

# Training, guideline access and knowledge of antiretroviral interactions: Is the South African private sector being left behind?

B S Chisholm,<sup>1</sup> BPharm, Dip HIV TB Man; A M Swart,<sup>1</sup> BSc (Pharm); M Blockman,<sup>2</sup> MB ChB, MMed (Clin Pharmacol)

<sup>1</sup> National HIV and TB Healthcare Worker Hotline, Medicines Information Centre, Division of Clinical Pharmacology, Faculty of Health Sciences, Department of Medicine, University of Cape Town, South Africa

<sup>2</sup> Division of Clinical Pharmacology, Faculty of Health Sciences, Department of Medicine, University of Cape Town, South Africa

Corresponding author: B S Chisholm ([briony.chisholm@uct.ac.za](mailto:briony.chisholm@uct.ac.za))

**Background.** South Africa (SA) has the largest antiretroviral therapy programme in the world. While the majority of the country accesses healthcare in the public sector, 15.2% access private healthcare. In 2019, dolutegravir was introduced as first-line treatment for HIV. Dolutegravir has clinically significant interactions with numerous commonly used medicines, e.g. rifampicin and cation-containing medicines such as calcium and iron. They require dosage adjustments, detailed in public and private HIV guidelines.

**Objectives.** To describe SA healthcare workers' guideline access, training and knowledge of dolutegravir's interactions, focusing on differences between the public and private sectors.

**Methods.** A cross-sectional, descriptive study was done using an online survey of healthcare workers in the field of HIV in SA, conducted by the National HIV and TB Healthcare Worker Hotline. Convenience sampling was used, with electronic dissemination to users of the hotline and by relevant HIV-focused organisations. Simple descriptive statistics and statistical analyses were used.

**Results.** A total of 1 939 surveys were analysed, with 22% from the private sector. Training on the dolutegravir guidelines was received by significantly fewer healthcare workers in the private sector v. the public sector: 42.4% (95% confidence interval (CI) 37 - 48) v. 67.5% (95% CI 65 - 70), respectively. Significantly fewer healthcare workers in the private sector had access to the guidelines (63.8%; 95% CI 59 - 69 v. 78.8%; 95% CI 77 - 81). When asked if they were aware that dolutegravir has interactions, just over half (56.9%) of healthcare workers in the private sector responded 'yes', 24.6% responded 'no' and 18.5% did not answer. Of those who were aware that dolutegravir has interactions, 48.9% knew that dolutegravir interacts with calcium, 44.6% with iron and 82.0% with rifampicin. Private sector knowledge of dosing changes was lower for all interacting drugs, with the difference only significant for calcium and iron. Private sector healthcare workers reported significantly lower levels of counselling on dolutegravir use in all appropriate situations.

**Conclusion.** Private sector healthcare worker access to HIV training and guidelines requires attention. In a high-burden HIV setting such as SA, it is vital that healthcare workers across all professions, in both the public and private sector, know how to adjust antiretroviral dosing due to clinically significant interactions. Without these adjustments, there is a risk of treatment failure, increased mother-to-child transmission and morbidity and mortality.

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With an estimated 8.2 million people living with HIV in South Africa (SA) in 2021, and an estimated adult (15 - 49 years old) population prevalence of 19.5%, SA has the largest antiretroviral therapy (ART) programme in the world.<sup>[1]</sup> In terms of the Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 targets, 92% of South Africans knew their status, 72% were on ART and 66% were virally suppressed in 2020.<sup>[2]</sup>

The majority of South Africans receive healthcare in the public sector. However, 9 million people (15.2%) were covered by a medical aid scheme (private sector) in 2020.<sup>[3]</sup> According to the Council for Medical Schemes 2020/21 annual report, 47.7/1 000 members were registered on an HIV management programme.<sup>[4]</sup> Govender *et al.*'s<sup>[5]</sup> interview-based study of patients receiving care at private and public facilities in SA found that 48% usually visited public facilities, 32% private and 20% both. With the high HIV prevalence in SA, it is vital that healthcare workers (HCWs) in both the public and private sector have up-to-date ART knowledge.

