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# Risk of elevation of serum creatine kinase among HIV-positive individuals receiving dolutegravir-based combination antiretroviral therapy

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**Abstract**

We aimed to compare the risks of creatine kinase (CK) elevation between patients receiving dolutegravir-based antiretroviral therapy (ART) and those receiving non-integrase strand transfer inhibitor (InSTI)-based ART.

HIV-positive patients seeking HIV outpatient care between February 2017 and March 2018 were retrospectively reviewed to collect information on ART, practices of vigorous exercise, and laboratory tests including CK level, plasma HIV RNA load, and concurrent medications. The incidences of CK elevation were estimated among patients receiving dolutegravir-based ART and those receiving non-InSTI-based ART.

During the 14-month study period, 1406 patients (mean age 39.4 years and 96.9% being male) were included. The incidence rate of grade 3 or grade 4 CK elevation (>10-fold of the upper limit of normal) was 2.0 per 100 person-years of follow-up (PYFU) and 1.3 per 100 PYFU in the dolutegravir and non-InSTI group, respectively ($P = .32$). While dolutegravir group had a higher rate of CK elevation of any level than non-InSTI group (22.9 vs 17.4 per 100 PYFU, $P = .01$), the risk was associated with weight (adjusted odds ratio [aOR], per 10-kg increase, 1.03; 95% CI, 1.02–1.04), duration of exercise (aOR, per 1-hour increase, 1.02; 95% CI 1.01–1.03), but not with dolutegravir-based ART (aOR, 1.00; 95% CI, 0.99–1.06) after adjusting for the testing frequency of serum CK in the multivariate generalized estimating equation model. No patients were hospitalized or switched ART due to CK elevation.

Serum CK elevation was associated with weight and duration of exercise among HIV-positive patients receiving ART, but not with dolutegravir-based ART.

**Abbreviations:** aOR = adjusted odds ratio, ART = antiretroviral therapy, CK = creatine kinase, DTG = dolutegravir, GEE = generalized estimating equation, InSTI = integrase strand transfer inhibitor, PVL = plasma HIV RNA load, PYFU = person-years of follow-up, ULN = upper limit of normal.

**Keywords:** integrase inhibitor, lipid-lowering agent, myopathy, protease inhibitor, skeletal muscle

## 1. Introduction

Integrase strand transfer inhibitors (InSTIs) inhibit the integration of HIV DNA to human genome and, therefore, inhibit the replication of HIV.[1] InSTIs are known to possess excellent antiretroviral potency with fewer adverse effects than other classes of antiretroviral agents. After the introduction of the first antiretroviral agent in the class, raltegravir, InSTIs are increasingly recommended in both initial and salvage antiretroviral therapy (ART) across different local and international guidelines.[2,3] Despite its well-recognized efficacy and tolerability, raltegravir has been shown to be associated with an increased risk of serum creatine kinase (CK) elevation in early clinical trials. In the Protocol-004 and BENCHMRK studies, 9.4% and 8% of the participants receiving raltegravir-based ART developed grade 3 and grade 4 elevation of CK by 240 weeks, respectively, compared to 5% and 5.4% of the comparators.[4,5] Real-life cohorts from Italy and Spain also demonstrated that around 20% of the patients receiving raltegravir developed grades 1–4 elevation of CK in long-term follow-up.[6–8] In another cohort including HIV-negative individuals receiving raltegravir as non-occupational post-exposure prophylaxis for HIV, 5 of 91 individuals developed grade 4 elevation of CK, compared to 0 of 34 individuals receiving only co-formulated tenofovir disoproxil fumarate and emtricitabine ($P = .16$).[9] In these cohort

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studies, other risk factors for raltegravir-associated CK elevation included recent exercise, male sex, higher body-mass index, and higher baseline CK levels.[6–9] Although the elevations of CK levels in these studies were mostly self-limited and rarely led to modification of ART, cases of severe symptomatic rhabdomyolysis necessitating hospitalization and even transient renal replacement therapy have been reported in the literature.[10–14]

