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Pretreatment HIV-1 drug resistance in Argentina: results from a surveillance study performed according to WHO-proposed new methodology in 2014–15

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Background: In Argentina, current national guidelines recommend starting with NNRTI-based regimens. Recently, there have been some local reports regarding concerning levels of NNRTI-transmitted resistance, but surveillance has never been carried out at a national level.

Objectives: To determine the prevalence of HIV drug resistance in people starting ART in Argentina using a WHO-proposed methodology.

Methods: This was a cross-sectional, nationally representative study. Twenty-five antiretroviral-dispensing sites throughout the country were randomly chosen to enrol at least 330 persons starting ART, to generate a point prevalence estimate of resistance-associated mutations (RAMs) with a 5% CI (for the total population and for those without antiretroviral exposure). All consecutive patients older than 18 years starting or restarting ART in the chosen clinics were eligible. Samples were processed with Trugene and analysed using the Stanford algorithm.

Results: Between August 2014 and March 2015, we obtained 330 samples from people starting ART. The mean ± SD age was 35 ± 11 years, 63.4% were male, 16.6% had prior antiretroviral exposure and the median (IQR) CD4 count was 275 cells/mm^3 (106–461). The prevalence of RAMs found was 14% (±4%) for the whole population (3% NRTI-RAMs; 11% NNRTI-RAMs and 2% PI-RAMs) and 13% (±4%) for those without prior antiretroviral exposure (3%, 10% and 2%, respectively). The most common mutation was K103N.

Conclusions: This surveillance study showed concerning levels of HIV drug resistance in Argentina, especially to NNRTIs. Due to this finding, Argentina's Ministry of Health guidelines will change, recommending performing a resistance test for everyone before starting ART. If this is taken up properly, it also might function as a continuing surveillance tool.

Introduction

The emergence and transmission of HIV drug resistance (HIVDR) constitutes a severe threat to achieving the global goal of at least 90% of viral suppression among all people on ART, as it may not only jeopardize individual treatment efficacy, but also the effectiveness of ART delivery programmes and their sustainability.[1,2] Even though the extent of HIVDR at the global level remains manageable,[3] it is slowly increasing, and transmitted resistance rates of 10% to NNRTIs have recently been described in some countries.[3]

In order to maximize the long-term effectiveness of first-line antiretroviral regimens, and to ensure the sustainability of ART programmes, it is essential to minimize the further spread of HIVDR. Even in settings with optimal ART programme management, some degree of drug resistance is expected to emerge in populations on ART, and some is expected to be transmitted to previously uninfected individuals. Therefore, WHO recommends that HIV treatment scale-up should always be accompanied by a robust assessment and prevention of drug resistance emergence and transmission, based on a series of surveillance tools that

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have been recently published.[4,5] WHO's HIVDR Monitoring and Surveillance Strategy is a critical component of the public health approach to ART delivery. Population-level data on HIVDR in different groups can be used for programme-level decision-making. This strategy is composed of four key elements: (i) monitoring of early warning indicators of HIVDR; (ii) surveillance of pretreatment HIVDR in adult populations initiating ART (pretreatment HIVDR); (iii) surveillance of acquired HIVDR in populations of adults and children receiving ART (acquired HIVDR); and (iv) surveillance of HIVDR in treatment-naive children <18 months of age.[6,7] Implementation of the WHO strategy by countries permits generation of strategic information that can be used to make public-health-related decisions regarding HIVDR prevention and management. This in time might have a positive impact on the improvement of HIV care policies and on the quality and sustainability of national HIV programmes.

In Argentina, the Direction of AIDS (DoA) has been delivering ART since 1992, which makes it Latin America's longest-lasting HIV programme. The latest DoA guidelines recommend starting with NNRTI-based regimens;[8] and resistance testing at diagnosis or at treatment initiation is optional. Currently, ~70% of ART initiators start with NNRTI-based regimens,[9] the vast majority (>85%) without previous resistance testing being performed. Recently, concerning levels of NNRTI-transmitted resistance have been described in Argentina, and according to some authors, resistance to NNRTIs has been increasing in the last few years.[10–13] Some reports indicate a prevalence of transmitted or pretreatment drug resistance of >15% in some subpopulations.[14,15] However, these studies were not representative of the whole population, and many did not provide CIs for the prevalence found, or these were too wide. Despite these findings, HIVDR surveillance had never been carried out in Argentina using a nationally representative probabilistic sampling methodology. In 2013, the DoA started planning the implementation of a national HIVDR survey in people starting ART, to be implemented in 2014. The aim of this study was to calculate a nationally representative prevalence estimate of HIVDR among all ART initiators, and among initiators without prior exposure to ART, using the WHO-proposed methodology (Pretreatment Drug Resistance Survey).[16]

