Analysis of antiretroviral therapy modification in routine clinical practice in the management of HIV infection

Carmen Sobrino-Jiménez,¹ Inmaculada Jiménez-Nácher,¹ Francisco Moreno-Ramos,¹ María Ángeles González-Fernández,¹ Mercedes Freire-González,¹ Juan González-García,² Alicia Herrero-Ambrosio¹

¹Pharmacy Department, La Paz University Hospital, Madrid, Spain

²Internal Medicine Department, La Paz University Hospital, Madrid, Spain

Correspondence to

Dr Carmen Sobrino-Jiménez, Pharmacy Department, La Paz University Hospital, Hospital La Paz, Paseo de la Castellana 261, Madrid 28046, Spain; carmen.sobrino@salud.madrid.org

Received 28 March 2016

Revised 21 June 2016

Accepted 28 June 2016

Published Online First

21 July 2016

EAHP Statement 4: Clinical Pharmacy Services

ABSTRACT

Objectives The main goal was to assess the reasons for antiretroviral therapy (ART) change in patients with HIV in a hospital setting in routine clinical practice. The economic impact of ART modification was also analysed.

Methods Patients with HIV who changed their ART between 24 November and 24 December 2014 were registered. Length of initial therapy, type of ART before and after therapy modification, and reasons for the ART change were analysed. To assess the economic impact, antiretroviral drug costs at the time of the study were recorded.

Results Of a cohort of 3850 patients with HIV, 1976 attended for pharmaceutical care consultation at Hospital Universitario La Paz during the study period. Ninety-two patients (4.7%) had their ART modified. The median length of the previous therapy was 26 months (range 1–144). The most common initial therapy regimen was 2 nucleoside reverse transcriptase inhibitors (NRTI)+1 non-nucleoside reverse transcriptase inhibitor (NNRTI) (29.4%), and the most common one after modification was 2 NRTI+1 integrase strand transfer inhibitor (INSTI) (40.2%). Forty-three modifications were made because of toxicity and adverse effects (46.7%), 25 because of therapy simplification (27.2%), 16 because of treatment failure (17.4%), and 8 because of drug–drug interactions (8.7%). ART costs increased by a mean of €14 (SD €216; range –€528 to +€831) per month per patient after therapy modification at the time of study.

Conclusions Toxicity and adverse effects were the most common reason for ART alteration in patients with HIV in routine clinical practice in a hospital setting. Better knowledge about factors that motivate these changes may contribute to decreased toxicity and increased treatment success. ART modification had a variable but not very substantial economic impact.

INTRODUCTION

Marked reductions in the morbidity and mortality associated with AIDS have been achieved thanks to the introduction of antiretroviral therapy (ART). Thus, patients with AIDS can now experience an improved quality of life and longer disease-free periods.¹

Antiretroviral guidelines are updated annually. Current ART is based on combinations of at least three drugs,² and it is the treatment of choice for HIV infection. The goal of ART is to control HIV replication, with undetectable plasma viral load as

a marker, and to restore or preserve immune function.

When ART is initiated, the preferred regimens are two nucleoside reverse transcriptase inhibitors (NRTI) plus one protease inhibitor with ritonavir (PI/r), two NRTIs plus one non-NRTI (NNRTI) or two NRTIs plus one integrase strand transfer inhibitor (INSTI).² However, a change of therapy may be necessary for several reasons.^{3–5}

The antiretroviral drug (AR) toxicity profile has improved considerably, and ARs are now considered to be well-tolerated drugs. Furthermore, changing one AR to another from the same family can sometimes reduce the adverse effects.^{6–7} Also, as these are chronic therapies, patients may need to receive treatment for concomitant diseases. When a new therapy is initiated, pharmacokinetic interactions must be checked, especially when NNRTI or PI is received as part of ART. NNRTI and PI are metabolised by the cytochrome P450 (CYP450) enzyme system; at the same time, these drugs can be inducers or inhibitors of different CYP450 isoenzymes.⁸ Depending on the final effect, interactions between ARs should be managed differently. When coadministration is not indicated, ARs must be changed. However, in some cases, it is possible to manage these interactions by making dose and dosing-interval adjustments or by closely monitoring drug levels and their effects. As HIV is a virus with a high mutation rate, another reason to change an AR regimen could be the development of drug resistance.

