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BRIEF REPORT

Clinical and Laboratory Follow-up After Hospitalization for COVID-19 at an Italian Tertiary Care Center

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We evaluated 100 postacute coronavirus disease 2019 (COVID-19) patients a median (interquartile range) of 60 (48–67) days after discharge from the Careggi University Hospital, Italy. Eighty-four (84%) had at least 1 persistent symptom, irrespective of COVID-19 severity. A considerable number of hospital readmissions (10%) and/or infectious diseases (14%) during the postdischarge period were reported.

Keywords. COVID-19; follow-up; sequelae, SARS-CoV-2; long-term.

On December 31, 2019, the world received the first notice of a cluster of atypical pneumonia cases due to a novel coronavirus, later named severe acute respiratory syndrome 2 (SARS-CoV-2) [1]. Twelve months later, nearly 90 million cases of coronavirus disease 2019 (COVID-19) have been reported worldwide, with almost 2 million deaths [2].

Clinical presentation can be variable, ranging from SARS-CoV-2 asymptomatic carriers to life-threatening and fatal disease. The most common symptoms include fever, cough, and shortness of breath. Musculoskeletal symptoms, such as myalgia, joint pain, headache, and fatigue have also been reported, as well as enteric symptoms (abdominal pain, vomiting, and diarrhea), anosmia, and dysgeusia [3, 4]. Critically ill patients often require prolonged hospital stay, mechanical ventilation, and an intensive level of treatment, being at higher risk of severe complications, such as septic shock, thromboembolic events, and acute kidney injury [5].

Initial reports are emerging about the persistence of a significant symptom burden in the aftermath of recovery from acute COVID-19; this phenomenon has been called "long COVID" [6–8]. More insight about the short- and long-term consequences of SARS-CoV-2 infection is essential to properly inform follow-up programs for patients who experienced symptoms of COVID-19 [9]. An earlier clinical review within 4–8 weeks postdischarge has been recommended, at least in patients who experienced more severe symptoms [10]. In Tuscany, Italy, a comprehensive 12-month follow-up, including multidisciplinary evaluations according to disease severity and patient characteristics, is guaranteed to all individuals diagnosed with SARS-CoV-2 infection [11].

In this paper, we report the results of the first step of the follow-up program for postacute COVID-19 patients discharged from Careggi University Hospital, Florence, Italy, consisting of a clinical and biochemical assessment 8 weeks after hospital discharge.

METHODS

Since May 20, 2020—soon after the end of the epidemic phase—an outpatient service dedicated to the follow-up of postdischarge COVID-19 patients has been active at the Careggi University Hospital, Florence, Italy, in accordance with the program of the Tuscany Region. Several specialists from different disciplines are involved with this program, including infectious diseases specialists, pulmonologists, cardiologists, immunologists, and physiotherapists.

All patients discharged from the hospital were offered a clinical visit. Exclusion criteria were (i) patients discharged for more than 10 weeks; (ii) patients unable to attend the visit because of hospitalization or residents in care facilities; (iii) patient refusal. Data on subjects' death after discharge were collected.

Data on previous hospital admissions were retrieved from electronic medical records. Disease severity was classified as mild, moderate, severe, and critical, according to World Health Organization (WHO) definitions [12]. A detailed postdischarge clinical history was collected through a standardized questionnaire focused on persistence of symptoms potentially related to recent SARS-CoV-2 infection. Symptom count included any self-reported symptom persisting at the time of the follow-up visit. Postdischarge symptoms resolved before the visit were not considered in the count. The symptom inventory questionnaire used for the study is shown in the Supplementary Data. Moreover, hospital readmissions and postdischarge infections

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were ascertained by medical record review, or, alternatively, they were self-reported and supported by all available medical documentation. A full physical examination was performed.

Laboratory tests included complete blood count, coagulation profile, serum biochemical tests and serum inflammatory markers, and arterial blood gas test.

Descriptive analysis was used to illustrate population characteristics. Categorical variables were evaluated with the Pearson chi-square/Fisher exact test, as appropriate. Continuous variables were evaluated with the Mann-Whitney test. A multivariate logistic regression was performed, aiming to investigate the association between symptom persistence (categorical) and demographic factors (age, gender), comorbidity burden (by Charlson comorbidity index), and clinical severity of COVID-19 (as per WHO classification).