Besides raltegravir, newer InSTIs such as elvitegravir, dolutegravir (DTG), and bictegravir are also associated with serum CK elevations.[15] In the FLAMINGO study, more participants receiving DTG-based therapy developed grade 4 elevation of CK level than those receiving boosted darunavir-based therapy (4% vs 2%).[16] However, currently real-life data describing the risk of DTG-associated CK elevations are scarce, and it is not clear whether other factors are associated with CK elevations among HIV-positive patients who receiving DTG-based ART. This retrospective observational study aimed to exam the risk of elevation of serum CK level among HIV-positive patients receiving DTG-based ART; and to identify associated factors with CK elevation.

## 2. Methods

### 2.1. Study population

This was a single-center, retrospective cohort study that included HIV-positive individuals who were aged 20 years or more and received HIV outpatient care at the National Taiwan University Hospital from 1st February, 2017 to 31st March, 2018. We excluded HIV-positive patients who were not taking ART and those receiving raltegravir-based ART (Fig. 1). HIV-positive patients who did not have CK testing during the observation period were also excluded from further analysis. Elvitegravir or bictegravir was not available at the hospital during the study period.

For patients who had received DTG-based ART during the study period (DTG group), the observation period were defined as the interval between the initiation of DTG-based ART or the start of designated study period (1st Feb., 2017), whichever occurred later, and the discontinuation of DTG-based ART or the end of designated study period (31st March, 2018), whichever occurred first. For patients who did not receive DTG or raltegravir during the study period (non-InSTI group), the observation period were defined as the interval between the initiation of antiretroviral regimens not containing InSTI or the start of designated study period, whichever occurs later, and the discontinuation of antiretroviral regimens or the end of designated study period, whichever occurred first.

### 2.2. Data collection

Medical records of the included patients were retrospectively reviewed to collect information on demographic and clinical characteristics. Per the recommendations of national HIV treatment guidelines in Taiwan, all HIV-positive individuals were followed at the designated hospitals every 3 months and laboratory tests were performed every 3 to 6 months, which included plasma HIV RNA load (PVL), CD4 count, serologies of viral hepatitis, renal function, liver function, lipid profiles, as well as serum glucose and glycated hemoglobin levels. At each clinic visit, the prescribed antiretroviral regimens, concomitant medications and serum CK levels were recorded. To identify potential factors associated with CK elevation, information on illicit drug use, alcohol consumption and the average duration engaging in weight training or other vigorous exercise was retrieved from the electronic medical records. The reference range of serum CK is less than or equal to 223 U/L. Patients who developed symptomatic rhabdomyolysis necessitating in-hospital treatment and renal replacement therapy were also recorded throughout the study period.

