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SHORT COMMUNICATION

Treatment outcomes of integrase inhibitors, boosted protease inhibitors and nonnucleoside reverse transcriptase inhibitors in antiretroviral-naïve persons starting treatment

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Objectives
Although outcomes of antiretroviral therapy (ART) have been evaluated in randomized controlled trials, experiences from subpopulations defined by age, CD4 count or viral load (VL) in heterogeneous real-world settings are limited.

Methods
The study design was an international multicohort collaboration. Logistic regression was used to compare virological and immunological outcomes at 12 ± 3 months after starting ART with an integrase strand transfer inhibitor (INSTI), contemporary nonnucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI/b) with two nucleos(t)ides after 1 January 2012. The composite treatment outcome (cTO) defined success as VL < 200 HIV-1 RNA copies/mL with no regimen change and no AIDS/death events. Immunological success was defined as a CD4 count > 750 cells/μL or a 33% increase where the baseline CD4 count was ≥ 500 cells/μL. Poisson regression compared clinical failures (AIDS/death ≥ 14 days after starting ART). Interactions between ART class and age, CD4 count, and VL were determined for each endpoint.

Results
Of 5198 ART-naïve persons in the International Cohort Consortium of Infectious Diseases (RESPOND), 45.4% started INSTIs, 26.0% PI/b and 28.7% NNRTIs; 880 (17.4%) were aged > 50 years, 2539 (49.4%) had CD4 counts < 350 cells/μL and 1891 (36.8%) had VL > 100 000 copies/mL. Differences in virological and immunological success and clinical failure among ART classes were similar across age groups (≤ 40, 40–50 and > 50 years), CD4 count categories (≤ 350 vs. > 350 cells/μL) and VL categories at ART initiation (≤ 100 000 vs. > 100 000 copies/mL), with all investigated interactions being nonsignificant ($P > 0.05$).

Conclusions
Differences among ART classes in virological, immunological and clinical outcomes in ART-naïve participants were consistent irrespective of age, immune suppression or VL at ART initiation. While confounding by indication cannot be excluded, this provides reassuring evidence that such subpopulations will equally benefit from contemporary ART.

Keywords: antiretroviral naïve, integrase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors

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Introduction

Randomized clinical trials of antiretroviral therapy (ART)-naïve persons suggest either similar or superior immunological and virological responses with integrase strand transfer inhibitor (INSTI)-containing regimens compared to contemporary boosted protease inhibitors (PI/bs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) [1–7]. There are no adequately powered studies assessing longer term clinical outcomes with INSTIs. Most randomized clinical trials report results within relevant subgroups, such as viral load (VL), CD4 count and age subgroups. In general, such trials report no differences across these relevant subgroups [2], or small and sometimes nonsignificant differences favouring INSTI-containing regimens in older persons [6], those with higher baseline CD4 counts [4,6] or those with higher baseline VLs [1,4,8]. Smaller differences were reported between an INSTI (dolutegravir) and an NNRTI (efavirenz) in those with high VL or low CD4 count or aged > 50 years at baseline [7]. In contrast, cohort studies lack randomization, but they may represent a more real-world setting for investigating the response to different ART classes and are often better powered for subgroup comparisons. Previous cohort studies, including an analysis from the International Cohort Consortium of Infectious Diseases (RESPOND), have shown a more favourable virological and/or immunological response in those starting INSTIs compared to other ART classes [9–11], but it is not clear if this finding is consistent across key subpopulations.

The aim of this study was to compare shorter term virological and immunological outcomes and clinical events of AIDS/death in ART-naïve persons starting ART in RESPOND with either an INSTI, PI/b or NNRTI regimen in key subgroups.

Methods

Study design and participants

The International Cohort Consortium of Infectious Diseases (RESPOND) is a collaboration of 17 cohort studies, including 29 432 HIV-1-positive persons from across Europe and Australia [12]. Standardized data including information on demographics, HIV-related factors, ART, coinfections, comorbidities and various biomarkers are collected at enrolment and updated annually (details at https://www.chip.dk/Studies/RESPOND). All cohorts used the HIV Cohorts Data Exchange Protocol (HICDEP) for data collection (details at https://hicdep.org/) and deaths are centrally validated using the Coding of Death in HIV (CoDe) methodology [13].