In line with World Health Organization recommendations,<sup>[6]</sup> SA adopted dolutegravir-based ART as the preferred first line at the end of 2019.<sup>[7,8]</sup> Dolutegravir is preferred over efavirenz-based ART because of

its safety, efficacy, high barrier to resistance and smaller propensity for drug-drug interactions (DDIs).<sup>[9,10]</sup> While these characteristics make dolutegravir preferable, the drug does have some clinically important interactions with other commonly used drugs, including cation-containing drugs such as calcium and iron, metformin, rifampicin and some anti-epileptic drugs (AEDs).<sup>[11-17]</sup> These require changes in dosing and/or dosing regimen, detailed in both public and private sector guidelines (Table 1). Non-adherence to the recommended adjustments may cause HIV-1 resistance, treatment failure and increased HIV transmission.

While information on DDIs, and the steps to take to mitigate them, is freely available, data on HCW knowledge of ART DDIs are sparse, especially in the SA setting and among all HCWs involved in HIV care. Two small international studies of HCWs' knowledge of ART DDIs showed low levels of knowledge: a UK-based hospital study showed that only 36% of clinically relevant interactions were identified by physicians,<sup>[18]</sup> and a US-based survey using 10 case-based ART questions, including 4 on DDIs, showed that a mean of 33% of residents, 37% of attending physicians and 93% of infectious disease specialists correctly answered the questions.<sup>[19]</sup> One study in an African

**Table 1. Summary of dolutegravir pharmacokinetic interactions and dosing recommendations**

Interacting drug(s)	Effect on concentration of DTG or interacting drug	SA guideline recommendations <sup>[7,8]</sup>
Cations	Multivitamin decreased DTG AUC by 33%; aluminium/magnesium hydroxide decreased DTG AUC by 74%. Counteracted by dosage separation. <sup>[11]</sup> Calcium decreased DTG AUC by 39%; iron decreased DTG AUC by 54%. Counteracted by dosage separation and/or concomitant food. <sup>[12]</sup>	Magnesium/aluminium-containing antacids should be taken a minimum of 2 hours after or 6 hours before DTG. DTG and calcium or iron supplements can be taken at the same time if taken with food.
Metformin	DTG increased metformin AUC by 79%. <sup>[13]</sup>	Maximum metformin dose 500 mg 12-hourly.
Rifampicin	Rifampicin reduced the DTG AUC by 56%. <sup>[14]</sup> Double dose of DTG counteracted this interaction safely and effectively. <sup>[15]</sup>	Double DTG dose to 50 mg 12-hourly.
AEDs	Carbamazepine reduced DTG AUC by 49%. <sup>[16,17]</sup> Decreased DTG levels expected with phenytoin and phenobarbital due to UGT1A1 and CYP3A enzyme induction by phenytoin and phenobarbital. <sup>[17]</sup>	Avoid coadministration with carbamazepine, phenobarbital, and phenytoin, if possible. Double DTG dose to 50 mg 12-hourly for carbamazepine if an alternative cannot be used.

DTG = dolutegravir; SA = South Africa; AUC = area under the curve; AED = anti-epileptic drug; UGT = uridine 5-glucuronosyltransferase; CYP = cytochrome P450.

setting found that 43% of patients on ART included in a prospective observational study at a Tanzanian chronic disease clinic had one or more clinically relevant DDIs that were not recognised or incorrectly managed by the treating physician.<sup>[20]</sup>

An online survey to describe SA HCWs' knowledge of dolutegravir's interactions, guideline access and training, and the variables associated with gaps in knowledge was conducted. The full study has been reported on previously,<sup>[21]</sup> and this article focuses on gaps in the private sector.

## Methods

### Study design

A cross-sectional, descriptive study using an online survey of HCWs in the field of HIV in SA (appendix: <https://www.samedical.org/file/1878>) ran for 8 weeks in August and September 2020. Full details of the survey design have been previously published.<sup>[21]</sup>

The study was conducted by the National HIV and TB Healthcare Worker Hotline, based at the Medicines Information Centre, in the Division of Clinical Pharmacology at the University of Cape Town. The hotline has been running since 2008 and is toll-free. Specially trained pharmacists answer around 500 HIV- and tuberculosis (TB)-related clinical queries a month from HCWs across SA, mainly telephonically but also via email and WhatsApp.