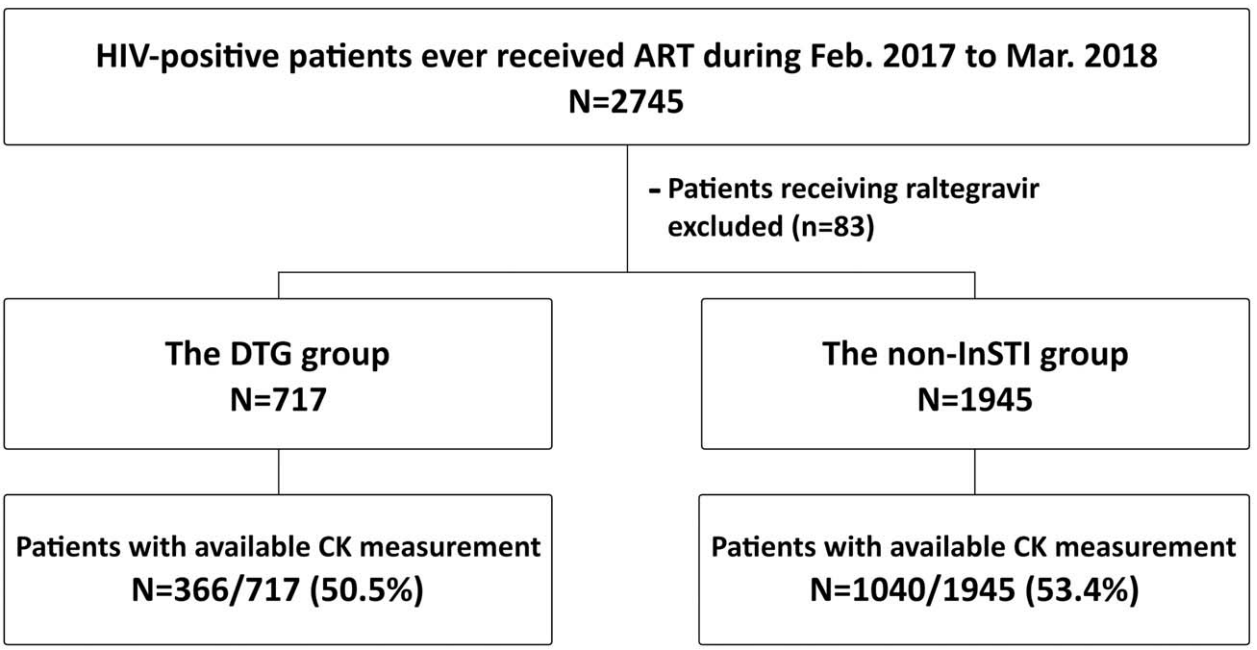


**Figure 1.** Study flow.

The cumulative rates of serum CK elevation of any level and the rate of grade 3 or grade 4 CK elevation (defined as >10-fold of upper limit of normal [ULN]) between the DTG group and non-InSTI group were estimated and compared using Kaplan–Meier estimates and log-rank test. The rates of symptomatic CK elevation or hospitalization and/or ART discontinuation or switch related to CK elevations were also compared between the 2 groups. To adjust for the imbalance of testing frequency of serum CK levels between these 2 groups of patients and take into account repeat measurements, a generalized estimating equation (GEE) model was applied to identify potential factors associated with CK elevation.[17] This study was approved by the Research Ethics Committee of the National Taiwan University Hospital (registration no., 201003112R) and informed consent was waived.

### 2.3. Statistical analysis

Comparisons of demographic and clinical characteristics were made between the patients in the DTG group and those in the non-InSTI group. Non-categorical variables were compared using Student's *t* test or Mann–Whitney *U* test and categorical variables were compared using Chi-square test or Fisher exact test. When comparisons of categorical variables were required for more than 2 groups, Kruskal–Wallis test were used and post-hoc analysis with Dunn test were applied for pair-wise comparison if needed.[18] Survival analysis was conducted using Kaplan–Meier estimation and comparison of survival function was performed by log-rank test. For the multivariate analysis, a simple GEE model was applied. We used a backward elimination process during the multivariate analysis, in which all possible associated factors were included in the model initially and factors were removed from the model starting those with the largest *P* value. The process was repeated until all factors in the model with *P* value less than .2. The statistical analyses were performed using STATA software, version 14.0 S/E (Stata Corporation, College Station, Austin, TX). All *P* values were 2-sided.

## 3. Results

### 3.1. Patient inclusion and baseline characteristics

During the 14-month study period, 2745 patients who ever received ART in the outpatient clinics at the National Taiwan University Hospital were screened. After excluding those who were receiving raltegravir-based ART, 1406 patients (366 in the DTG group and 1040 in the non-INSTI group) had at least 1 measurement of CK during the observation period and were included for further analysis (Fig. 1). The total duration of observation was 357.54 person-years in the DTG group and 1179.35 person-years in the non-InSTI group.