Persons aged > 18 years were included in this analysis if they were ART-naïve with a VL > 200 HIV-1 RNA copies/mL and started exactly three antiretrovirals during prospective follow-up after 1 January 2012 with either an INSTI (dolutegravir, elvitegravir, raltegravir or bictegravir), PI/b (darunavir or atazanavir) or NNRTI (efavirenz or rilpivirine) and had a CD4 count and VL measured in the 12 months prior to starting ART (for those without baseline data, the first CD4 count or VL after starting ART was used, at most 12 weeks after ART initiation).

Outcomes

Baseline was defined as the date of starting ART. Persons were stratified *a priori* according to baseline VL (≤ 100 000 or > 100 000 copies/mL), baseline CD4 count (≤ 350 or > 350 cells/μL), age (≤ 40, 41–50 or > 50 years) and presence of severe immunosuppression (CD4 count ≤ 200 cells/μL or clinical AIDS).

Immunological success was defined as a CD4 count > 750 cells/μL (where the baseline CD4 count was < 500 cells/μL) or a 33% increase in CD4 count (where the baseline CD4 count was ≥ 500 cells/μL), reflecting the finding that the incidence of AIDS/death is no longer increased at CD4 counts > 750 cells/μL [14]. The composite treatment outcome (cTO) defined success as VL < 200 copies/mL with no regimen change and no AIDS/death events. Switches in coformulation or change of booster were not considered to be a regimen change, while switches to a two-drug regimen or of an individual component, such as tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF), were considered to be changes as they may be related to drug toxicity.

A VL < 200 copies/mL was used following consensus agreement within the RESPOND virological outcomes working group reflecting cohort differences in lower limits of detection. A window of 3 months was used; immunological and cTO success was assessed at 12 ± 3 months. Clinical outcome was defined as the first new AIDS diagnosis or death from any cause occurring > 14 days after baseline.

Statistical methods

Logistic regression was used to assess the odds of cTO and immunological success, testing the interaction between ART class and baseline VL, CD4 count, presence of severe immunosuppression and age. Further analyses used VL < 50 copies/mL to define cTO success, and an on-treatment analysis considered only VL < 200 copies/mL (or 50 copies/mL) among those with data who

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remained on their initial regimen (on-treatment virological success). Poisson regression was used to investigate AIDS/death, testing the interaction between treatment class and baseline VL, CD4 count, presence of severe immune suppression and age. Analyses were adjusted for demographic (race, HIV exposure group, gender, ethnic origin, viral hepatitis B and C status, year of starting ART, cohort and age group), clinical (duration of HIV infection and nucleoside backbone) and laboratory (CD4 count and VL) parameters, all measured at baseline.

Results

Of 5198 eligible ART-naïve persons in RESPOND, 2358 (45.4%) started INSTIs (1342 dolutegravir, 429 raltegravir, 580 elvitegravir and seven bictegravir), 1349 (26.0%) PI/bs (976 darunavir and 373 atazanavir) and 1491 (28.7%) NNRTIs (823 efavirenz and 668 rilpivirine). The majority were male (n = 4248; 81.7%), of white ethnicity (n = 3617; 69.6%), and men who have sex with men (n = 2908; 55.9%). The most commonly used nucleoside backbones were tenofovir disoproxil fumarate/emtricitabine (n = 3728; 71.7%) and abacavir/lamivudine (n = 925; 17.8%). Those starting PI/bs were more likely to be female, to have a higher VL and to have a lower nadir CD4 count. Those starting INSTIs had started ART more recently.

