline, 3) received ART for >5 years, and 4) received >2.0 g/day KRG [30].

Table 1
Baseline characteristics and outcomes in 58 patients before and on INSTI treatment.

Parameter	Group		
	GCT	Control	P-value
Before INSTI treatment			
No. of patients (n)	26	32	
Sex (male: female)	22 : 4	30: 2	
Age at enrollment (yr)	39.4 ± 9	42.3 ± 13	
Subtype			
B	20	29	
Non-B	6	3	
$CD4^+$ T cell count (/μL)	155 ± 124	179 ± 136	
Follow-up period (months)	164 ± 64	128 ± 49	<0.05
Increase in $CD4^+$ T cells (/μL)	526 ± 273[d]	388 ± 254[d]	0.053
No. of patient genotyped	25	28	
Patients without CVS (%)	2 (7.7)[a]	9 (31.0)[b]	<0.05
Overall resistance rate with DRM (%)	0.12 (1/846)	9.5 (28/295)	<0.0001
On INSTI treatment			
Follow-up period with INSTI	81 ± 36	68 ± 26	
$CD4^+$ T cell count (/μL)	641 ± 270	579 ± 326	
Increase in $CD4^+$ T cell on INSTI (/μL)	71 ± 298	34 ± 305	
Patients without CVS (%)	1/24[c]	7/29	0.059
Overall resistance rate with DRM (%)	0.64 (5/777)	14.9 (55/369)	<0.0001

[a, b] and [c].
[a-c] Due to poor compliance in two, two and one patients.
[d] $P < 0.0001$ compared with baseline in each group.
Abbreviations: CVS, complete viral suppression: GCT, ginseng based combination antiretroviral therapy (ginseng plus ART); DRM, drug resistance mutation; INSTI, integrase strand transfer inhibitor.

2.3. Counting of $CD4^+$ and $CD8^+$ T cells and measurement of viral copies

Peripheral blood mononuclear cells (PBMCs) were stained with phycoerythrin and fluorescein isothiocyanate (FITC)-conjugated antibodies to CD4 and CD8, respectively (Simultest reagents, Becton-Dickenson [BD], CA, USA) [8,9,11–13,17], and subjected to flow cytometry using a FACScan flow cytometer (BD). HIV-1 RNA copy number was measured using AMPLICOR HIV-1 monitoring kits (Roche Diagnostics Systems, Branchburg, NJ, USA) [16].

2.4. KRG treatment

The KRG used in this study was a commercial product prepared from 6-year-old KRG roots by the Korea Ginseng Corporation. Beginning in 1991, male patients were instructed to take 5.4–6.0 g a day [8,9,11–13,17]. The dose was halved for women owing to potential adverse effects, such as weight gain and vaginal hemorrhage. In the GCT group, 20 patients had been treated with KRG alone (8896 ± 8544 g) for a significant period before receiving ART, and 12 of these patients had progressed slowly (Fig. S1). Of the 32 patients in the GCT group, nine had received ART for 2–7.5 years (median 3.5 years) at the time KRG was added. The average amount of KRG supplied to the 26 patients during GCT was 12,087 ± 8095 g (range, 4050–35,214 g).

2.5. DNA preparation and pol amplification

Proviral DNA was extracted from PBMC samples as described [8,12,18]. Denatured DNA samples (5 μL) were amplified by nested PCR, using several sets of outer primer pairs for the full-length *pol* gene, including HXB2/550, HXB2/OBP2k, HXB2-MHI/OBP2-MHI, and HXB2-HHC/OBP2-HHC, with each sample amplified 4–8 times. A 0.5 μL aliquot of the first PCR product was transferred to a second tube, along with the inner primer sets, such as PO1/OBP4, P2/P16, PO1-MHI/550, and PO1-HHC/550 [12,18]. If long PCR failed, three overlapping primer sets were used [12]. The PCR products were purified and sequenced directly using various primers (Table S1).

2.6. Detection of drug resistance mutations

Major and accessory resistance mutations were identified using the Stanford HIV Drug Resistance Database (http://hivdb.stanford.edu/HIVdb/by-sequences/).