The demographics and baseline characteristics of the two groups are shown in Table 1. Patients in the DTG group were slightly younger than those in the non-InSTI group (37.8 vs 40.0 years, $P=.01$). There were no statistically significant differences between the 2 groups in terms of weight, prescription of statins, and habit of weight training or exercise. However, patients in the DTG group were more likely to be antiretroviral-naïve before including in this study (15.3% vs 3.9%, $P<.001$), more likely to report use of illicit drugs (8.7% vs 5.7%, $P=.04$), and had received more tests for serum CK level when compared with those in the non-InSTI group.

### 3.2. Rate of CK elevation

During the study period, 7 patients (1.9%) in the DTG group and 15 (1.4%) in the non-InSTI group developed grade 3 or grade 4 CK elevation, resulting in a rate of 2.0 per 100 person-years of follow-up (PYFU) and 1.3 per 100 PYFU, respectively ($P=.32$). The rate of patients who developed at least 1 episode of CK elevation of any level was 22.9 per 100 PYFU in the DTG group

**Table 1**

**Baseline characteristics of the included patients receiving ART.**

| | Patients on DTG-based ART (n = 366) | Patients on non-InSTI-based ART (n = 1040) | *P* value |
|---|---|---|---|
| Age, mean (SD), years | 37.8 (10.5) | 40.0 (11.1) | .001 |
| Male sex, n (%) | 352 (96.2) | 1011 (97.2) | .38 |
| Men who have sex with men, n (%) | 344 (94.0) | 991 (95.3) | .33 |
| Weight, mean (SD), kg | 67.4 (11.4) | 68.3 (11.7) | .17 |
| Positive HBsAg, n (%) | 37/335 (11.0) | 133/965 (13.8) | .20 |
| Positive anti-HCV, n (%) | 37/352 (10.5) | 79/1002 (7.9) | .13 |
| ART-naïve, n (%) | 56 (15.3) | 41 (3.9) | <.001 |
| Baseline PVL, median (IQR), $\log_{10}$ copies/ml | 1.3 (1.3–1.9) | 1.3 (1.3–1.3) | <.001 |
| Baseline PVL <20 copies/ml, n (%) | 247 (67.5) | 919 (88.4) | <.001 |
| Receiving PI-based regimens, n (%) | 0 (0) | 301 (28.9) | – |
| Self-reported use of illicit drugs, n (%) | 32 (8.7) | 59 (5.7) | .04 |
| Concomitant use of statins, n (%) | 26 (7.1) | 92 (6.9) | .90 |
| Use of other lipid-lowering agents, n (%) | 3 (0.8) | 15 (1.4) | .59 |
| Duration of follow-up, median (IQR), weeks | 58.0 (42.9–60.1) | 60.1 (60.1–60.1) | <.001 |
| Self-report having regular weight training, n (%) | 107 (29.2) | 335 (32.2) | .29 |
| ≤0.5 hours per day, n (%) | 73 (19.9) | 209 (20.1) | |
| >0.5 hours per day, n (%) | 34 (9.3) | 126 (12.1) | |
| Average available results of CK, median (IQR), n | 2 (1–3) | 2 (1–2) | <.001 |
| 1 laboratory test of CK, n (%) | 101 (27.6) | 310 (29.8) | |
| 2 laboratory tests of CK | 114 (31.1) | 566 (54.4) | |
| ≥3 laboratory tests of CK | 151 (41.3) | 164 (15.8) | |

anti-HCV = anti-hepatitis C antibody, ART = antiretroviral therapy, CK = creatine kinase, DTG = dolutegravir, HBsAg = surface antigen of hepatitis B virus, InSTI = integrase strand transfer inhibitor, IQR = interquartile range, PI = protease inhibitor, PVL = plasma HIV RNA load, SD = standard deviation.