Overall, 4700 persons (90.4%) had 12 months of follow-up; 2762 [58.8%; 95% confidence interval (CI) 56.9–60.6%] achieved cTO success (Table 1). The proportion with cTO success was highest for INSTIs and NNRTIs and lowest for PI/bs (61.7%, 63.3% and 49.5%, respectively). After adjustment, those on PI/bs had lower odds of cTO success [adjusted odds ratio (aOR) 0.74; 95% CI 0.64–0.87] with no significant differences comparing INSTIs and NNRTIs. There was no evidence that the differences in cTO success between INSTIs, PI/bs and NNRTIs differed according to age group, CD4 count or VL at baseline, or according to the presence or absence of severe immunosuppression (all P-interactions > 0.1). A much higher proportion achieved virological success in the on-treatment analysis (96.8%; 95% CI 96.2–97.4%; Table 1 and Fig. 1). After adjustment, those on PI/bs had lower odds of cTO success (aOR 0.44; 95% CI 0.22–0.89), with nonsignificant differences comparing INSTIs and NNRTIs. There was no evidence that the differences in on-treatment virological success between INSTIs, PI/bs and NNRTIs differed according to age group, CD4 count or VL at ART initiation, or according to the presence or absence of severe immunosuppression (all P-interactions > 0.1).

In total, 3979 (76.5%) persons had 12 months of follow-up and a CD4 count measured at 12 months, and 905 (22.7%; 95% CI 21.4–24.0%) achieved immunological success (Table 1). The proportion with immunological success was highest for those starting INSTIs (Table 1). After adjustment, particularly for age and nadir CD4 count, those on NNRTIs had lower odds of immunological response (aOR 0.67; 95% CI 0.52–0.85), with no statistically significant differences comparing INSTIs and PI/bs (Fig. 1). There was no evidence that the differences in immunological response between INSTIs, PI/bs and NNRTIs varied according to age group, CD4 count or VL at ART initiation, or presence or absence of severe immunosuppression (all P for interactions > 0.1).

A total of 258 persons had a new AIDS diagnosis or died > 14 days after ART initiation during 15 466 person-years of follow-up (PYFU) (incidence rate 16.7/1000 PYFU; 95% CI 14.6–18.7). Among those with an event, the median time to event was 4 months [interquartile range (IQR) 1–15 months]. The most common event was death (n = 63; 24.4%), followed by pulmonary tuberculosis (n = 28; 10.9%) and non-Hodgkin's lymphoma (n = 26; 10.1%). There were no differences in the proportion with VL > 200 copies/mL at event (132/258; 51.2%) across ART classes (P = 0.028). Those starting INSTIs had lower CD4 counts at events (median 139 cells/μL) compared to those starting NNRTIs (median 221 cells/μL) and PI/bs (median 212 cells/μL; P = 0.013). The crude incidence was highest for those starting INSTIs and lowest for those starting NNRTIs (Table 1). After adjustment, particularly for age and nadir CD4 count, there were no significant differences in the incidence of new AIDS diagnoses or death between ART classes (Fig. 1). Importantly, this finding was consistent across age groups, CD4 counts and VLs at baseline, and between those with and without severe immune suppression (all P for interactions > 0.1).

Results were consistent for cTO and virological success using a lower limit of detection of 50 copies/mL, when immunological success was defined as a CD4 count increase to > 500 cells/μL (baseline CD4 count < 400 cells/μL) or a 25% increase in CD4 count (baseline CD4 count > 400 cells/μL), for cTO, virological and immunological success at 6 months after starting ART, and for clinical progression to new AIDS diagnosis/death censoring at first change to regimen started (data not shown).

Discussion

This analysis of ART-naïve persons starting contemporary ART in the large RESPOND cohort collaboration focused on a composite treatment outcome and immunological success at 12 months and new AIDS diagnosis or death occurring more than 14 days after starting ART. While there were some differences in cTO and immunological success in favour of INSTIs, findings were consistent

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Table 1 Summary of persons included and outcomes