2.7. Statistical analysis

All data were expressed as mean ± standard deviation. Statistical significance was evaluated using Student's two-tailed t-tests, Chi-square tests, or Fisher's exact tests. All statistical analyses were performed using MedCalc program version 22.001 (Ostend, Belgium), with statistical significance defined as $P < 0.05$.

2.8. Sequences note

The GenBank accession numbers for the identified sequences are; MW660370-537, OK490514-610, PP175954-176173, PQ032162-272 and PQ094907-944.

3. Results

Evaluation of treatment regimens in the two groups showed that three of the 26 patients in the GCT group received INSTI from the beginning of treatment, whereas five others were administered GCT without receiving INSTI treatment. By comparison, four of the 32 patients in the control group received INSTI from the beginning of

treatment, whereas three others were administered ART without receiving INSTI treatment.

3.1. Comparison of drug resistance rates based on amplicons before INSTI treatment

Drug resistance rates for >15 years prior to INSTI treatment and for >6 years during INSTI treatment were compared in the GCT and control groups. A total of 561 full-length *pol* genes were amplified from 325 PBMC samples in the GCT group, whereas 223 full-length *pol* genes were amplified from 108 PBMC samples in the control group.

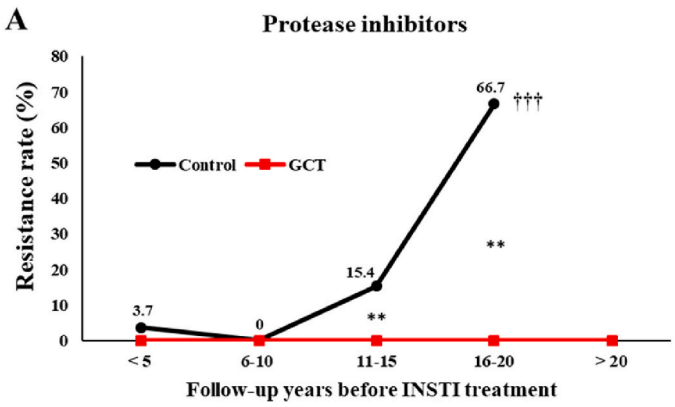
The 26 patients in the GCT group were treated with GCT for 159 ± 65 months (Table 1). The initial sample from one of these patients (98-60) harbored a single DRM to reverse transcriptase inhibitors (RTI) (L74V); it was identified as a single resistance mutation (Fig. S1 and Table S2). This DRM was also detected after 37 months of GCT, but was not detected in any of the 28 amplicons from 15 PBMC samples in this patient or in samples from the remaining 25 patients in the GCT group. Two patients in this group had been treated for more than 20 years, with all 10 amplicons from these patients being wild type and one (90-38) of these patients still doing well without INSTI treatment (Fig. S1). The overall rate of resistance to protease inhibitors (PI), RTI, and INSTI was 0.12 % (1/846) in the GCT group (Fig. 1A, B and C).

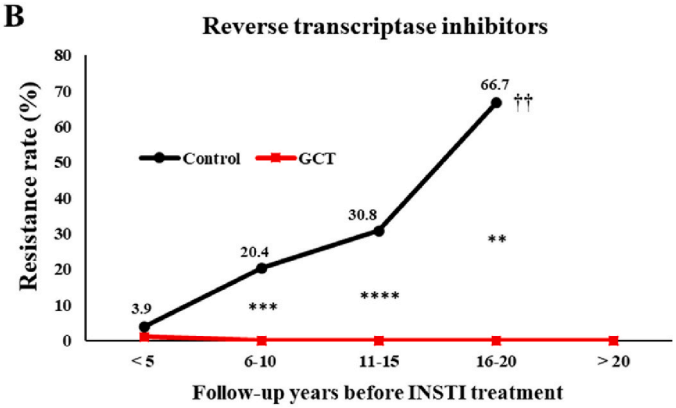
The 32 patients in the control group were treated with ART for 127 ± 49 months. The total overall resistance rate for >15 years in this group was 9.5 % (28/295), with overall rates of resistance to PIs, RTIs and INSTIs being 6.7 % (7/105), 19.8 % (21/106), and 0 % (0/84), respectively. The rates of resistance to PIs ($P < 0.001$) and RTIs ($P < 0.01$) increased significantly over 16–20 years of follow-up (Fig. 1A and B), as did the overall resistance rate ($P < 0.0001$ by Chi-squared test for trend) (Fig. 1C). The overall disparity between the two groups was 80.3-fold.