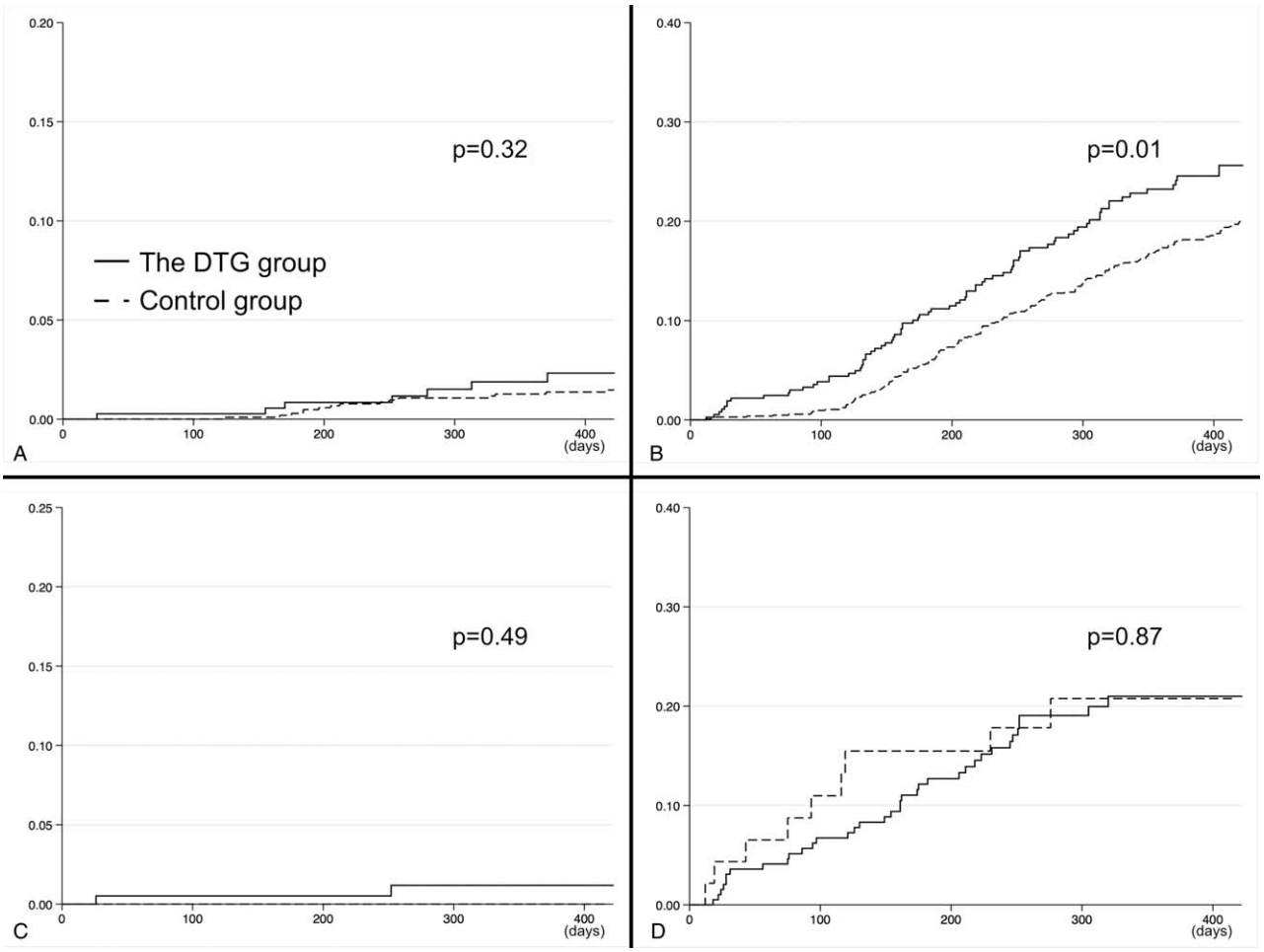


**Figure 2.** (A) Cumulative rates of grade 3 or grade 4 CK elevation for the DTG group (solid line) and non-InSTI group (dash line); (B) cumulative rates of CK elevation of any level for the DTG group (solid line) and non-InSTI group (dash line); (C) cumulative rates of grade 3 or grade 4 CK elevation for the patients who initiated or switched to DTG-based ART (solid line) and those who initiated or switched to non-InSTI-based ART during the study period (dash line); (D) cumulative rates of CK elevation of any level for the patients who initiated or switched to DTG-based ART (solid line) and those who initiated or switched to non-InSTI-based ART during the study period (dash line). ART = antiretroviral therapy, CK = creatine kinase, DTG = dolutegravir, InSTI = integrase strand transfer inhibitor.