Multiple clinical trials have shown a relationship between adherence to therapy and treatment success.^{9–12} Simplified ART regimens enhance adherence, treatment satisfaction and quality of life.^{13–15} Therefore, treatment goals should be (1) to control HIV replication and restore immune function and (2) to simplify the regimen by decreasing the number of pills or dose frequency or using coformulated regimens.

ART has been a major advance in the management of patients with HIV, and has nowadays become a lifelong treatment. Its consolidation has increased the economic resources needed to handle it, with a substantial impact on pharmaceutical spending; this has made tighter control of the economic impact of initial and modified therapies necessary. A recent systematic review of the economic impact of HIV–AIDS reported that, taking 2010 as the reference year, in Spain, the estimated

CrossMark

To cite: Sobrino-Jiménez C, Jiménez-Nácher I, Moreno-Ramos F, et al. *Eur J Hosp Pharm* 2017;24:96–100.

treatment cost per patient-year was €11.638, with an SD of €3.756, showing the profound effect that HIV–AIDS treatment costs have had.¹⁶

The aim of this study was to assess the reasons for ART change in patients with HIV in a hospital setting in routine clinical practice. The economic impact of ART modification was also analysed.

METHODS

Patients with HIV who attended for pharmaceutical care consultation at Hospital Universitario La Paz and changed their ART between 24 November and 24 December 2014 were registered. The switch, addition or withdrawal of at least one AR was considered an ‘ART change’.

In pharmaceutical care consultation, patients were followed using the Farmatools Dominion programme device Dispensación a Pacientes Externos (DPE) (Outpatient dispensing). When a modification in the AR regimen was detected, the following variables were recorded: medical record number, gender, age, previous ART, length of previous ART treatment, reason for change, and current ART.

Data were obtained from the patient’s prescription and medical report provided by the patient and from the patient’s clinical history, where the reason for the change and the new antiretroviral regimen were checked. When the reason for ART switching was not clearly stated on the medical report, we interviewed the patient during dispensation to clarify. In seven cases, the reason for the therapy change was not identified and so we contacted the prescribing physician. Information about previous therapy and its length was obtained from dispensation records available on DPE Farmatools device.

Reasons to change therapy were classified into the following categories: toxicity and adverse effects, treatment failure, therapy simplification, and drug–drug interactions.

Antiretroviral regimens before and after modification were analysed globally, as well as individually, by reason for changing therapy. ART schemes most commonly related to therapy switches because of toxicity and adverse effects or for therapy simplification were further studied.

To assess the economic impact of ART change, AR costs at the time of study were recorded. Costs were obtained from Farmatools device Maestro de artículos (Item master). Maestro de artículos (Item master) provides updated information about drug prices. The economic impact of ART change in every patient was calculated as the difference between the cost per month of the ART scheme after the modification and the cost per month of the ART scheme before. Global economic impact per patient was assessed by calculating the mean of the individual results.

RESULTS

Of a cohort of 3850 patients with HIV, 1976 attended for pharmaceutical care consultation at Hospital Universitario La Paz during the study period; 92 of these (4.7%) had had their ART modified. The main demographic characteristics of these patients were median age 47 years (range 22–72) and male predominance (73.9%; 68 patients). The median length of time receiving the initial ART was 26 months (range 1–144). The distribution of patients according to initial ART duration is shown in figure 1.

The most common initial antiretroviral regimen was 2 NRTI + 1 NNRTI (29.4% of patients), and the most common regimen after modification was 2 NRTI + 1 INSTI (40.2%). The regimen with the greatest decrease was 2 NRTI + 1 PI/r (28.3% before

and 7.6% after therapy modification). The distribution of the different ART schemes before and after change is shown in figure 2.

Figure 3 shows the main reasons for the 92 therapy changes; toxicity and adverse effects are shown to be the most common reason, with a frequency of 46.7% (43 changes). The distribution of antiretroviral regimens according to reason for change is reported in table 1.

The drug responsible for ART change was determined in 24 out of the 43 changes due to toxicity and adverse effects. Tenofovir was the AR most often implicated in ART changes due to toxicity (13/24). The distribution of ART modifications due to toxicity and adverse effects according to the drug is shown in figure 4.