### Study setting and participants

SA HCWs (i.e. doctors, nurses, pharmacists, community HCWs or other HCWs) were invited to participate, targeting those working in the field of HIV, with dissemination via email, SMS and social media to users of the hotline and by relevant HIV-focused organisations (convenience sampling). The survey was in English, and therefore required participants to be able to read English, and was designed to exclude respondents who did not fit within the inclusion criteria, i.e. those who stated they were from outside of SA or not involved in HIV care.

### Statistical analysis

Simple descriptive statistics (frequencies, median, interquartile range (IQR)), were calculated in Excel (Microsoft, USA), and statistical analyses were performed using Stata software (StataCorp., USA). Branching logic was used in the survey – for example, only those who responded that they were aware that dolutegravir has interactions

saw the question on which drugs interact. The denominator used was the total number of responses to each question. Blanks (where a respondent did not answer that question) were included, where appropriate, in the descriptive statistics, and excluded in the inferential analyses. A full description of the analyses has been published in the primary article.<sup>[21]</sup>

### Ethical considerations

Research ethics approval was obtained from the University of Cape Town's Human Research Ethics Committee (ref. no. 357/2020). The survey was conducted anonymously, and an opt-in draw for a prize hamper was offered at the end. Personal details entered for the draw were collected and stored independently from survey answers.

## Results

Due to the online nature of the survey, response rates could not be calculated, but 1 950 analysable surveys were submitted. Of these, 11 did not specify their sector, so were excluded from the analysis, leaving 1 939 surveys analysed: 427 respondents were from the private sector (22%). Demographics are detailed in Table 2, and provincial distribution in Fig. 1.

Training on the dolutegravir guidelines had been received by significantly fewer HCWs in the field of HIV in the private sector: 42.4% (95% confidence interval (CI) 37 - 48) compared with 67.5% (95% CI 65 - 70) in the public sector. Most training in both sectors included training on dolutegravir. Training was desired across the board, regardless of whether any had been received before (Table 3).

When asked about the preferred format of training, HCWs in the private sector were significantly more likely than their public sector colleagues to prefer computer-based online training (61.0; 95% CI 55 - 67 v. 44.9%; 95% CI 42 - 48), and less likely to prefer cellphone-based online training (31.5%; 95% CI 26 - 37 v. 40.8; 95% CI 38 - 44) (Table 3).

Less than two-thirds of HCWs in the private sector had access to HIV guidelines, significantly fewer than those in the public sector (63.8%; 95% CI 59 - 69 v. 78.8%; 95% CI 77 - 81). Private sector HCWs were more likely than those in the public sector to access online ART guidelines (79.2%; 95% CI 74 - 84 v. 58.5%; 95% CI 56 - 62) and less likely to have access to hard copy ART guidelines (34.3%; 95% CI 28 - 41 v. 61.2%; 95% CI 58 - 64). Less than half of HCWs in both the private and public sectors reported having access to prevention of mother-to-child

**Table 2. Private sector and total respondent demographics (N=1 939)**

Characteristic	Sector	
	Private (n=427), n (%)*	All (N=1939), n (%)*
<b>Profession</b>		
Doctor	172 (40.3)	698 (36.0)
Nurse	157 (36.8)	909 (46.9)
Pharmacist	61 (14.3)	173 (8.9)
Other/allied†	36 (8.4)	154 (7.9)
Unanswered	1 (0.2)	5 (0.3)
<b>Area</b>		
Rural	99 (23.2)	796 (41.1)
Urban	328 (76.8)	1 138 (58.7)
Unanswered	0 (0.0)	5 (0.3)
<b>HIV experience, years</b>		
Median (IQR)	10 (5 - 20)	10 (5 - 15)
<1	11 (2.6)	39 (2.0)
1 - 5	98 (23.0)	577 (29.8)
6 - 10	105 (24.6)	587 (30.3)
11 - 20	143 (33.5)	577 (29.8)
21 - 30	61 (14.3)	143 (7.4)
>30	9 (2.1)	16 (0.8)
<b>Age, years</b>		
Median (IQR)	44 (34 - 55)	41 (33 - 51)
<20	1 (0.2)	2 (0.1)
20 - 29	39 (9.1)	288 (14.9)
30 - 39	122 (28.6)	599 (30.9)
40 - 49	93 (21.8)	518 (26.7)
50 - 59	108 (25.3)	349 (18.0)
≥60	59 (13.8)	174 (9.0)
Blank‡	5 (1.2)	9 (0.5)

IQR = interquartile range.