3.2. Decrease of DRM on INSTI treatment

Resistance rates during treatment with INSTI were analyzed at 2-year intervals (Fig. 2). Patients (n = 24) in the GCT group were treated with INSTI for 81 ± 36 months (range, 10–169 months), whereas patients (n = 30) in the control group received INSTI treatment for 68 ± 26 months (range, 14–128 months). The overall resistance rate in the GCT group was 0.64 % (5/777), with the overall rates of resistance to PI, RTI, and INSTI being 0.83 % (2/241), 0.83 % (2/241), and 0.34 % (1/295), respectively.

Viral genotypes were determined in 24 of the 30 patients in the





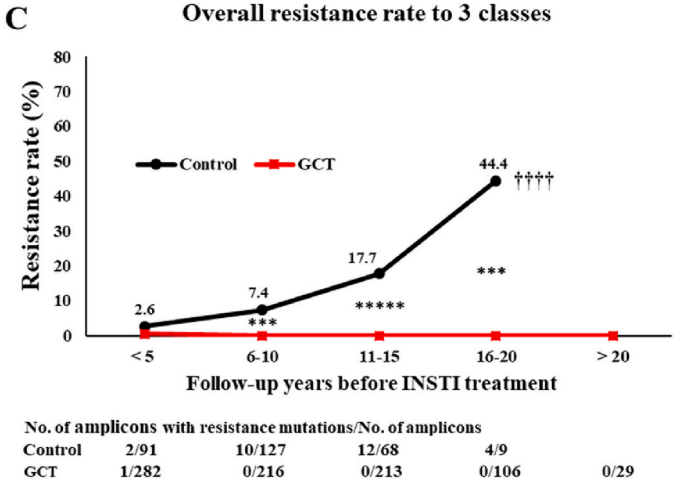


Fig. 1. Rates of resistance to antiretroviral drugs for >20 years of follow-up prior to INSTI treatment. The overall rates of resistance of HIV-1 patients in the control group to (A) protease inhibitors (PI) ($P < 0.0001$ for trend) and (B) reverse transcriptase inhibitors (RTI) ($P < 0.01$ for trend) increased significantly increased over 16–20 years). (C) Lack of DRMs to INSTI in both the GCT and control groups, indicating that the overall rates of resistance to the three classes of ART significantly increased over 16–20 years in the control group ($P < 0.0001$ for trends). The numbers below the graphs are the numbers of amplicons with resistance mutations/the numbers of PCR amplicons contributing to the mean. ***P < 0.01*, ****P < 0.001*, *****P < 0.0001*. ††$P < 0.01$, †††$P < 0.001$ and ††††$P < 0.0001$ were determined by Chi-squared test for trend.