Figure 1 Patient distribution according to antiretroviral therapy (ART) duration before the change.

Figure 2 Antiretroviral scheme distribution before and after therapy change. ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI/r, protease inhibitor with ritonavir.

Figure 3 Analysis of the reasons for the 92 therapy modifications.

Table 1 Antiretroviral therapy (ART) distribution by reason to change

Initial ART	Patients with changes in initial ART	Toxicity (incidence)	Therapy simplification (incidence)	Treatment failure (incidence)	Drug–drug interactions (incidence)
2 NRTI+1 INSTI	13	6 (46)	6 (46)	1 (8)	0
2 NRTI+1 NNRTI	27	17 (63)	4 (15)	4 (15)	2 (7)
2 NRTI+PI/r	26	13 (50)	6 (23)	2 (8)	5 (19)
1 INSTI+PI/r	4	2 (50)	1 (25)	1 (25)	0
1 NRTI+1 INSTI+PI/r	3	1 (33)	2 (67)	0	0
PI/r±1 NRTI	5	1 (20)	0	3 (60)	1 (20)
Other schemes	14	3 (21)	6 (43)	5 (36)	0
Total	92	43 (47)	25 (27)	16 (17)	8 (9)

Values are n (%).

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI/r, protease inhibitor with ritonavir.

Figure 4 Distribution of antiretroviral therapy (ART) modifications due to toxicity by identified responsible drug. 3TC, lamivudine; ABC, abacavir; EFV, efavirenz; ETR, etravirine; FPV/r, fampiravir with ritonavir; LPV/r, lopinavir with ritonavir; RTV, ritonavir; TDF, tenofovir.

The second most common reason for ART switching was to simplify the therapy. Twenty-five of the 92 patients (27.2%) changed their ART for this reason. The antiretroviral regimen distribution before and after simplification is given in table 2.

The third most common reason for ART change was treatment failure (16 out of 92 changes; 17.4%). Monotherapy or dual therapy with PI/r±NRTI was most commonly changed because of treatment failure. Of five patients on monotherapy or dual therapy with PI/r±NRTI, three changed because of treatment failure (60.0%): one treated with dual therapy with darunavir/ r (DRV/r)+lamivudine (3TC), and two treated with DRV/r monotherapy. The ART schemes with the lowest frequency of treatment failure were 2 NRTI+1 INSTI (7.7%) and 2 NRTI+1 PI/r (7.7%).

Finally, drug–drug interactions were also identified as a reason for ART switching, with 8 out of 92 therapy modifications (8.7%). The antiretroviral regimens with the highest frequency of ART changes due to drug–drug interactions were PI/r ±1 NRTI (20.0%) and 2 NRTI+1 PI/r (19.2%).

Regarding economic impact, ART changes during the study period generated a mean additional cost of €14 (SD €216; range –€528 to +€831) per month per patient when ART was modified.

DISCUSSION

At the pharmaceutical care consultation unit at Hospital Universitario La Paz, medication is dispensed annually to 11 400 patients on different therapeutic programmes, such as oral antineoplastics and drugs for autoimmune inflammatory diseases, viral liver diseases, multiple sclerosis and HIV. Of a cohort of 3850 patients with HIV, 1976 attended pharmaceutical care consultation at Hospital Universitario La Paz during the study period.

Table 2 Antiretroviral therapy (ART) distribution before and after simplification

ART before change	Changes	Simplified ART
MRV+RAL	1	FTC/TDF+DRV/r
	1	MRV+DOL
MRV+DRV/r	1	MRV+DOL
RAL+DRV/r	1	DOL+DRV/r
TDF+RAL+DRV/r	2	TDF+DOL+DRV/r
ETR+RAL+DRV/r	1	DOL+DRV/r
	1	ETR+DOL+DRV/r
ETR+DRV/r	1	DOL+DRV/r
FTC/TDF+RAL	2	FTC/TDF+DOL
ABC/3TC+RAL	2	ABC/3TC+DOL
FTC/TDF+RAL	2	FTC/TDF/RPV
TDF+ABC+EFV	1	ABC/3TC+DOL
FTC/TDF+NVP	1	DRV/r
ABC/3TC+ETR	1	ABC/3TC+RPV
FTC/TDF+ETR	1	FTC/TDF/RPV
FTC/TDF+DRV/r	1	3TC+DRV/r
	2	FTC/TDF+DOL
	1	ABC/3TC+RPV
FTC/TDF+LPV/r	1	FTC/TDF/EFV
	1	FTC/TDF+DRV/r
Total	25	

3TC, lamivudine; ABC, abacavir; DOL, dolutegravir; DRV/r, darunavir with ritonavir; EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; LPV/r, lopinavir with ritonavir; MRV, maraviroc; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir.