Patient Consent Statement

Data collection was approved by the local ethics committee (17104_oss). Patient consent was obtained. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practice guidelines.

RESULTS

Between May 20 and August 26, 2020, 178 patients were potentially eligible for the 8-week follow-up review, of whom 71 presented at least 1 exclusion criterion (41 residents of health care facilities, 7 patients readmitted to the hospital, 3 already followed by other outpatient services, 20 refused or did not answer). In addition, 7 patients died after discharge. One hundred patients (41% female; median age [interquartile range {IQR}], 67.5 [56–78.5] years) attended the postdischarge follow-up visit. Baseline characteristics and data on the COVID-19-related hospitalization of the 100 patients are reported in detail in Table 1. In brief, 12/100 (12%) and 47/100 (47%) experienced severe and critical COVID-19, respectively; the median hospital length of stay (IQR) was 16 (8–27) days, with 31/100 (31%) admitted to the intensive care unit (ICU). Most of the evaluated subjects received antiretrovirals (76/100, 76%) and/or hydroxychloroquine (88/100, 88%). Immune-modulator drugs (such as tocilizumab and ruxolitinib) and high-dose steroids (methylprednisolone equivalent ≥1 mg/kg/d) were used in 48/100 (48%) and 26/100 (26%) cases, respectively; 90/100 (90%) required oxygen supplementation, including high-flow nasal cannulae (7/100, 7%), noninvasive ventilation (26/100, 26%), and mechanical ventilation (21/100, 21%).

At the time of the follow-up visit, a median (IQR) of 60 (48–67) days after hospital discharge, 84/100 (84%) had at least 1 persistent symptom, and 36/100 (36%) reported >2 symptoms. The more frequent symptoms were fatigue (46%), dyspnea (30%), insomnia (26%), anosmia (20%), and dysgeusia and palpitation (15%). Unusual symptoms, such as visual disorders (11%), hair loss (8%), and impaired hearing (6%), were also reported. Other neurological disorders included mental confusion (10%), peripheral neuropathies (5%), and vertigo (3%). Furthermore, 4% of patients had psychological symptoms, such as anxiety and depression (Figure 1).

The persistence of symptoms was not associated with COVID-19 severity (83% vs 85% in patients with mild/moderate vs severe/critical disease, respectively; $P = .807$) or with ICU admission (84% vs 84% in ICU- vs non-ICU-admitted patients, respectively; $P = .981$) or with length of hospital stay (16 vs 13.5 days in patients with and without persistent symptoms, respectively; $P = .559$) (Table 2).

Table 1. Baseline Characteristics and Data on COVID-19-Related Hospitalization of the Studied Population (n = 100 Patients)

Baseline Characteristics	Total (n = 100)
Gender female, No. (%)	41 (41)
Age, y	
Median (IQR)	67.5 (56–78.5)
Range	24–90
Charlson comorbidity index, median (IQR)	3 (1–4)
Hypertension, No. (%)	50 (50)
Diabetes, No. (%)	21 (21)
COPD, No. (%)	12 (12)
CHD, No. (%)	12 (12)
CKD, No. (%)	7 (7)
Obesity, No. (%)	25 (25)
Length of hospital stay, median (IQR), d	16 (8–27)
Time to microbiological cure, median (IQR), d[a]	27 (14–44)
Treatments, No. (%)	
Antiretrovirals (LPV/r, DRV/c)	76 (76)
Hydroxychloroquine	88 (88)
Remdesivir	9 (9)
Immune-modulators	48 (48)
High-dose steroid (≥1 mg/kg 6-MP)	26 (26)
Antibiotics	49 (49)
ICU admission, No. (%)	31 (31)
Highest oxygen supplementation, No. (%)	
No support	13 (13)
Standard oxygen therapy	33 (33)
High flow nasal cannulae	7 (7)
Noninvasive ventilation	26 (26)
Mechanical ventilation	21 (21)
COVID-19 severity (WHO), No. (%)	
Mild	9 (9)
Moderate	32 (32)
Severe	12 (12)
Critical	47 (47)
Follow-up timing, median (IQR)	
Days since symptoms onset	82 (70–101)
Days since hospital discharge	60 (48–67)
Days since microbiological cure	50 (36–66)

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; LPV/r, lopinavir/ritonavir; DRV/c, darunavir/cobicistat; ICU, intensive care unit; IQR, interquartile range; WHO, World Health Organization.