	All *N* (%)	INSTIs *N* (%)	PI/bs *N* (%)	NNRTIs *N* (%)
Total	5198 (100)	2358 (45.4)	1349 (26.0)	1491 (28.7)
Characteristics at baseline				
HIV VL				
≤ 100 000 copies/mL	3285 (63.2)	1417 (60.1)	759 (56.3)	1109 (74.4)
> 100 000 copies/mL	1913 (36.8)	941 (39.9)	590 (43.7)	382 (25.6)
CD4 count				
≤ 350 cells/μL	2570 (49.4)	1124 (47.7)	822 (60.9)	624 (41.9)
> 350 cells/μL	2628 (50.6)	1234 (52.3)	527 (39.1)	867 (58.1)
Severe immune suppression*				
No	3702 (71.2)	1653 (70.1)	838 (62.1)	1211 (81.2)
Yes	1496 (28.8)	705 (29.9)	511 (37.9)	280 (18.8)
Age				
≤ 40 years	2906 (55.9)	1303 (55.3)	763 (56.6)	840 (56.3)
41–50 years	1390 (26.7)	600 (25.4)	369 (27.4)	421 (28.2)
> 50 years	902 (17.4)	455 (19.3)	217 (16.1)	230 (15.4)
Outcomes				
(1) cTO success				
n (%) with data	4700 (90.4)	1963 (83.2)	1326 (98.3)	1411 (94.6)
n (%) response	2762 (58.8)	1212 (61.7)	657 (49.5)	893 (63.3)
95% CI	(56.9-60.6)	(59.0-64.5)	(45.7-53.4)	(60.1-66.4)
(2) On-treatment virological success				
n (%) with data	2912 (56.0)	1254 (53.2)	715 (53.0)	943 (63.2)
n (%) response	2819 (96.8)	1233 (98.3)	676 (94.5)	910 (96.5)
95% CI	(96.2-97.4)	(97.6-99.0)	(92.9-96.2)	(95.3-97.7)
(3) Immunological success				
n (%) with data	3979 (76.5)	1667 (70.7)	1117 (82.8)	1195 (80.1)
n (%) response	905 (22.7)	454 (27.2)	207 (18.5)	244 (20.4)
95% CI	(21.4-24.0)	(25.1-29.4)	(16.3-20.8)	(18.1-22.7)
(4) Clinical progression				
n (%) with data	5198 (100.0)	2358 (100.0)	1349 (100.0)	1491 (100.0)
Number of events (PYFU)	258 (15 465.8)	106 (5093.0)	92 (5175.9)	60 (5196.9)
Rate/1000 PYFU	(16.7)	(20.8)	(17.8)	(11.5)
95% CI	(14.6-18.7)	(16.9-24.8)	(14.1-21.4)	(8.6-14.5)

Values are *n* (%), unless otherwise stated.
CI, confidence interval; cTO, composite treatment outcome; INSTI, integrase strand transfer inhibitor; PI/b, boosted protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PYFU, person-years of follow-up. (1) VL < 200 copies/mL, no change in ART regimen and no AIDS or death. Missing VL = failure. (2) VL < 200 copies/mL and no treatment change; missing VL = excluded. (3) CD4 count > 750 cells/μL if baseline CD4 count < 500 cells/μL or 33% increase if baseline CD4 count > 500 cells/μL. (4) New AIDS event or death > 14 days after baseline; rates per 1000 PYFU.
*AIDS or CD4 count ≤ 200 cells/μL.

across subgroups defined by age, CD4 count, VL and severe immune suppression (AIDS or CD4 count ≤ 200 cells/μL).

We found some evidence that virological treatment response to INSTIs was better than that to contemporary PI/bs using both composite outcomes and an on-treatment analysis, consistent with recent meta-analyses [15,16], open-label studies [17] and findings from observational studies [9,11,18]. We also found a slightly better immunological response with INSTIs compared to NNRTIs, as has been previously shown [6,7,19]. Importantly, the differences in immunological and virological responses found when comparing the three antiretroviral classes were consistent in the key subgroups investigated. While we adjusted for important confounders, such as age and nadir CD4 count, we cannot exclude confounding by indication. We chose a relatively high CD4 count for immunological response, reflecting the comparatively high CD4 count nadir in the included individuals, as well as evidence that the incidence of AIDS no longer decreases at CD4 counts > 750 cells/μL [14], but found consistent results in sensitivity analyses using lower CD4 count increases to define immunological response.