When ART is initiated, the main goal is to control HIV replication, restore immune function and decrease the risk of HIV transmission.² Nowadays, most patients with HIV in developed countries achieve stable control of their disease. However, 4.7% of the participants in our study had to modify their therapies because of toxicity and adverse effects, treatment failure or drug–drug interactions or for therapy simplification in order to preserve or improve efficacy and guarantee adherence.

Although there are several possible reasons for modifying ART, previous studies reported development of toxicity and adverse effects as the main reason.^{17–18} Our results are similar to those studies, with 46.7% of patients (43/92) switching their ART because of toxicity and adverse effects.

The ART scheme with the highest frequency of change due to toxicity and adverse effects was 2 NRTI+1 NNRTI (63.0%). Regarding NRTIs, in our study, tenofovir was the drug most commonly responsible for antiretroviral regimen modifications

because of toxicity and adverse effects (13/24). Tenofovir can induce renal toxicity, as described by Woodward *et al.*,¹⁹ inducing renal tubular dysfunction, which causes Fanconi syndrome and a reduction in calculated glomerular filtration. In different assays, nephrotoxicity due to tenofovir has been linked to risk factors, exposure and AR regimens that include PI/r.^{20–21} Also, Mitra *et al.*²² concluded that tenofovir-associated renal dysfunction had a long incubation period, since their patients developed renal dysfunction after a mean duration of 42.6 months under tenofovir-based ART. In our study, the mean duration of the previous ART was 33.8 months (data not shown), which suggests therapy modifications due to late toxicity.

Tenofovir treatment has also been linked to the development of osteopenia. Brown *et al.*²³ and Dravid *et al.*²⁴ demonstrated how tenofovir-based regimens contributed to reduction in bone mineral density, together with HIV-related factors, such as low CD4+ count.

From the NNRTI group, efavirenz was the AR that generated the highest number of changes due to toxicity and adverse effects (5/24). Several authors have reported that patients on efavirenz therapy develop neurological symptoms (dizziness, confusion, vivid dreams). Although these symptoms usually disappear after the first few weeks of treatment, sometimes it may be necessary to discontinue it.^{25–26} In our patients, central nervous system (CNS) toxicity was mild and with low impact on quality of life (data not shown). The development of new drugs without this toxicity makes changing of efavirenz because of CNS toxicity acceptable nowadays.

Simplification was the second most common reason for changing ART. ART simplification is defined as modification of an antiretroviral regimen that has achieved virological suppression to a new and simpler antiretroviral scheme able to maintain that suppression. Reducing the number of drugs, number of pills or dose frequency are different strategies used to simplify ART. The goal of simplification is to improve quality of life as well as adherence to medical treatment. Adherence to ART is essential to achieve good disease control. In our study, 25 patients (27.2%) simplified their ART. The most common antiretroviral scheme after simplification was 2 NRTI+1 INSTI (7/25). This fact can be explained by the introduction of dolutegravir (an INSTI that requires just one daily dose) in the pharmacotherapeutic protocols of our hospital at the time of the study.

Another important reason for therapy change is treatment failure;^{27–28} in this study it was the third most common reason for ART modification. Regimens with the lowest frequency of treatment failure were 2 NRTI+1 INSTI, 2 NRTI+1 PI/r and 2 NRTI+1 NNRTI. These results are consistent with the last updates of HIV guidelines, where these regimens are recommended as first-line ART.²

Potential drug–drug interactions must be checked when ART is started or changed and even when new medication is started for concomitant conditions, so as not to compromise treatment success and to avoid toxicity development.²⁹ The main antiretroviral family responsible for drug–drug interactions in this study was the PI family (six out of eight patients). PIs are metabolised by the CYP450 enzyme system—more specifically, by the CYP3A4 isoenzyme. Drugs sharing this metabolic pathway and drugs that modify CYP3A4 activity can interact, so that PIs may modify the pharmacokinetic profile of other drugs and vice versa. CYP450 inducers (NNRTI, carbamazepine, phenobarbital, phenytoin, dexamethasone, rifampicin and others) decrease plasma levels of compounds metabolised by this complex, compromising drug efficacy. On the other hand,