\*Unless otherwise indicated.

†Community health workers, counsellors and those defining themselves as 'other' profession, e.g. clinical associate, pharmacist assistant.

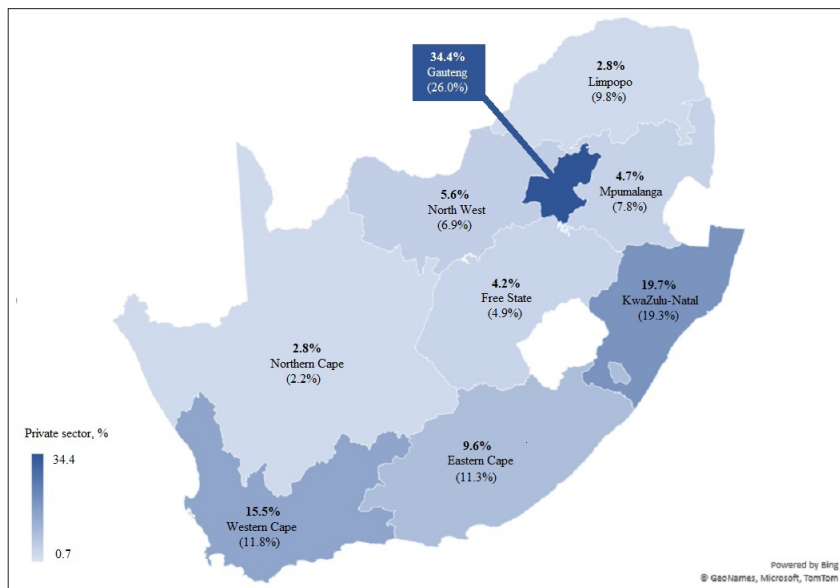


Fig. 1. Provincial breakdown of private sector respondents and national estimated population proportions (in brackets) in 2020.<sup>[22]</sup>

transmission guidelines (both online and hard copy). Access to apps was similarly low in both sectors, at ~15% (Table 4).

When asked if they were aware that dolutegravir has interactions, just over half (56.9%) of HCWs in the private

sector responded 'yes', 24.6% responded 'no' and 18.5% did not answer. Looking by profession, just under half of private sector nurses (49.0%) answered 'yes', 30.6% 'no' and 20.4% left this question blank, compared with 72.5%, 11.2% and 16.4% of those practising in the public sector, respectively. Two-thirds of doctors and three-quarters of pharmacists answered 'yes', compared with >80% of their public sector colleagues (Table 5).

Of the private sector HCWs who were aware that dolutegravir has interactions, less than half knew that dolutegravir interacts with calcium (48.9%), iron (44.6%) and magnesium/aluminium (48.1%). Over 80% knew there is an interaction with rifampicin, and 73.4% knew it interacts with metformin (Table 5).

When asked about interactions with AEDs, 57.5% were aware of the interaction with carbamazepine, 46.8% with phenobarbitone and 51.9% with phenytoin. With AEDs that do not interact with dolutegravir, 18.5% thought that there are interactions with lamotrigine and 28.8% with sodium valproate (Table 5).

Only the respondents who marked that they were aware of each interaction saw the question on dosing/dosage adjustments needed when using those drugs with dolutegravir. Looking at knowledge of the required dosing in combination with dolutegravir (correct dosing adjustment in boxes on Fig. 2), private sector knowledge was lower for all interacting drugs, but the difference was only significant for calcium (48.9%; 95% CI 42 - 56 v. 61.3 - 67) and iron (44.6%; 95% CI 38.1 - 51.3 v. 55.5%; 95% CI 52.5 - 58.4).

When asked about which patients were counselled on dolutegravir interactions, private sector HCWs reported significantly lower levels of counselling in all appropriate situations than public sector HCWs (19.8%; 95% CI 15 - 25 v. 34.9%; 95% CI 32 - 38), which was reflected across the board, and in their confidence in counselling (47.0%; 95% CI 43 - 50 v. 56.4%; 95% CI 55 - 58) (Fig. 3).