[a]Time from the first positive to the first negative nasopharyngeal swab.

Likewise, no statistical difference was observed between patients with and without symptom persistence by gender, frequency of comorbidities (including hypertension, diabetes, chronic obstructive pulmonary disease, coronary heart disease, chronic kidney disease, and obesity), or median Charlson comorbidity index. By multivariate analysis, only age was associated with an increased risk of symptom persistence (odds ratio, 1.09 for each 1-year increase; 95% CI, 1.02–1.16) (data not shown).

Some patients required hospital readmission (10/100, 10%). Causes for hospital readmission included cardiac disease, such as heart failure and myocardial infarction (n = 5), infectious diseases (n = 2), respiratory symptoms (n = 1), and neurologic disorders (n = 2). Overall, 14 patients (14%) experienced an infection during the postdischarge period, including urinary tract infections, skin and soft tissue infections, and *Clostridioides difficile* colitis. Nineteen (19%) presented rectal colonization with multidrug-resistant bacteria (vancomycin-resistant *Enterococcus* spp. and/or carbapenem-resistant *Enterobacterales*) during the hospital stay, with a higher risk in more severe patients (16/59, 27%) in comparison with milder cases (3/41, 7%; $P = .010$), and ICU-admitted patients (11/31, 5%) in comparison with non-ICU patients (8/69, 12%; $P = .016$) (Table 2).

No significant alteration was observed in the median values of the blood test (Table 2). In our population, 22% (22/100) and 14% (14/100) showed persistence of elevated C-reactive protein and ferritin, respectively. Thirteen (13%) patients presented high D-dimer values (>1000 ng/mL). None presented respiratory failure (pO2 < 60 mmHg). Fifteen patients (15/100, 15%) were discharged with long-term oxygen therapy (LTOT), 5 of whom (5/100, 5%) were still on LTOT at the time of the follow-up visit (2 were already on LTOT before SARS-CoV-2 infection).

DISCUSSION

We analyzed clinical and laboratory results from follow-up reviews of 100 COVID-19 patients a median of 60 days after hospital discharge. At the time of the visit, a high percentage of patients (84%) complained of 1 or more persistent symptoms. Similar findings have been observed in recent studies, based on face-to-face reviews or telephone/web surveys, on both COVID-19 inpatient and outpatient populations [6–8, 13–14]. In our study, persistence of symptoms was not related to COVID-19 severity, ICU admission, or length of hospital stay. Among demographic and clinical characteristics, only increasing age was independently associated with higher risk of SARS-CoV-2 infection sequelae. Moreover, in most cases, symptoms were not accompanied by blood test abnormalities, as median values of lymphocyte count, D-dimer, and inflammation markers resulted in range and abnormal results occurred in a minority of patients. Fatigue was the most frequent self-reported symptom (46%). Persistent fatigue has been already reported as a common sequela following SARS-CoV-2 infection, raising concern that SARS-CoV-2 has the potential to trigger postviral chronic fatigue syndrome, similarly to other infectious diseases [15]. In the same study, postviral fatigue was associated with female gender and a preexisting diagnosis of