CYP450 inhibitors (PI, cimetidine, macrolides, imidazoles and others) increase plasma levels, which may lead to undesirable side effects.³⁰

Regarding economic impact, ART changes during the study period generated a 2% increment in pharmaceutical spending on this patient group, which is not a large economic effect. The large range of the additional cost per patient, from –€528 to +€831, should be taken into consideration, making extrapolation of the conclusions difficult.

There are limitations to this study that deserve attention. First, in some cases, the reasons for stopping AR were not classified prospectively, but retrospectively, which may have resulted in inaccurate classification. Furthermore, only the main reason was recorded, whereas there may be several contributory factors to switching AR.

To conclude, toxicity and adverse effects were the main reason for ART modification. Better knowledge about the factors that motivate these changes may contribute to selection of the most suitable ART regimen to guarantee treatment success and decrease the risk of toxicity. Further development of simplified ART regimens through development of new drugs with improved posology and coformulated ones with easier therapy schemes will help to improve adherence.

What this paper adds

What is already known on this subject

- Adverse effects have been reported with the use of all antiretroviral drugs and this is one of the most common reasons cited for switching or discontinuing therapy and for medication non-adherence.
- A simplified combination antiretroviral therapy regimen enhances adherence.
- Drug resistance and drug–drug interactions are risk factors for treatment failure.

What this study adds

- Analysis of the distribution of the reasons for antiretroviral therapy change in patients with HIV in current routine clinical practice.
- Assessment of the economic impact of antiretroviral therapy modification.

Twitter Follow Carmen Sobrino Jiménez at @csobrinioj

Acknowledgements The authors would like to thank Dr Soledad Santos, Madrid, Spain for help with the English manuscript.

Contributors CSJ, IJN, FMR, MAGF, MFG and JGG conducted the study, including data collection and data analysis. CSJ and IJN prepared the manuscript draft with important intellectual input from JGG and AHA. All authors approved the final manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Palella FJ, Jr, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853–60.
- 2 http://www.eacsociety.org/files/guidelines_8.0-english-revised_20160610.pdf (accessed 19 Jun 2016).