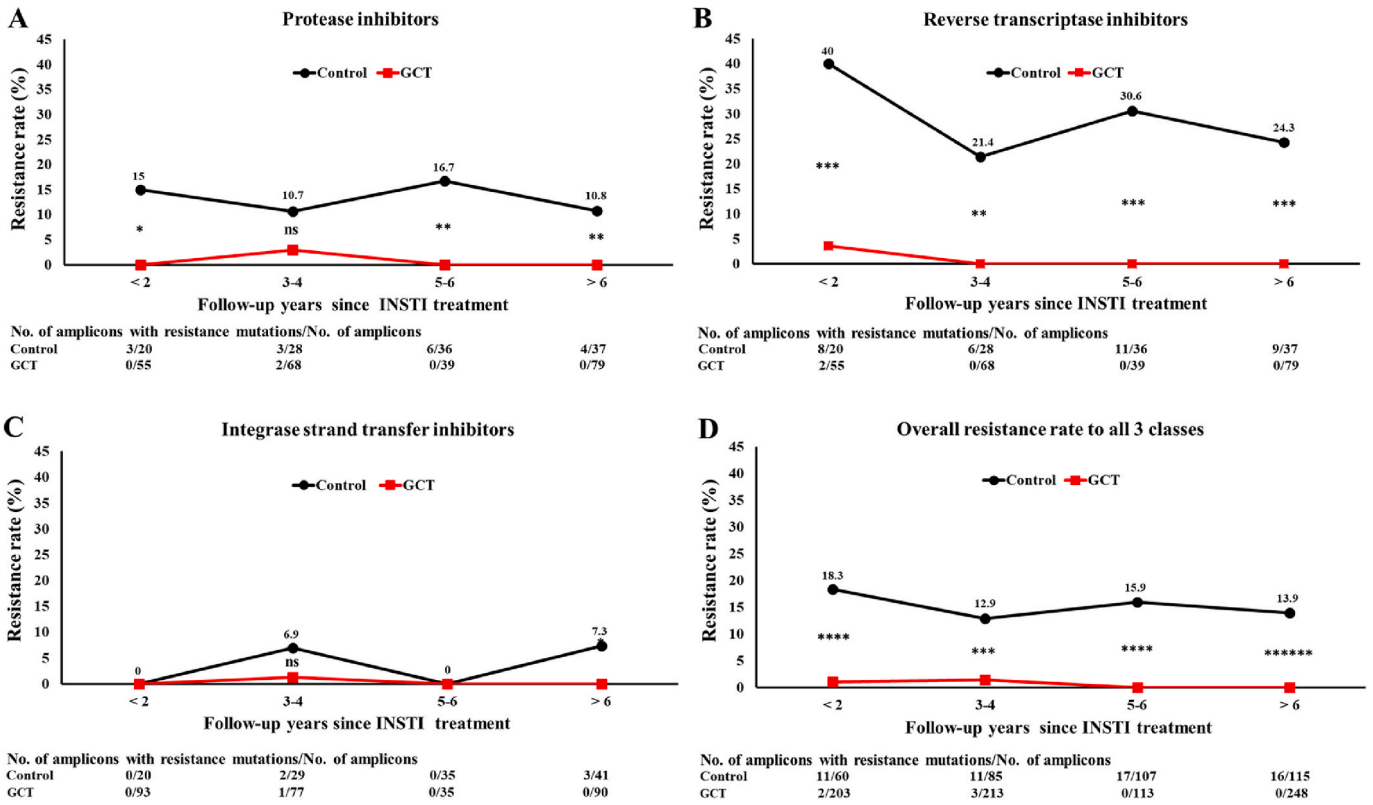


Fig. 2. Rates of resistance to antiretrovirals after introduction of integrase strand transfer inhibitors (INSTI). (A) Rates of resistance to protease inhibitors (PI) in the control group decreased gradually to 10.8 %. (B) Rates of resistance to reverse transcriptase inhibitors (RTI) gradually decreased from 40 % at baseline to 24.3 % at >6 years of treatment in the control group (P > 0.05 for trends) and from 3.6 % to zero in the GCT group. (C) The rate of resistance to INSTI increased to 7.3 % at >6 years of follow-up. (D) The overall rate of resistance in the GCT group remained at 0 % after 5–6 years of treatment, while gradually decreasing in the control group. The numbers below the graphs are the numbers of amplicons with resistance mutations/the numbers of PCR amplicons contributing to the mean. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

control group. Eleven of these 24 patients had been treated with INSTI for more than 6 years, with three showing DRM (Table S2). The overall resistance rate in the control group was 14.9 % (55/369), with the overall rates of resistance to PIs, RTI, and INSTI being 13.2 % (16/121), 28.1 % (34/121), and 3.9 % (5/127), respectively. The rate of resistance to PIs decreased from 15 % at baseline to 10.8 % at >6 years of follow-up (Fig. 2A), and the rate of resistance rate to RTI decreased from 40 % at baseline to 24.3 % at > 6 years (Fig. 2B). In response to INSTI treatment, the rate of resistance to INSTI in the control group increased to 7.3 % after >6 years of follow-up, whereas there was only one DRM (E138K) in patient 92-22 in the GCT group (Fig. S1 and Table S2), making the overall resistance rate to INSTI significantly higher in the control (4.0 %) than in the GCT (0.34 %; 1/292) group (P < 0.01) (Fig. 2C). The overall rate of resistance to all three classes of drugs remained at 0 %, beginning at 5–6 years of follow-up in the GCT group, but tended to decrease in the control group (Fig. 2D). Over the entire period of treatment with INSTI,