and 17.4 per 100 PYFU in the non-InSTI group ($P = .01$) (Fig. 2). In our cohort, all cases of CK elevation were asymptomatic and self-limited, and none of the patients were hospitalized due to elevations of CK levels. There was no modification of ART due to CK elevation, either.

To understand whether recent initiation of DTG was associated with higher risk of CK elevation, we also performed a sensitivity analysis by including only those who initiated or newly switched to DTG- or non-InSTI-based ART during the study period. In the sensitivity analysis, patients who newly started DTG was not at increased risk of developing CK elevation as compared with patients who started non-InSTI regimens (Fig. 2).

### 3.3. Risk factor for CK elevation

As patients in the DTG group were more likely to undergo testing of serum CK levels in our cohort (Table 1), we performed a multivariate analysis using GEE model to adjust for the imbalance of testing frequency of CK within the 2 groups. The results are shown in Table 2. In our analysis, the risk of CK elevation was positively associated with weight (adjust odds ratio [aOR], per 10-kg increase, 1.03; 95% confidence interval [CI], 1.02–1.04) and reported duration of daily vigorous exercise (aOR, per 1-hour increase of exercise duration, 1.02; 95% CI, 1.01–1.03). Treatment with DTG-based ART was not associated

**Table 2**

**Factors associated with CK elevation using GEE models.**

| Variable | Odds ratio (95% CI) |
|---|---|
| Factors associated with CK elevation at any level | |
| Use of dolutegravir-based regimens | 1.03 (0.99–1.06) |
| Weight, per 10-kg increase | 1.03 (1.02–1.04) |
| Use of illicit drugs | 0.96 (0.91–1.02) |
| Average time of weight training per week, per 1-hour increase | 1.02 (1.01–1.03) |
| Use of statins | 1.02 (0.96–1.08) |
| Factors associated with CK elevation of grade 3 or grade 4 | |
| Use of dolutegravir-based regimens | 1.00 (0.99–1.01) |
| Weight, per 10-kg increase | 1.00 (0.997–1.004) |
| Use of illicit drugs | 1.00 (0.99–1.02) |
| Average time of weight training per week, per 1-hour increase | 1.002 (1.001–1.003) |
| Use of statins | 0.99 (0.98–1.01) |

CI = confidence interval, CK = creatine kinase, GEE = generalized estimating equation.

with CK elevation of any level after adjusting for the imbalanced testing frequency of CK levels between the 2 groups (aOR, 1.03; 95% CI, 0.99–1.06). In terms of grade 3 or grade 4 CK elevation, there was a slightly increased risk associated with the duration of vigorous exercise (aOR, per 1-hour increase of exercise duration, 1.002; 95% CI, 1.001–1.003).

The elevations of CK level were not associated with the use of statins. In our cohort, only 7.1% of patients in the DTG group and 6.9% in the non-InSTI group had received statins during the observation period (Table 1). Moreover, all of these patients received low-intensity statin treatment according to current guidelines of the American Heart Association,[19] and only 7 patients in the non-InSTI group had concurrent use of statins and boosted protease inhibitors (data not shown).