## Discussion

To the authors' knowledge, this is the first study done in SA to quantify HCWs in the field of HIV's guideline access, training on updated guidelines and knowledge of what is in those guidelines. Our study provides sector-level insight on this. There are significant gaps in SA HCW awareness that dolutegravir has interactions, which drugs interact with it and the changes in administration needed to mitigate the effects of the interaction.

The gaps in knowledge are understandable, especially in the private sector, considering that less than half of the respondents in this sector reported having received training on dolutegravir (42.4%), and under two-thirds (63.8%) reported having easy access to HIV guidelines. This was significantly lower than those in the public sector. High computer proficiency and good internet access would be expected in the private sector, and HIV guidelines are available electronically, which begs the question: why is private sector guideline access poor? The root cause(s) of poor access are beyond the scope of this study, and importantly, require further research. A study conducted at public sector urban and rural facilities in the Western Cape Province reinforced that training, mentorship and clinical experience were associated with HIV knowledge and confidence in professional nurses.<sup>[23]</sup>

Less than half of private sector-based HCWs reported that they felt confident to counsel patients on how to take dolutegravir with interacting medicines, with only 19.8% reporting counselling their patients on dolutegravir in all appropriate situations. This highlights the fact that gaps in knowledge and a lack of guideline access and training ultimately affect patient care. While not implicitly comparable, a standardised patient study of private sector SA general practitioners showed that they did not provide optimal management of HIV in the context of TB and did not perform as well as their public sector colleagues in previous studies.<sup>[24]</sup> Our results add to this knowledge: only 64.3% of private sector doctors in our study responded that they

were aware that dolutegravir has interactions. With the interaction between dolutegravir and rifampicin requiring a doubling of the dolutegravir dose, a lack of awareness will

contribute to poor management and outcomes of HIV/TB-co-infected patients.

Our study's main strength was the good response – which was due to the online

**Table 3. Training received, training desired and preferred training method of respondents, by sector**

Training characteristic	Private sector		Public sector	
	%	95% CI	%	95% CI
<b>Training</b>				
Received training on DTG	42.4	37.4 - 47.5	67.5	64.9 - 69.9
Training included DTG interactions	89.6	83.8 - 93.8	94.6	92.9 - 95.9
<b>Desire more training/training on DTG</b>				
Received training previously	84.4	78.9 - 89.0	82.3	79.8 - 84.7
No training received	91.1	83.8 - 95.8	92.5	87.3 - 96.1
<b>Preferred training method</b>				
Face to face	17.6	13.5 - 22.5	24.7	22.1 - 27.4
Online (computer)	61.0	55.2 - 66.6	44.9	41.8 - 48.0
Online (cellphone)	31.5	26.3 - 37.2	40.8	37.8 - 43.9
Hard copy (e.g. posters)	38.3	32.7 - 44.1	47.1	44.1 - 50.2
Other	1.4	0.4 - 3.4	1.4	0.8 - 2.3

CI = confidence interval; DTG = dolutegravir.

**Table 4. Guideline access and type, by sector**

Guideline access	Private sector		Public sector	
	%	95% CI	%	95% CI
Access to 2019 guidelines	63.8	58.8 - 68.6	78.8	76.6 - 81.0
<b>Type of guideline access</b>				
Online ART guidelines	79.2	73.6 - 84.1	58.5	55.6 - 61.5
Online PMTCT guidelines	44.1	37.8 - 50.5	41.6	38.7 - 44.6
Hard copy ART guidelines	34.3	28.4 - 40.6	61.2	58.2 - 64.1
Hard copy PMTCT guidelines	16.7	12.3 - 22.0	41.0	38.1 - 44.0
App	14.7	10.5 - 19.8	14.4	12.4 - 16.7

CI = confidence interval; ART = antiretroviral therapy; PMTCT = prevention of mother-to-child transmission; app = mobile application.