Methods

This protocol was performed according to the WHO *Concept Note for Surveillance of HIV Drug Resistance in Adults Initiating Antiretroviral Therapy (Pre-Treatment HIV Drug Resistance)*, published in March 2014.[16] Based on the total number of antiretroviral dispensing sites in Argentina (310), as well as on the HIV Programme characteristics, a predetermined number of 30 sites throughout the country was defined for the implementation of the study. The sampling frame included all antiretroviral dispensing sites in Argentina, with the exception of the smallest clinics that, all together, represent <10% of all ART initiators in the country. Sites were stratified by region in order to ensure geographical and administrative representativeness, and sampled using the probability proportional to proxy size (PPPS) method, as described by WHO.[16] The duration of the enrolling period was 6 months at each site; participant enrolment and specimen collection started in August 2014 and ended in April 2015 (8 months).

Study participants

All persons starting ART for HIV-1 infection in the selected sites during the study period were eligible, irrespective of the history of previous antiretroviral use, as long as they were ≥18 years old, accepted to participate and signed informed consent, and were prescribed a first-line antiretroviral regimen. Exclusion criteria were: infection by HIV-2 and being transferred from other clinic but already on ART. Individuals restarting ART were included provided they were prescribed a first-line regimen and had been off treatment for >3 months. All persons starting ART in the selected clinics were consecutively offered participation until study completion.

After being enrolled, participants were interviewed and their history was reviewed in order to complete a survey gathering demographic, laboratory and clinical data, with special focus on retrieving the history of previous antiretroviral exposure (or not), the type of previous exposure and the antiretroviral regimen prescribed at the time of study entry.

After gathering the survey data, a 10 mL blood specimen was collected in order to perform resistance testing. For this study, we defined HIVDR with respect to one or more of the following drugs or drug classes: nevirapine, efavirenz, any nucleoside/nucleotide analogue reverse transcriptase inhibitor, darunavir/ritonavir, lopinavir/ritonavir or atazanavir/ritonavir. The Stanford HIVdb algorithm[17] was used to determine and classify HIVDR. The Stanford algorithm classifies HIVDR into five levels: susceptible, potential low-level, low-level, intermediate or high-level drug resistance. We measured the prevalence of any HIVDR, defined as low-, intermediate- or high-level resistance according to the Stanford HIVdb to one or more antiretroviral drugs. Sequences classified as susceptible and potential low-level resistance were considered as having no HIVDR.

Laboratory methods

Plasma was the specimen type used for this survey, and was handled according to WHO recommendations on plasma collection, processing and storage for HIVDR testing.[18]

All specimens collected were processed by any of the three national reference laboratories [Unidad de Virologia, Hospital Muñiz; Instituto de Investigaciones Biomédicas en Retrovirus y SIDA (INBIRS), Universidad de Buenos Aires; Laboratorio Central de Córdoba]. The samples were sequenced using the Trugene® HIV-1 Genotyping Kit (Siemens Healthcare Diagnostics, Tarrytown, NY, USA), following the manufacturer's instructions.[19] The sequences corresponding to two regions of the viral genome that includes the reverse transcriptase (RT) gene from codon 40 to 247 and the protease (PR) gene from codon 1 to 99, were analysed using the Stanford University Genotypic Resistance Interpretation Algorithm HIVdb program (version 7.0, last updated 27 February 2014).[20] The HIV Stanford database program was also used as the HIV variant subtyping tool.

Since none of the three national reference laboratories in Argentina is accredited by WHO, for quality control purposes, all the specimens that harboured resistance mutations and a random 10% of the remaining samples were submitted to a WHO-accredited laboratory (CIENI, Mexico) for external quality control, as suggested by WHO.