### 3.4. Intensity of exercise and CK elevation

After stratifying all HIV-positive individuals on ART in our cohort according their duration of daily exercise, the cumulative rate of CK elevation during the observation period for those who reported no habit of regular weight training was 15.1% (146/964), which was 29.9% (84/282) for those who had regular weight training for less than 30 minutes per day and 35.6% (57/150) for those who had regular weight training for more than 30 minutes per day. In the Kaplan–Meier estimate and log-rank test comparison, the risk of CK elevation increased with the duration of weight training (Fig. 3). Compared with patients who reported having no regular weight training, those who reported having regular weight training for less than 30 minutes per day and those for 30 minutes or longer had an increased risk of CK elevation, with an aOR of 1.08 (95% CI, 1.04–1.12) and 1.15 (95% CI 1.10–1.21), respectively, after adjustments made for weight and use of DTG-containing antiretroviral regimens in the GEE model.

## 4. Discussion

In this observational cohort study, we found that the rate of developing grade 3 or grade 4 CK elevation, defined as CK elevation greater than 10 times of ULN, was similar in Kaplan–Meier estimation between patients receiving DTG-based ART and those receiving non-InSTI-based ART (2.0 per 100 PYFU in the DTG group vs 1.3 per 100 PYFU in the non-InSTI group, $P = .32$). While the rate of CK elevation of any level was slightly higher in DTG group than that in the non-InSTI group (22.9 per 100 PYFU vs 17.4 per 100 PYFU, $P = .01$), the risk was similar between the 2 groups after adjusting for testing frequency of CK level in the GEE model (Table 2). Of the 366 patients receiving DTG-based therapy and 1040 patients in the non-InSTI group, none of them were hospitalized or had to switch ART due to CK elevation.

The reported frequency of CK elevation varied significantly across different randomized trials. While only less than 1% of HIV-positive patients had CK elevation when receiving DTG, abacavir and lamivudine in the SINGLE study,[20] 19.4% of patients in the SPRING-1 study had at least grade 1 CK elevation.[21] Reasons for this discrepancy remain unclear, and different study participants enrolled, treatment regimens used and definitions applied may be contributory. The rate of CK elevation is even higher in our study if we applied a lower threshold for CK elevation (any level of elevation above the ULN). If we address only those with grade 3 or grade 4 CK elevation,[22] the rates (1.3–2.0%) observed in our study were similar to the rates in controlled trials (0.5–5.2%).[16,20–24]

The mechanism of muscle toxicity during ART is poorly understood. While HIV itself might cause polymyositis, zidovudine has been known to cause reversible myopathy via its mitochondrial toxicity which, on microscopic examination, is characterized by ragged-red fibers with cytoplasmic body formation.[25,26] However, this specific change has not been