- 3 Rappold M, Rieger A, Steuer A, *et al.* Treatment modification in HIV-Infected individuals starting antiretroviral therapy between 2011 and 2014. *J Int AIDS Soc* 2014;17(Suppl 3):19768.
- 4 Moniz P, Alcada F, Peres S, *et al.* Durability of first antiretroviral treatment in HIV chronically infected patients: why change and what are the outcomes? *J Int AIDS Soc* 2014;17(Suppl 3):19797.
- 5 Pedreira-Vazquez I, Margusino-Framinan L, Perez-Fernandez K, *et al.* Change of antiretroviral therapy in HIV-infected patients. *Farm Hosp* 2004;28(Suppl 1):48–54.
- 6 Negro E, Domingo P, Pérez-Álvarez N, *et al.* Improvement in bone mineral density after switching from tenofovir to abacavir in HIV-1-infected patients with low bone mineral density: two-centre randomized pilot study (OsteoTDF study). *J Antimicrob Chemother* 2014;69:3368–71.
- 7 Bloch M, Tong WW, Hoy J, *et al.* Switch from tenofovir to raltegravir increases low bone mineral density and decreases markers of bone turnover over 48 weeks. *HIV Med* 2014;15:373–80.
- 8 Greene M, Steinman MA, McNicholl IR, *et al.* Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. *J Am Geriatr Soc* 2014;62:447–53.
- 9 Cingolani A, Antinori A, Rizzo MG, *et al.* Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *AIDS* 2002;16:369–79.
- 10 Wood E, Hogg RS, Yip B, *et al.* The impact of adherence on CD4 cell count responses among HIV-infected patients. *J Acquir Immune Defic Syndr* 2004;35:261–8.
- 11 de Olalla PG, Knobel H, Carmona A, *et al.* Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *J Acquir Immune Defic Syndr* 2002;30:105–10.
- 12 Gardner EM, Sharma S, Peng G, *et al.* Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. *AIDS* 2008;22:75–82.
- 13 Parienti JJ, Bangsberg DR, Verdon R, *et al.* Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis* 2009;48:484–8.
- 14 Bangsberg DR, Ragland K, Monk A, *et al.* A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS* 2010;24:2835–40.
- 15 Airoldi M, Zaccarelli M, Bisi L, *et al.* One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Prefer Adherence* 2010;4:115–25.
- 16 Trapero-Bertran M, Oliva-Moreno J. Economic impact of HIV/AIDS: a systematic review in five European countries. *Health Econ Rev* 2014;4:15. <http://www.healtheconomicreview.com/content/4/1/15> (accessed 19 Jun 2016).
- 17 Abah IO, Darin KM, Ebonyi AO, *et al.* Patterns and predictors of first-line antiretroviral therapy modification in HIV-1-infected adults in a large urban outpatient cohort in Nigeria. *J Int Assoc Provid AIDS Care* 2015;14:348–54.
- 18 Pedrol E, Viciano P, Arranz A, *et al.* Reasons for antiretroviral treatment change in HIV+ patients in Spain in 2010–2011. SWITCH AUDIT Study. *Rev Esp Quimioter* 2014;27:93–7.
- 19 Woodward CL, Hall AM, Williams IG, *et al.* Tenofovir-associated renal and bone toxicity. *HIV Med* 2009;10:482–7.
- 20 Górriz JL, Gutiérrez F, Trullas JC, *et al.* Executive summary of the consensus document on the management of renal disease in HIV-infected patients. *Nefrologia* 2014;34:768–88.
- 21 Post F. Adverse events: ART and the kidney: alterations in renal function and renal toxicity. *J Int AIDS Soc* 2014;17(Suppl 3):19513.
- 22 Mitra S, Priscilla R, Rajeev K, *et al.* Renal tubular dysfunction associated with tenofovir therapy. *J Assoc Physicians India* 2014;62:580–2.
- 23 Brown TT, Hoy J, Borderi M, *et al.* Recommendations for evaluation and management of bone disease in HIV. *Clin Infect Dis* 2015;60:1242–51.
- 24 Dravid A, Kulkarni M, Borkar A, *et al.* Prevalence of low bone mineral density among HIV patients on long-term suppressive antiretroviral therapy in resource limited setting of western India. *J Int AIDS Soc* 2014;17(Suppl 3):19567.
- 25 Suvada J. Neuropathic and neurocognitive complications of antiretroviral therapy among HIV-infected patients. *Neuro Endocrinol Lett* 2013;34(Suppl 1):5–11.
- 26 Ramírez-Duque N, López-Cortés LF. Efectos adversos neuropsiquiátricos asociados con efavirenz. *Enferm Infecc Microbiol Clin* 2006;24:64–6.
- 27 Jiamsakul A, Sungkanuparph S, Law M, *et al.* HIV multi-drug resistance at first-line antiretroviral failure and subsequent virological response in Asia. *J Int AIDS Soc* 2014;17:19053.
- 28 Vanobberghen FM, Kilama B, Wringe A, *et al.* Immunological failure of first-line and switch to second-line antiretroviral therapy among HIV-infected persons in Tanzania: Analysis of routinely collected national data. *Trop Med Int Health* 2015;20:880–92.
- 29 Manzardo C, Tuset M, Miró JM, *et al.* Severe or life-threatening interactions between antiretrovirals and non-HIV drugs. *Enferm Infecc Microbiol Clin* 2015;33:e15–30.
- 30 Jiménez-Nácher I, Alvarez E, Morello J, *et al.* Approaches for understanding and predicting drug interactions in human immunodeficiency virus-infected patients. *Expert Opin Drug Metab Toxicol* 2011;7:457–77.

APPENDIX

The Farmatools™ Dominion programme is a tool for hospital pharmacy management. It provides different clinical tools to control drug use. These tools facilitate warehouse management, prescription and pharmacy validation. Tools cited in the text:

Dispensación a pacientes externos (Outpatient dispensing): tool for prescription and drug dispensing. It records the medication history of the patients.

Maestro de artículos (Item master): tool for warehouse management. It includes drug costs.