Statistical analysis

The sample size was calculated aiming to obtain an HIVDR point prevalence number with a CI of maximum ±5% for two populations: (i) all individuals starting ART; and (ii) all individuals starting ART without previous antiretroviral exposure. The following assumptions were made for the sample size calculation: clinics to be sampled using PPPS method, 30; estimated prevalence of pretreatment HIVDR, 10%; proportion of genotyping failure, 20%; proportion of ART initiators with (or unknown) prior exposure to antiretrovirals, 25%; and proportion of individuals starting NNRTI-based regimens in Argentina, 70%. Based on these parameters, the number needed to produce a point prevalence with a ±5% CI for both populations was 330 (11 samples per site).

Participants were classified as having pretreatment drug resistance if they harboured HIV with drug resistance mutations (DRMs) that conferred resistance to at least one of the antiretroviral drugs according to the Stanford algorithm, as described above. We used the χ^2 or Fisher's exact test to compare the prevalence of drug resistance across groups.

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Ethics

All participants provided written informed consent at enrolment. The study protocol was reviewed and approved by a central ethics committee (CIEIS del Niño y del Adulto, approval date: 28 July 2014); and by the institutions' local ethics committees in case any of the participating institutions required it.

Results

Participants were recruited from 25 survey sites, but this counted as 30 since the two largest clinics in the country were randomly selected more than once based on the PPPS sampling method (Hospital Muñiz was randomly chosen five times, with 55 assigned participants enrolled at the site; and Hospital Fernandez was chosen twice, with 22 assigned participants). Overall, clinic selection reflected the characteristic of the HIV epidemic in Argentina, which is concentrated in Buenos Aires City and its metropolitan area. In fact, 7 clinics (which accounted for 12 sites) were located in Buenos Aires City and another 7 clinics in the suburban region of the metropolitan area. The remaining 11 clinics were distributed throughout the country (Figure 1).

We enrolled 330 participants from whom we collected plasma specimens for resistance testing, and 14 other participants (total

Figure 1. Distribution of randomly selected sites throughout the country. CABA, Ciudad Autónoma de Buenos Aires.

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Table 1. Baseline characteristics of all included participants ($n=344$)

Gender, *n* (%)	male		218 (63.4)
	female		124 (36.0)
	transgender		2 (0.6)
Age (years), mean ± SD			35 ± 11
CD4 (cells/mm^3), median (IQR)			275 (106–461)
Viral load (copies/mL), median (IQR)			36999 (7534–119000)
Previous exposure, *n* (%)		62 (18)	previous ART: 76% MTCTP: 19% PEP: 2% unknown: 3%
Time since HIV diagnosis (years), median (IQR)			2.2 (0.3–2.5)
Antiretroviral regimen prescribed to start (or restart), *n*	NNRTI based		238
	PI based		102
	INSTI based		4

MTCTP, mother to child transmission prevention; PEP, post-exposure prophylaxis; INSTI, integrase strand transfer inhibitor.

344) from whom we only obtained clinical and demographic data (clinics that finished enrolling participants for resistance testing before 3 months were asked to continue enrolling for data gathering without specimen collection until that time was reached). The mean ± SD age was 35 ± 11 years, 63.4% were male, 0.6% were transgender, the median (IQR) CD4+ cell count was 275 cells/mm^3 (106–461), the median (IQR) viral load was 36999 copies/mL (7534–119000) and 18% (62/344) had prior exposure to antiretroviral drugs (Table 1). Among those with prior exposure, 76% had received HAART and discontinued it; 19% were women who had received antiretroviral drugs as mother-to-child transmission prevention; 2% had received post-exposure prophylaxis and in 3% it was not possible to classify prior exposure due to lack of data. The reasons for discontinuation in all cases were: self-decision, intolerance and/or adverse events. Median time since diagnosis was 2.2 years (0.3–2.5); however, 60% of study participants were diagnosed within 6 months prior to study entry.