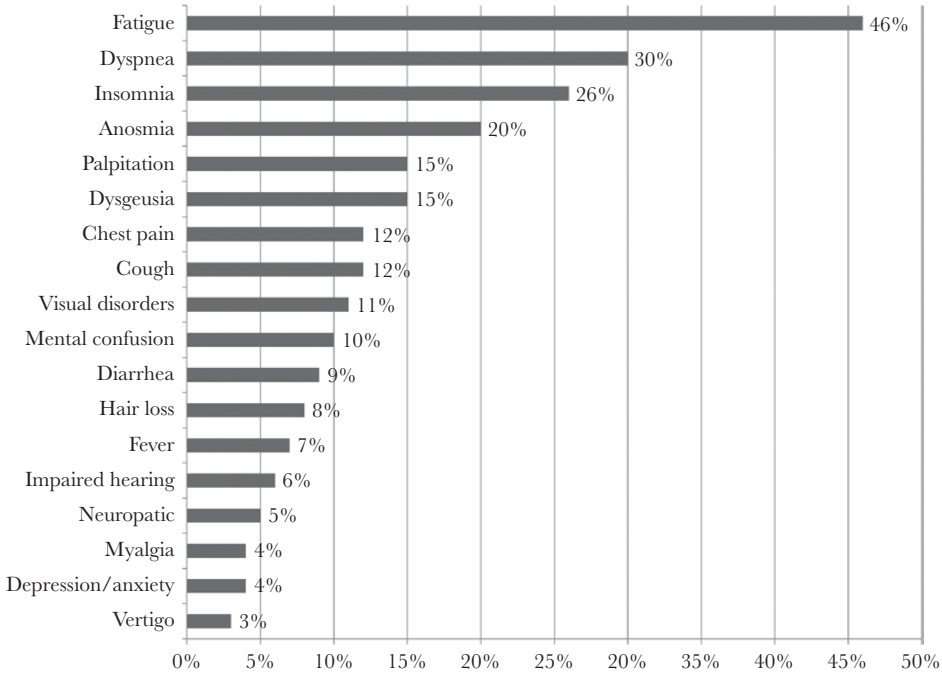

Figure 1. Persistent symptoms reported among 100 postacute coronavirus disease 2019 patients a median of 60 days after hospital discharge.

depression/anxiety, while no correlation was observed with the severity of initial SARS-CoV-2 infection, nor with inflammatory biomarker abnormalities.

The available data suggest that chronic sequelae are not limited to more severe COVID-19 cases. The results of a multistate telephone survey in the United States confirmed that return to baseline health after COVID-19 can take a long time, even in young adults with milder diseases and no chronic conditions [13]. Age, female gender, obesity, and burden of comorbidities have been variously identified as predictors of long-term symptom persistence during follow-up assessment performed from a few weeks to 6 months after acute illness [7, 16–17].

Hospital readmission after an initial COVID-19 hospitalization was experienced in 10% of the patients in our population. A large nationwide US study, including more than 100 000 electronical records of COVID-19 patients' hospitalizations, found a 9% rate of readmission to the same hospital within 2 months of discharge [18]. The odds of hospital readmission increased with age and in the presence of chronic conditions, such as chronic obstructive pulmonary disease, heart failure, diabetes, chronic kidney disease, and obesity. In our study, heart failure and other cardiac conditions accounted for half of hospital readmissions within the 8-week postdischarge period, including an 82-year-old man diagnosed with heart failure and referred to the emergency room during the follow-up visit. Moreover, at least 1 case of sudden death due to heart attack was recorded close to the follow-up visit in a 70-year-old man with a previous history of coronary heart disease. Although it is hard to definitively establish whether these events are due to direct or indirect effects of COVID-19, rather than concurrent complications of underlying conditions, more information about burden and risk factors for COVID-19 patients' readmission is needed to inform both clinical practice and public health decisions [19–20]. However, postdischarge cardiopulmonary manifestations, such as dyspnea, palpitations, and chest pain, require careful consideration, especially in elderly patients with multiple comorbidities. The wide range of reported symptoms reflects the multi-organ involvement of COVID-19, mediated by direct tissue damage, hyperinflammation, and COVID-19-related coagulopathy. A number of symptoms reported in our study, like chemosensory dysfunction, insomnia, mental confusion, and vertigo, belong to the neuropsychiatric sphere. SARS-CoV-2 tropism of the central nervous system (CNS), likely due to widespread angiotensin-converting enzyme 2 (ACE2) expression in the brain tissue, has been documented [21]. Long-term neurological sequelae in patients with previous SARS-CoV-2 infection will be fully understood only in the coming months, when longitudinal assessments will be performed.

In addition, several patients complained of unusual symptoms, like visual disorders, impaired hearing, and hair loss. Vision and hearing impairment may be part of peripheral nervous system manifestations [22]. A high frequency of male pattern hair loss among patients hospitalized for COVID-19 has been observed in Spain, suggesting that androgen expression might be a clue to COVID-19 severity [23]. Although the aforementioned symptoms are not life-threatening conditions, they can affect patients' overall well-being and functional status.