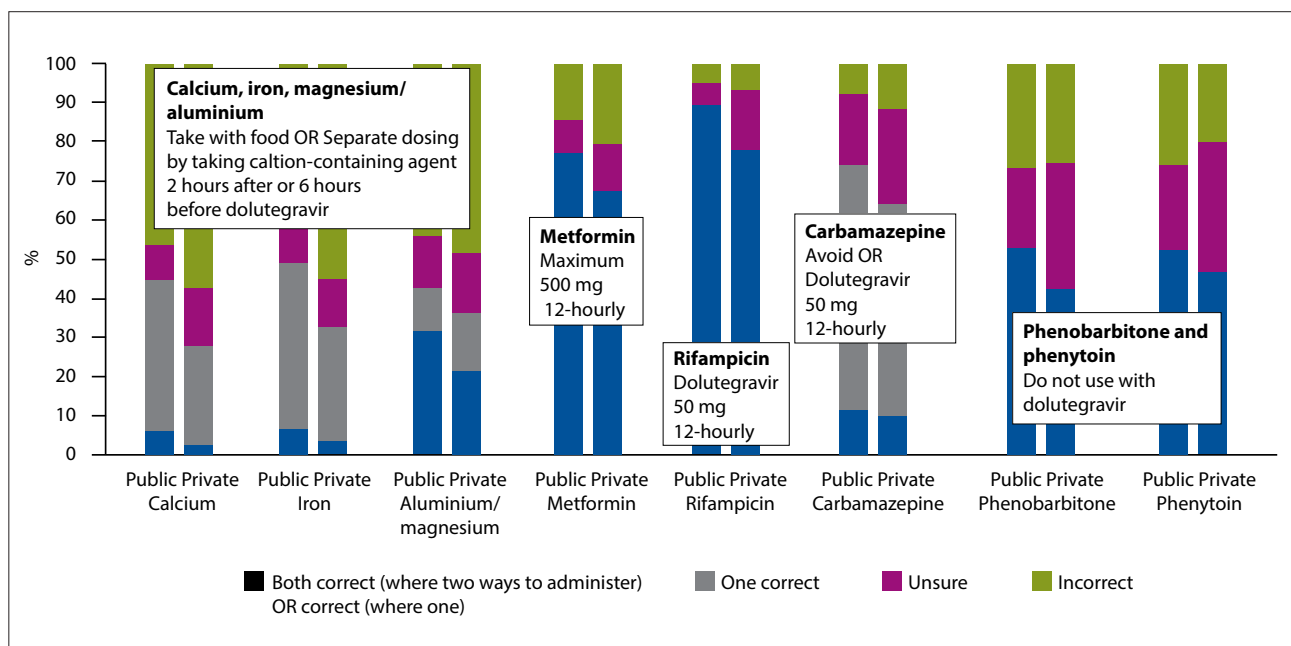


Fig. 2. Knowledge of dosage adjustments required with concomitant dolutegravir use, by sector.



nature of the study, the large database of contacts collected through the hotline over 5 years and long-standing associations with

HIV-based organisations. The proportion of public and private respondents also reflect the SA healthcare landscape.

**Table 5. Healthcare worker broad and specific awareness of dolutegravir interactions, by sector**

Are you aware that DTG has interactions?	Private sector (n=427), n (%)	Public sector (n=1 512), n (%)	Total (N=1 939), n (%)
Yes	243 (56.9)	1 122 (74.2)	1 365 (70.4)
Doctor	109 (64.3)	440 (83.7)	549 (78.7)
Nurse	77 (49.0)	545 (72.5)	622 (68.4)
Pharmacist	44 (72.1)	91 (81.3)	135 (78.0)
Other/allied profession*	13 (36.1)	46 (39.0)	59 (38.3)
No	105 (24.6)	166 (11.0)	271 (14.0)
Doctor	30 (17.4)	26 (4.9)	56 (8.0)
Nurse	48 (30.6)	84 (11.2)	132 (14.5)
Pharmacist	9 (14.8)	6 (5.4)	15 (8.7)
Other/allied profession*	18 (50.0)	50 (42.4)	68 (44.2)
Unanswered	79 (18.5)	224 (14.8)	303 (15.6)
Doctor	33 (19.2)	60 (11.4)	93 (13.3)
Nurse	32 (20.4)	123 (16.4)	155 (17.1)
Pharmacist	8 (13.1)	15 (13.4)	23 (13.3)
Other/allied profession*	5 (13.9)	22 (18.6)	27 (17.5)
Unspecified	1 (100.0)	4 (100.0)	5 (100.0)
Awareness of specific interactions	n=233 <sup>†</sup>	n=1 100 <sup>†</sup>	n=1 333 <sup>†</sup>
Calcium	114 (48.9)	706 (64.2)	820 (61.5)
Iron	104 (44.6)	610 (55.5)	714 (53.6)
Magnesium/aluminium	112 (48.1)	601 (54.6)	713 (53.5)
Rifampicin	191 (82.0)	967 (87.9)	1 158 (86.9)
Metformin	171 (73.4)	871 (79.2)	1 042 (78.2)
Carbamazepine	134 (57.5)	649 (59.0)	783 (58.7)
Phenobarbitone	109 (46.8)	483 (43.9)	592 (44.4)
Phenytoin	121 (51.9)	547 (49.7)	668 (50.1)
Non-interacting drugs			
Oral contraceptives	53 (22.7)	181 (16.5)	234 (17.6)
Lamotrigine	43 (18.5)	138 (12.5)	181 (13.6)
Sodium valproate	67 (28.8)	282 (25.6)	349 (26.2)