Regarding the prescribed ART regimens in the study population, 69% initiated NNRTI-based regimens, 30% started PI-based regimens and 1% were prescribed integrase strand transfer inhibitor (INSTI)-based regimens. The most commonly prescribed combinations were: tenofovir/emtricitabine/efavirenz or tenofovir/lamivudine + efavirenz (56%); zidovudine/lamivudine + atazanavir/ritonavir (6%); abacavir/lamivudine + efavirenz (4%); tenofovir/emtricitabine + atazanavir/ritonavir (4%); zidovudine/lamivudine + lopinavir/ritonavir (4%); zidovudine/lamivudine/nevirapine (3%); zidovudine/lamivudine + efavirenz (3%); abacavir/lamivudine + atazanavir/ritonavir (3%); other (17%).

Out of the 330 samples, 294 (89%) were successfully sequenced and analysed. Regarding viral subtype distribution, 46% were subtype B, 46% were subtype BF, 4% were subtype C, 2% subtype F and in 2% the viral subtype could not be determined.

The point prevalence (95% CI) of HIVDR obtained was 14% (10–18) (41/294 samples). The prevalence of NNRTI RAMs was 11% (7–15) (33/294), the prevalence of NRTI RAMs was 3% (10/294) and the prevalence of PI RAMs was 2% (6/294) (Table 2). Thirty-four samples (12%) had RAMs for only one family of antiretroviral drugs (27 for NNRTIs, 4 for NRTIs, 3 for PIs); six samples (2%) had RAMs for two families (4 for NRTIs and NNRTIs, 1 for NRTIs and PIs and 1 for NNRTIs and PIs) and one sample (0.3%) had RAMs for three families.

Table 2. Prevalence of RAMs

	No prior exposure	With prior exposure	Total
Total number of samples	270	58	330[a]
Samples successfully sequenced	239	54	294[a]
HIVDR prevalence (95% CI)	31/239 13% (9–17)	10/54 19% (9–29)	41/294 14% (10–18)
NNRTI RAM prevalence (95% CI)	24/239 10% (6–14)	9/54 17% (7–27)	33/294 11% (7–15)
NRTI RAM prevalence	8/239 3%	2/54 4%	10/294 3%
PI RAM prevalence	5/239 2%	1/54 2%	6/294 2%

[a]There were two participants with unknown prior exposure, and one of these two samples was successfully sequenced.

There were no differences in the prevalence of RAMs according to gender: 14% (9–19) in men versus 14% (7–21) in women ($P=1.0$); or viral subtype: prevalence among subtype B: 13% (7–19) versus subtype BF: 16% (10–22) ($P=0.5$). When we stratified according to area of residence, i.e. Buenos Aires City metropolitan area ($n=177$) versus the rest of the country ($n=117$), the prevalence found was identical: 14% in both areas ($P=1.0$).

The most commonly found mutations were: K103N ($n=17$), G190A ($n=6$), M41L ($n=6$) and K101E ($n=5$) (Table 3).

The point prevalence (CI) of HIVDR in the population without previous antiretroviral exposure was 13% (9–17) (31/239). In this group, the prevalence of NNRTI RAMs was 10% (6–14) (24/239), the prevalence of NRTI RAMs was 3% (8/239) and the prevalence of PI RAMs was 2% (5/239). Twenty-six samples (11%) had RAMs for only one family of antiretroviral drugs (20 for NNRTIs, 4 for NRTIs, 2 for PIs); four samples (2%) had RAMs for two families (2 for NRTIs and NNRTIs, 1 for NRTIs and PIs and

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Table 3. Frequency of RAMs found

Mutation		No prior exposure (*n*)	With prior exposure (*n*)	Total (*n*)
NNRTIs	K103N	11	6	17
	G190A	4	2	6
	K101E	5	—	5
	Y181C	3	1	4
	V179D	4	—	4
	P225H	4	—	4
	V106I	3	—	3
	A98G	2	—	2
	V108I	—	2	2
	Y188L	2	—	2
	K103S	1	—	1
	V106M	—	1	1
	V106A	1	—	1
	V179T	1	—	1
	Y188H	1	—	1
	G190S	1	—	1
	F227L	1	—	1
NRTIs	M41I	5	1	6
	M184V	1	1	2
	T215A/D	1	1	2
	T215C	2	—	2
	D67N	1	—	1
	D67G	1	—	1
	K70E	1	—	1
	V75I	—	1	1
	Y115F	1	—	1
	T215D	1	—	1
	K219Q	1	—	1
PIs	M46L	3	1	4
	L90M	3	—	3
	V82A	1	1	2
	I50L	1	—	1
	N88S	1	—	1

1 for NNRTIs and PIs) and one sample (0.5%) had RAMs for three families. Among this group there were no differences in the prevalence of RAMs between those with recent diagnosis (≤6 months) and those diagnosed >6 months ago: 13% (8–18) and 13% (5–21), respectively ($P=1.0$).