Finally, 14% of patients had an infectious event after discharge. Immune system damage induced by SARS-CoV-2 infection,

Table 2. Clinical and Laboratory Findings at Follow-up in a Postacute COVID-19 Population (n = 100 Patients)

Persistent Symptoms	Total (n = 100), No. (%)	Mild to Moderate (n = 41), No. (%)	Severe to Critical (n = 59), No. (%)	*P* Value	Non-ICU (n = 69), No. (%)	ICU (n = 31), No. (%)	*P* Value
No	16 (16)	7 (17)	9 (15)	.807	11 (16)	5 (16)	.981
Yes	84 (84)	34 (83)	50 (85)	.342	58 (84)	26 (84)	
No. of symptoms							
0	17 (17)	7 (17)	10 (17)		11 (16)	5 (17)	
1–2	47 (47)	16 (39)	31 (53)		30 (43)	17 (59)	
>2	36 (36)	18 (44)	18 (30)		28 (41)	7 (24)	.362
Postdischarge infectious diseases	14 (14)	5 (12)	9 (15)	.665	9 (13)	5 (16)	.681
Rectal colonization	19 (19)	3 (7)	16 (27)	.018	8 (12)	11 (35)	.005
Blood Test at Follow-up			Reference Values			Median Values (IQR)	
White blood cell, 10^9 cells per L			4.0–10.0			6.65 (5.38–7.72)	
Neutrophil count, 10^9 cells per L			1.5–7.5			3.98 (3.13–5.84)	
Lymphocyte count, 10^9 cells per L			0.5–5.0			1.84 (1.47–2.22)	
Platelet count, 10^9 cells per L			140–440			239 (194–290)	
ALT, U/L			10–50			15 (12–21)	
Creatinine mg/dL			0.7–1.2			0.9 (0.8–1.1)	
D-dimer, mg/L			<500			444 (302–816)	
C-reactive protein, mg/L			0–5			4 (4–5)	
Serum ferritin, μg/L			30–400			152 (69–276)	
Lactate dehydrogenase, U/L			135–225			194 (174–219)	

Abbreviations: ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range.

treatment with steroids and other immune-suppressing drugs, and longstanding hospitalization exposed patients to a high risk of infectious complications, which continued after hospital discharge. As a further element of concern, a significant rate of rectal colonization by multidrug-resistant (MDR) bacteria was detected in our population (19%), especially those admitted to the ICU. Considering that in 2019 the overall rate of rectal colonization by MDR bacteria in our hospital amounted to 14.4% (personal communication with Elisabetta Mantengoli, MD, Infectious and Tropical Diseases Unit, Careggi University and Hospital, Florence, Italy), it may be speculated that the COVID-19 pandemic has negatively influenced infection control practices.

Our study has some limitations. Only hospitalized patients were candidates for follow-up in our outpatient clinic, and no data were collected from COVID-19 outpatients. Moreover, due to the cross-sectional nature of the analysis, information about postdischarge symptoms that had resolved before the visit was missed. Finally, the study reflects an early follow-up review, limited to clinical and laboratory assessment. Further information, which is needed to better characterize the burden and pathogenesis of possible chronic sequelae, will be obtained from future radiological and functional testing, including chest radiograph, spirometry, exercise testing, and echocardiography, in addition to other specialist evaluations, to be selected case-by-case. Future studies may also confirm the real frequency of unusual symptoms reported in our study and may provide new insights into their pathogenesis.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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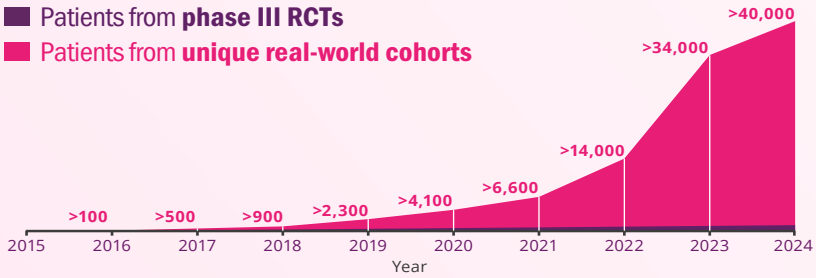

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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