DTG = dolutegravir.  
 \*Community health workers, counsellors and those defining themselves as 'other' profession, e.g. clinical associate, pharmacist assistant.  
<sup>†</sup>Only those who answered 'yes' to being aware that DTG has interactions saw the question on specific interactions. Multiple answers were allowed, and blank responses were excluded from the denominator.

Limitations of the study include the risk of both self-selection and non-response bias. Secondly, there is the potential for positive skewing because those invited are 'interactive' HCWs who have called the hotline or are members of relevant organisations and followers of relevant Facebook pages. Finally, due to the branching nature of the survey, those who said 'no' to the question asking if they were aware of dolutegravir's interactions did not see further questions on which drugs interact, and those who did not mark interacting drugs did not see the questions on dosing – meaning that the proportions reported may overestimate knowledge.

**Conclusion**

Of concern is that under half of private sector-based HCWs in this study, across all professions, had received training on dolutegravir, only two-thirds had access to HIV guidelines and just over half were aware that dolutegravir has interactions. In a high-burden HIV setting such as SA, it is vital that all HCWs know how to use, and dose-adjust, dolutegravir owing to clinically significant interactions. Without these dose adjustments, there is a risk of treatment failure, increased mother-to-child transmission, and morbidity and mortality. Private sector HCW access to HIV training and guidelines and, in particular, their awareness that dolutegravir has clinically significant interactions, require attention.

**Declaration.** None.

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**Author contributions.** BC, AS and MB conceived the research project. BC designed the survey with input from AS and MB. The survey was tested, piloted, disseminated and conducted by BC. Data were extracted by BC, cleaned by BC, in consultation with AS and MB, and analysed by BC and statisticians. The first draft of the manuscript was written by BC, and revised by BC, AS and MB. All authors have read and approved the final manuscript.

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**Conflicts of interest.** None.

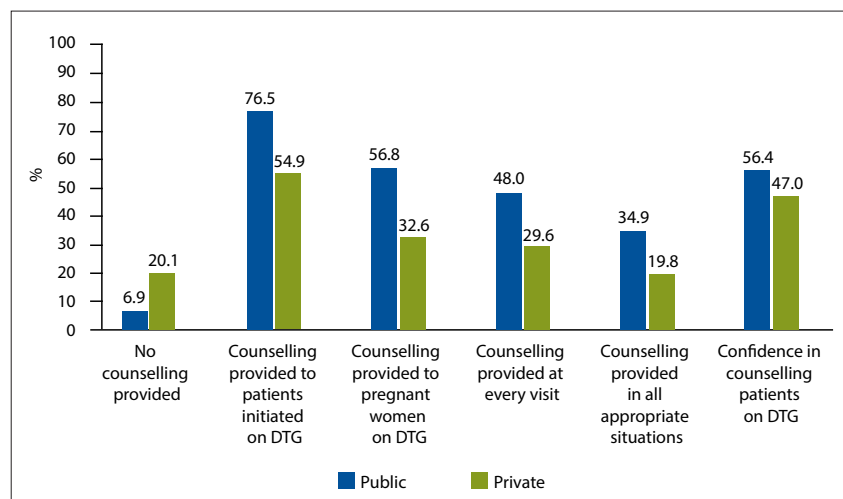


Fig. 3. Dolutegravir (DTG) interaction counselling, by sector.

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