In the population with prior exposure, the prevalence of HIVDR found was 19% (9–29). Among them, the prevalence of NNRTI RAMs was 17% (7–27), the prevalence of NRTI RAMs was 4% and the prevalence of PI RAMs was 2%. Eight samples (14%) had RAMs for only one family of antiretroviral drugs (7 for NNRTIs, 1 for PIs); and two samples (4%) had RAMs for two families (both for NRTIs and NNRTIs).

Discussion

Prevalence of HIVDR in people starting ART in Argentina is moderate according to the WHO definition, and could be high considering the upper CI limit obtained. This study confirmed the data produced by other studies performed in the country, with a point prevalence that is nationally representative and with a narrow CI. The level of resistance found is surprising, but is not unlikely since Argentina has a long history of ART delivery, available to all HIV-infected patients since 1992, and NNRTI-based regimens have been the preferred first-line ART regimens for more than a decade. This implies that the risk of early virological failure among ART beginners in Argentina is considerable, taking into account that 75% of those without prior exposure are prescribed NNRTI regimens, and the recommended first-line combinations are tenofovir/emtricitabine/efavirenz or tenofovir/lamivudine+efavirenz. There is much evidence about the higher risk of early virological failure in patients with HIV harbouring pretreatment RAMs both in high-income countries[21,22] and in resource-constrained settings.[23,24]

Not surprisingly, we did not find differences in resistance prevalence between men and women, or according to the area of residence (Buenos Aires metropolitan area or rest of the country) or viral subtype. The distribution of the viral subtypes found in this study matches the distribution described by many other studies performed in Argentina, confirming that the most frequent circulating viral subtypes are B and BF.[25,26] The proportion of genotyping failure in our study (11%) matched the data reported by WHO for the grouped analysis of 40 HIVDR surveys: 13%.[3] When analysing the samples that did not amplify and had a viral load determined, 80% of them had a viral load result of <1000 copies/mL. No single site had a significantly higher proportion of amplification failure than the average.

The prevalence of HIVDR evidenced by this study requires a call for action to develop a strategy to address HIVDR prevention and control at the national level, specifically a strategy that is adequate to formulate policies to deal with this situation from a public health perspective. Some models have explored the cost-effectiveness of different measures that may be undertaken to tackle high levels of HIVDR in low-resource countries.[27] However, the structure and functioning of Argentina's HIV programme is very different from those found in Africa, and so are the costs of the diverse supplies for HIV follow-up and treatment; hence the findings of these models might not be applicable unless local data and local adaptation are used. The cost-effectiveness of performing HIV resistance testing before prescribing ART has been demonstrated for high-income countries;[28] and a recent study showed that in Brazil, which has a national AIDS programme that works in a very similar way to that in Argentina, and where the costs of supplies are also comparable, the use of resistance testing before ART initiation would result in cost savings, even with low levels of pretreatment resistance.[29] Based on the result of this study, Argentina's DoA and its Advisory Board decided to recommend the implementation of resistance testing before ART initiation for all persons with HIV, and to perform a cost-effectiveness study with local data to confirm the benefits of this measure. Another measure discussed was a change in the preferred first-line regimen, from an NNRTI-based one to a PI-based or an INSTI-based regimen. However, the difference in costs between these regimens is significant in Argentina, where the cheapest PI-based regimen costs at least twice a tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) regimen, and an INSTI-based regimen is at least four times more expensive; this strategy was therefore dismissed for the short term.