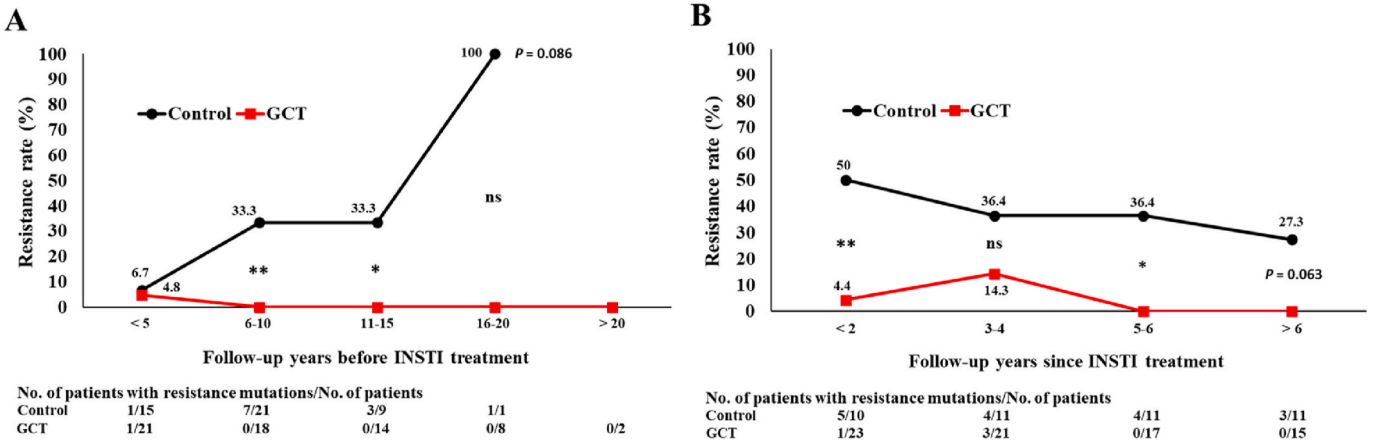


Fig. 3. Comparison of resistance rates before and after INSTI treatment at the patient level. (A,B) The resistance rate in the control group increased gradually before INSTI treatment (A) but gradually decreased during exposure to INSTI (B). However, the number of patients was less than the number of amplicons in Figs. 1 and 2, so the differences were mild statistically significant at >6 years of follow-up (P = 0.05). The numbers below the graphs are the numbers of amplicons with resistance mutations/the numbers of patients contributing to the mean. *$P < 0.05$, **$P < 0.01$.

the resistance rate was 23.2-fold higher in the control group than in the GCT group ($P < 0.001$).

3.3. Comparison of resistance rates at the patient level

Before INSTI treatment, the resistance rate at the patient level in the GCT group was approximately 3.4 % at <2 years of follow-up. Thereafter, this rate decreased to zero and remained there, and was significantly lower than in the control group at 6–10 years and 11–15 years of follow-up (Fig. 3A). During INSTI treatment, five patients in the GCT group (20.8 %) and 10 (41.7 %) in the control group harbored at least one DRM (Table S2). However, the number of patients with DRMs gradually decreased in both groups. After >6 years of follow-up, none (0.0 %) of 14 patients in the GCT group and three (27.3 %) of 11 patients in the control group harbored DRMs, indicating a gradual decrease in disparity between the two groups over time (Fig. 3B).

3.4. Association with $CD4^+$ T cells and viral load

The numbers of $CD4^+$ T cells in patients were significantly higher in the GCT than in the control group before INSTI ($P = 0.053$), remaining somewhat higher in the GCT group during the course of INSTI treatment (Table 1). The proportion of patients with incomplete viral suppression was significantly lower in the GCT than in the control group ($P < 0.05$) (Table 1).