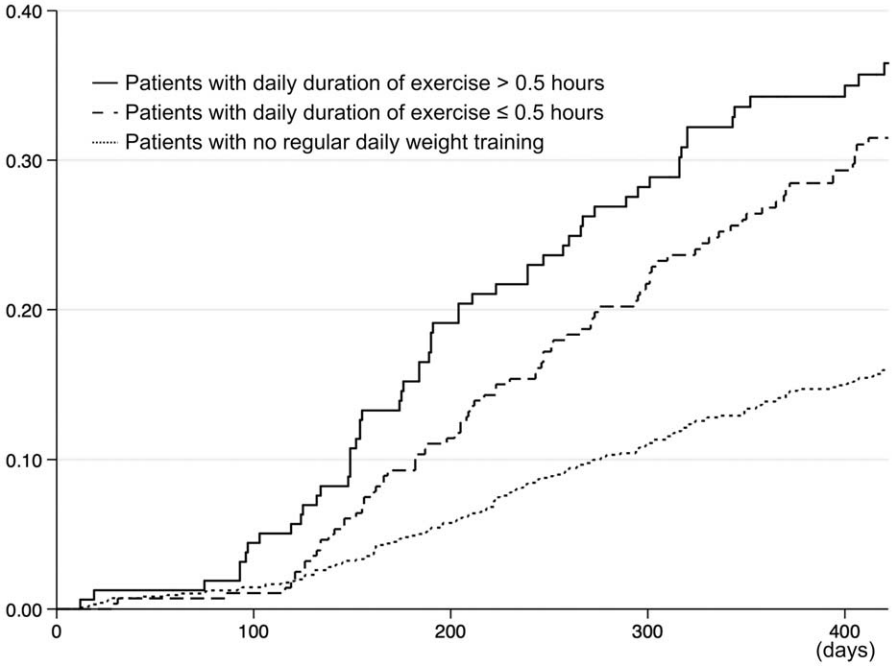


**Figure 3.** Cumulative rates of CK elevation, stratified by the duration of exercise.

shown to correlate with the use of raltegravir or other InSTIs. Some experts proposed that raltegravir might cause muscle toxicity by interfering the metabolism of statins via glucuronidation pathway.[8] However, drug–drug interactions between DTG and statins has not been reported clinically.[27]

Vigorous sports activities or exercise is known to induce various skeletal muscle damage including rhabdomyolysis.[28] However, this factor was seldom considered in the randomized clinical trials; therefore, whether exercise potentiates or enhances the risk of InSTI-related muscle toxicity has not been confirmed. While real-life cohort studies found CK elevations among patients receiving raltegravir-based ART, only two studies identified exercise as an associated factor with CK elevations. In the cohort study of individuals taking non-occupational post-exposure prophylaxis for HIV, McAllister et al found that all 5 individuals with raltegravir-associated CK elevations reported having had recent exercise before blood sampling.[9] In another 1:1 matched cohort study comparing patients receiving raltegravir-based vs non-raltegravir-based antiretroviral regimens, the elevation of serum CK level was only associated with recent strenuous exercise but not with the use of raltegravir in multivariate analysis.[29] However, both studies did not address the intensity or duration of exercise. In our cohort, the risk of CK elevation significantly increased with the increased duration of weight training or vigorous exercise, regardless of their antiretroviral regimens (Fig. 3). This provided an alternative explanation of CK elevation or rhabdomyolysis among HIV-positive patients who are receiving suppressive ART. Our findings suggest that detailed assessment of concurrent medications and exercise intensity and duration is warranted before a decision of switching antiretroviral regimen is to be made in cases of CK elevation or rhabdomyolysis.

Our study has several limitations and the findings should be interpreted with caution. First, the testing of serum CK level was performed every 3 to 6 months, which might have underestimated the rates of CK elevation or asymptomatic rhabdomyolysis in our cohort. Moreover, other clinical conditions might result in CK elevation among our patients and might lead to potential overestimation of risks associated with DTG-containing regimens. However, during the retrospective review of medical records, we were not able to identify any other situation related to CK elevation. Second, not every patient in our cohort had measurements of CK, and this might lead to potential selection and detection bias. However, the proportions of patients with at least 1 CK testing in both groups were similar (50.5% in the DTG group and 53.4% in the non-InSTI group), which indicates that the missing of CK testing might be at random. While patients in the DTG group had more frequent testing of serum CK levels compared to those in the non-InSTI group, the association between rhabdomyolysis or CK elevation and use of DTG-based ART remained statistically insignificant after adjustments with the use of simple GEE model. Third, we were unable to quantify precisely and consistently the intensity of exercise right before the blood testing, mainly due to the intervals between blood sampling and clinic appointments might be up to several months. Instead, the intensity of exercise was represented by the average self-reported duration of engaging in weight training or vigorous exercise every day, and, therefore, recall bias might occur. Finally, the observation duration of this study was only 14 months and the long-term effects of rhabdomyolysis or CK elevation among HIV-positive individuals could not be explored, though none of our patients developed symptomatic rhabdomyolysis or CK elevation necessitating hospitalization or dialysis.

In conclusion, DTG-containing antiretroviral regimens were not associated with an increased risk of CK elevation compared to non-InSTI-based regimens in the real-life clinical practices. The risk of isolated CK elevation while taking suppressive ART increased with the self-reported duration of weight training or exercise, but not with the use of DTG-based ART.

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## Author contributions

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