The data obtained also confirm the importance of performing HIVDR surveillance in a systematic way. Our experience after

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following WHO guidelines and pretreatment drug resistance concept notes was very encouraging. The protocol could be designed, performed and the data analysed in less than 18 months, producing timely information of extreme value for informing the national authorities and enabling them to effect a change in policy based on the results. Of note, this protocol produced not only information about HIVDR, but also very valuable information about the regimens prescribed, the CD4 count at ART start, the time from diagnosis at ART start and the proportion of people starting ART with prior exposure, from a representative sample—all very valuable data for use in developing programmes. It took us a little longer than recommended to enrol all the participants (recommended: 6 months) due to a delay in opening some of the sites because of regulatory issues affecting these clinics. However, no single site took more than 6 months to incorporate the corresponding participants. The costs of the study were low compared with the costs of ART and reagents for HIV follow-up that are borne by the state of Argentina, and the logistics were not difficult to set up since there was an existing network of clinics and labs already prepared for viral load and resistance testing, and for sample handling and management. Technical support from WHO and the Pan American Health Organization (PAHO) was very helpful and key for the development and outcome of the protocol. Programme data obtained from routine implementation of genotyping will allow us to continue monitoring resistance levels and keep adapting public policies according to the new data generated. However, policies and recommendations may also change as new antiretrovirals become available at reasonable prices. If integrase inhibitors (now recommended as an alternative for starting ART by WHO) replace NNRTIs for treatment initiation in Argentina, performance of resistance testing before initiation might not be necessary. Our experience proves that performing HIVDR surveillance as recommended by WHO is feasible and not difficult to implement in middle-income countries.

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Transparency declarations

None to declare.

References

1 Tang MW, Shafer RW. HIV-1 antiretroviral resistance: scientific principles and clinical applications. *Drugs* 2012; **72**: e1–25.

2 UNAIDS. *90-90-90 An Ambitious Treatment Target to Help End the AIDS Epidemic*. http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf.

3 WHO. *HIV Drug Resistance Report 2012*. http://www.who.int/hiv/pub/drugresistance/report2012/en/.

4 WHO. *Consolidated Strategic Information Guidelines for HIV in the Health Sector*. 2015. http://who.int/hiv/pub/guidelines/strategic-information-guidelines/en/.

5 WHO. *Global Health Sector Strategy on HIV, 2016–2021*. 2016. http://www.who.int/hiv/strategy2016-2021/ghss-hiv/en/.

6 WHO. *WHO Global Strategy for the Surveillance and Monitoring of HIV Drug Resistance 2012*. November 2012. http://www.who.int/hiv/pub/drugresistance/drug_resistance_strategy/en/.

7 WHO. *HIV Drug Resistance Surveillance Guidance: 2015 Update*. http://apps.who.int/iris/bitstream/10665/204471/1/9789241510097_eng.pdf.

8 Benetucci J, Bissio E, Bologna R *et al*. Guía para el manejo de los pacientes adultos con infección por VIH. Dirección de Sida y ETS, Ministerio de Salud de la Nación Argentina. http://www.msal.gob.ar/sida/index.php/equipos-de-salud/guias-y-recomendaciones#nueve.

9 Boletín sobre VIH-Sida en Argentina, número 28, 2011. Dirección de Sida y ETS, Ministerio de Salud de la Nación Argentina. http://www.msal.gob.ar/sida/index.php/publicaciones/boletines-sobre-vih-sida.

10 Petroni A, Deluchi G, Pryluka D *et al*. Update on primary HIV-1 resistance in Argentina: emergence of mutations conferring high-level resistance to nonnucleoside reverse transcriptase inhibitors in drug-naive patients. *J Acquir Immune Defic Syndr* 2006; **42**: 506–10.

11 Pando MA, Gómez-Carrillo M, Vignoles M *et al*. Incidence of HIV type 1 infection, antiretroviral drug resistance, and molecular characterization in newly diagnosed individuals in Argentina: a Global Fund Project. *AIDS Res Hum Retroviruses* 2011; **27**: 17–23.

12 Rodriguez-Rodrigues N, Duran A, Bouzas MB *et al*. Increasing trends in primary NNRTI resistance among newly HIV-1-diagnosed individuals in Buenos Aires, Argentina. *J Int AIDS Soc* 2013; **16**: 18519.