4. Discussion

This study investigated the duration of the beneficial effects of GCT (ginseng) in HIV-1-infected patients treated with INSTI. DRMs in the full-length *pol* gene of patients receiving ART, with or without KRG, were identified, and the relative frequencies of resistance genes were assessed in the GCT and control groups treated for >15 years prior to INSTI administration and for 6–7 years while on INSTI. DRMs were not consistently observed in the GCT group, even after 20 years of follow-up, whereas the overall resistance rate in the control group increased to 44.4 % before INSTI treatment ($P < 0.001$). The overall resistance rate over >15 years was 80.3-times higher in the control group than in the GCT group ($P < 0.0001$). During the >5-year period of INSTI treatment, the overall resistance rate to all three classes remained at 0 % in the GCT group. In the control group, however, the overall resistance rate to these drugs gradually decreased, from 18.3 % at baseline to 13.9 % after 6 years of follow-up. Similar findings were observed at the patient level, indicating that the disparity between the two groups gradually decreased over time. Taken together, these results indicated that the beneficial effects of KRG combination therapy were sustained for >20 years, even during the period of INSTI treatment.

The overall rates of resistance to INSTI in the GCT (4.2 %) and control (8.3 %) groups after INSTI treatment for >6 years were lower than in previous studies in Korea (22 %) [18], the USA (15.6 %) [31] and Turkey (29 %) [32]. By contrast, the resistance rate after INSTI treatment gradually decreased in the control group of the present study. Second generation INSTIs can inhibit many of the viruses harboring DRMs that arise during treatment with first-generation INSTIs [29]. Similarly, the resistant viruses present in two patients (HS and YG) in the control group disappeared in the most recent samples obtained, after 99 and 55 months of treatment with INSTI, respectively. The overall resistance rate to INSTI also decreased slowly in other patients with DRMs at baseline or after exposure to previous monotherapy or two-drug combination therapy. However, two patients harbored major DRMs to INSTI after treatment for 28 and 79 months, respectively, likely owing to poor compliance. These DRMs may have also resulted from coevolved multidrug-resistant mutations acting independently of the integrase and affecting INSTI drug susceptibility and replication fitness [33].

In general, hypermutated sequences comprise more than 9 % of archived viral DNA in resting $CD4^+$ T cells but are not found in plasma. The absence of hypermutated sequences in plasma indicates that hypermutation blocks virus production from these proviruses [34]. Thus, the rate of successful PCR amplification of full-length *pol* gradually decreases as the GCT period increases, regardless of the second primer set used [12]. Therefore, this study excluded resistance mutations due to G-to-A hypermutation [34] when determining resistance rates. The present study, along with a previous study [23], analyzed DRMs in PBMC samples, whereas other studies have used plasma samples [24, 32]. The proportion of premature stop codons did not differ in the two patient groups, both before and after INSTI.

KRG may delay the development of resistance mutations by a mechanism associated with its antiviral effects [10,15], as shown in the delayed coreceptor switch [9]. Several mechanisms have been suggested. First, KRG may potentiate cytotoxic $CD8^+$ T cell activity by reducing soluble CD8 antigen [14] and preventing "clonal exhaustion" or "replicative senescence" of $CD8^+$ T cells [35]. This may increase cellular release of antiviral molecules, such as IFN-γ, perforin and granzyme B [35]. Second, the efficacy of acid polysaccharide of ginseng (Ginsan), which induces IL-2 and IFN-γ, is directly associated with anti-HIV-1 replication [36]. Third, xylanase and panaxgin, as well as the ginsenosides Rb1, Rb2, Rb3, Rc, and polyacetylene ginsenoside-Ro from ginseng have been found to inhibit HIV-1 reverse transcriptase and HIV replication in vitro [37–39]. Fourth, KRG intake may nonspecifically and with high frequency induce defects in HIV-1 genes [11,12]. Fifth, the anti-inflammatory effects of ginseng may modulate innate and adaptive immunity [40,41].

The present study had several limitations. First, the follow-up period was significantly shorter in the control group than in the GCT group before INSTI treatment. Second, the start of KRG treatment in nine patients in the GCT group was delayed for a significant period of time. Third, many patients in the control group showed poor compliance and final samples were often not obtained, thereby underestimating the resistance rate in the control group. In this study, the beneficial effects of KRG were sustained for at least 20 years of GCT before INSTI treatment. Our data show that the KRG combination therapy is still beneficial in the era of INSTI regimen.

Despite the powerful INSTI regimen, the KRG combination therapy is still useful.

Declaration of Competing interest

The authors declare no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2024.09.003.

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