To our knowledge, we are the first to show no differences in AIDS or mortality outcomes comparing INSTIs, PI/bs and NNRTIs, albeit with limited power. We focused on events occurring > 14 days after ART to reduce the impact of early events caused by late presentation. The median time to event remained short, suggesting that some of the events were caused by uncontrolled HIV infection and/or late presentation. We focused on AIDS

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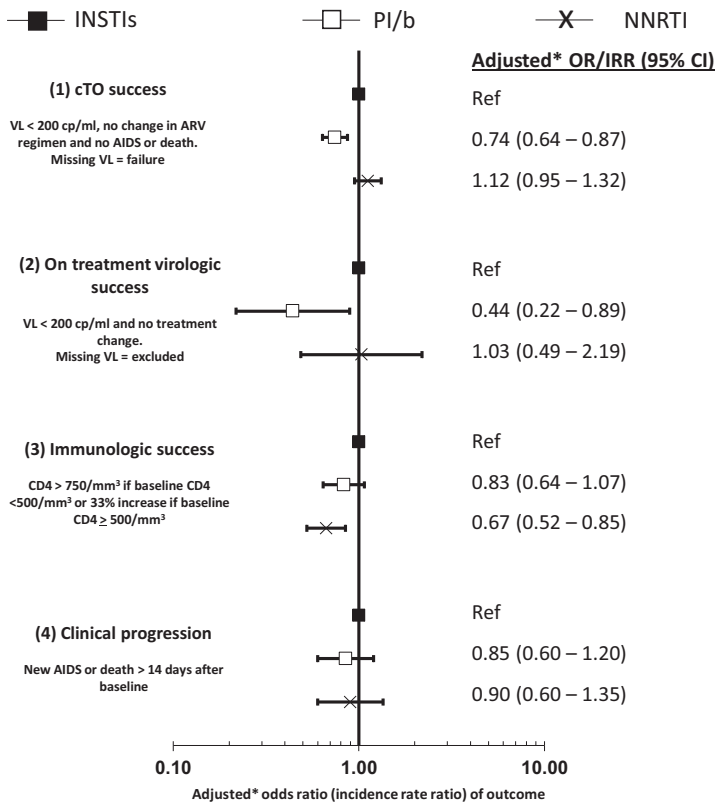

Interaction p-values: class ARV and	Age	VL	CD4	AIDS or CD4
(1) cTO success	0.65	0.14	0.38	0.14
(2) On treatment virologic success	0.74	0.96	0.16	0.23
(3) Immunologic success	0.31	0.26	0.85	0.18
(4) Clinical progression	0.42	0.67	0.10	0.30

Fig. 1 Outcomes after initiation of antiretroviral therapy (ART) in ART-naïve persons. *cTO, immunologic and on-treatment outcomes using logistic regression and adjusted odds ratio; clinical outcomes using Poisson regression and adjusted incidence rate ratios. Models adjusted for cohort, CD4, age, viral load, AIDS, HBV, HCV, year of starting ART, gender, race, HIV risk, time since HIV diagnosis, baseline date and nucleoside backbone (all at starting ART).

and death to reduce confounding by indication related to the choice of initial ART in persons with underlying comorbidities. Of note, our findings were similar across key subgroups, less often considered particularly in cohort studies. This finding is of direct clinical relevance and can be used in routine clinic settings to reassure persons starting ART.

The main limitation of our study is that we cannot rule out confounding by indication. We were not powered to look at individual antiretrovirals and it is possible that results differ within ART classes for specific agents. The major strengths of this study were the inclusion of routine clinic populations, inclusion of clinical events as an endpoint, and the focus on whether results were consistent across key subgroups.

To conclude, differences among ART classes in virological, immunological and clinical outcomes in ART-naïve participants were consistent irrespective of age, immune suppression or VL at ART initiation. While confounding by indication cannot be excluded, this provides reassuring evidence that such subpopulations will equally benefit from modern ART.

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