13 Petroni A, Deluchi G, Lopardo G *et al*. Update on transmission of HIV resistance to drug-naive patients in Argentina. *Antivir Ther* 2010; **15** Suppl 2: A179.

14 Rotryng F, Pryluka D, Lapadula P *et al*. Evolución de la resistencia primaria del HIV-1 en un centro de atención ambulatoria. In: *Resúmenes del XV Congreso de la Sociedad Argentina de Infectología, Ciudad de Buenos Aires, 2015*. Abstract 437. Sociedad Argentina de Infectología, Buenos Aires, Argentina. http://www.sadi2016.com.ar/trabajos/ABS-437.pdf.

15 Zapiola I, Fernández Giuliano S, Cecchini D *et al*. Prevalencia de mutaciones asociadas a resistencia en mujeres embarazadas infectadas con HIV: análisis comparativo del período 2008-2011 vs 2012-2014. In: *Resúmenes del XV Congreso de la Sociedad Argentina de Infectología, Ciudad de Buenos Aires, 2015*. Abstract 275. Sociedad Argentina de Infectología, Buenos Aires, Argentina. http://www.sadi2016.com.ar/trabajos/ABS-275.pdf.

16 WHO. *Concept Note for Surveillance of HIV Drug Resistance in Adults Initiating Antiretroviral Therapy (Pre-Treatment HIV Drug Resistance)*. March 2014. http://www.who.int/hiv/pub/drugresistance/pretreatment_drugresistance/en/.

17 Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis* 2006; **42**: 1608–18.

18 Bertagnolio S, Derdelinckx I, Parker M *et al*. World Health Organization/HIVResNet drug resistance laboratory strategy. *Antivir Ther* 2008; **13** Suppl 2: 49–57.

19 ACTG Laboratory Technologist Committee, ACTG Lab Man Bayer HIV-1 TRUGENE Genotyping Method, Revised Version 2.0 May 21, 2004. https://www.hanc.info/labs/labresources/procedures/ACTGIMPAACT%20Lab%20Manual/Bayer%20TruGene%20HIV-1%20Genotyping.pdf.

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20 *HIVdb Program Genotypic Resistance Interpretation Algorithm Version 7.0*. Last updated 27/02/14. http://sierra2.stanford.edu/sierra/servlet/JSierra.

21 Wittkop L, Günthard HF, de Wolf F *et al*. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infect Dis* 2011; **11**: 363–71.

22 Bansi L, Geretti AM, Dunn D *et al*. Impact of transmitted drug-resistance on treatment selection and outcome of first-line highly active antiretroviral therapy (HAART). *J Acquir Immune Defic Syndr* 2010; **53**: 633–9.

23 Hamers RL, Schuurman R, Sigaloff KCE *et al*. Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. *Lancet Infect Dis* 2012; **12**: 307–17.

24 Kantor R, Smeaton L, Vardhanabhuti S *et al*. Pretreatment HIV drug resistance and HIV-1 subtype C are independently associated with virologic failure: results from the multinational PEARLS (ACTG A5175) clinical trial. *Clin Infect Dis* 2015; **60**: 1541–9.

25 Dilernia DA, Gomez AM, Lourtau L *et al*. HIV type 1 genetic diversity surveillance among newly diagnosed individuals from 2003 to 2005 in Buenos Aires, Argentina. *AIDS Res Hum Retroviruses* 2007; **23**: 1201–7.

26 Rubio AE, Abraha A, Carpenter CA *et al*. Similar replicative fitness is shared by the subtype B and unique BF recombinant HIV-1 isolates that dominate the epidemic in Argentina. *PLoS ONE* 2014; **9**: e92084.

27 Phillips AN, Cambiano V, Miners A *et al*. Effectiveness and cost-effectiveness of potential responses to future high levels of transmitted HIV drug resistance in antiretroviral drug-naive populations beginning treatment: modelling study and economic analysis. *Lancet HIV* 2014; **1**: e85–93.

28 Sax PE, Islam R, Walensky RP *et al*. Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis* 2005; **41**: 1316–23.

29 Luz PM, Morris BL, Grinsztejn B *et al*. Cost-effectiveness of genotype testing for primary resistance in Brazil. *J Acquir Immune Defic Syndr* 2015; **68**: 152–61.

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