Research Letters

AIDS 2011, **25**:1665–1673

Ageing with HIV in South Africa

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We used an established microsimulation model, quantified to a rural South African setting with a well developed antiretroviral treatment programme, to predict the impact of antiretroviral therapy on the HIV epidemic in the population aged over 50 years. We show that the HIV prevalence in patients aged over 50 years will nearly double in the next 30 years, whereas the fraction of HIV-infected patients aged over 50 years will triple in the same period. This ageing epidemic has important consequences for the South African healthcare system, as older HIV patients require specialized care.

Antiretroviral therapy (ART) is changing the character of the HIV epidemic in sub-Saharan Africa. At the individual level, ART has increased survival of those infected. At the population level, widespread availability of ART could result in the overall ageing of the infected population. ART use in sub-Saharan Africa is expanding rapidly, with an estimated 3.9 million patients on treatment in 2009 [1]. Estimates show that there are already about 3 million people over 50 years living with HIV in sub-Saharan Africa [2]. Recently, Mills *et al.* [3] argued for more attention to be paid to HIV-infected older people in terms of prevention and care. In the USA, estimates from the Centers for Disease Control (CDC) show that about 29% of the entire population living with HIV was aged over 50 years in 2008 [4], and projections show that, in about 5 years time, more than half of all HIV-infected patients will be aged over 50 years [5]. Although it is clear that the number of HIV-infected elderly (aged over 50 years) in sub-Saharan Africa will rise as a result of the ART roll-out, the magnitude of this phenomenon has not yet been quantified. One of the countries most likely to be confronted with this shifting epidemic is South Africa, where nearly 6 million people are estimated to be HIV-infected, of whom 970 000 were on ART in 2009 [6]. HIV prevalence in the population aged over 50 years in South Africa is estimated at about 9% [2,7].

To predict the impact of the current ART roll-out on age-specific and sex-specific HIV prevalences in South Africa up to 2040, we used an established mathematical model (STDSIM) that simulates individuals in a dynamic network of sexual contacts [8,9]. The model is tailored to the Hlabisa sub-district in KwaZulu-Natal, South Africa (Supplementary Digital Content, http://links.lww.com/QAD/A150). This area has a high HIV prevalence [10] and a well developed ART programme [11,12]. In the model, the survival of ART-naive HIV-infected patients is on average 10 years. We assumed ART to increase survival from start of treatment by a factor of 3 and decrease infectivity by 92%, as observed in recent studies [13,14]. We assumed ART to be initiated at CD4 cell counts of 200 cells/μl or less in the period 2004–2010 and 350 cells/μl or less in 2011, according to the new WHO guidelines [15]. The model contains an age-specific partner change rate, as well as frequency of intercourse within a sexual relationship. In previous applications of our model [9], decreasing trends of sexual activity by age in the population aged 15–49 years were simply extrapolated to the over-50 years group because of a lack of available data on sexual behaviour in the population aged over 50 years. This resulted in a negligible level of risk behaviour and HIV incidence in the over-50 years group, which is inconsistent with recent local data in terms of HIV prevalence in this group [7]. Therefore, we now assumed partner acquisition rates to remain at the same level from age 45 years onwards, whereas the frequency of sexual contacts within a relationship is reduced by 25% for those aged over 50 years. The ART roll-out in Hlabisa is part of the South African national ART roll-out aimed at achieving universal coverage. Therefore, we assume that the impact of ART on the course of the epidemic is not affected by migration.

Figure 1a shows the projected trends in HIV prevalence in the population aged 15–49 years and over 50 years in Hlabisa. Whereas HIV prevalence in the 15–49 years group would more than halve in the period 2010–2040 from 28 to 9%, the HIV prevalence in the population aged 50 years and older is estimated to nearly double in the same period, from about 9% (8% in women; 11% in men) to 17% (16% in women; 17% in men). The total number of HIV infections in those aged over 50 years is expected to have increased by 51% in 2025 (49% for men; 53% for women), after which the number of HIV infections in this age group remains relatively stable (Fig. 1b). The absolute number of HIV infections in the elderly is estimated to even have doubled by 2025 compared to 2004, the year the ART roll-out in the area started. As a result, the age distribution of HIV-infected patients would change considerably (Fig. 1c). This is especially true for men, in which case currently less than one in 12 HIV-infected people is aged over 50 years; in 2040, this would be one in four.

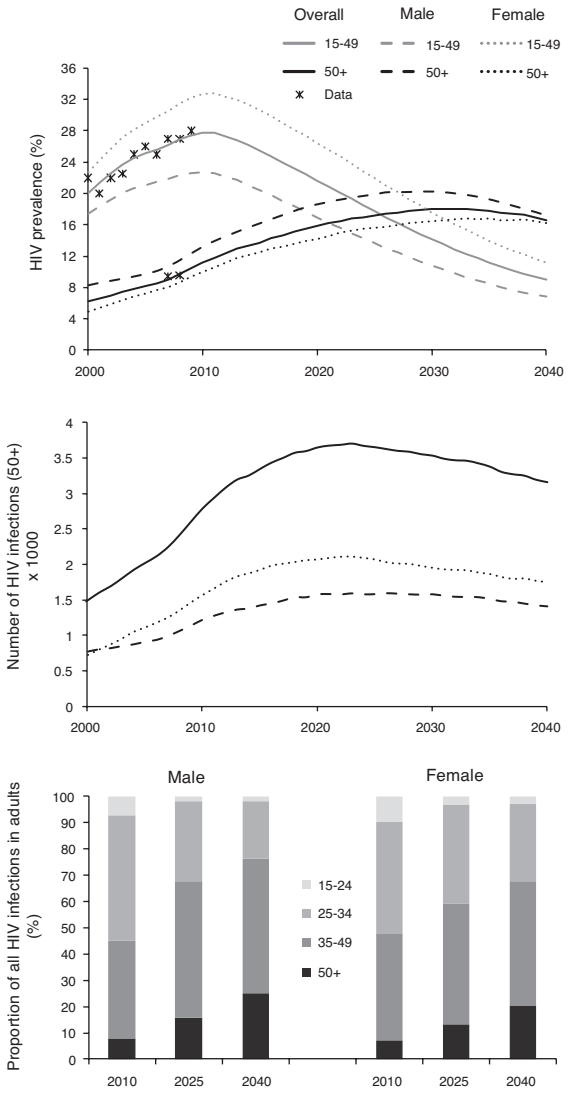

Fig. 1. HIV prevalence (in the 15–49 years and >50 years age groups), total number of infections, and age distribution of HIV-infected patients over the period 2000–2040 in the Hlabisa sub-district of KwaZulu-Natal, South Africa, predicted with the STDSIM model. (a) HIV prevalence in those aged 15–49 years and >50 years. Data points from HIV surveillance in Hlabisa [5,7]. (b) Absolute number of HIV infections among the population aged >50 years in the Hlabisa subdistrict (total population size approximately 280 000 in 2009). (c) Age distribution of HIV-infected men and women in 2010, 2025 and 2040.

We show that the number of HIV-infected elderly will increase substantially over the coming decades. This will further complicate an ongoing epidemiological transition in South Africa, where projections show that, despite the excess mortality due to HIV, the population aged over 60 years is estimated to more than double by 2030 due to lower all-cause mortality rates [16]. Cardiovascular risk factors are already prevalent among South African adults, with high levels of obesity, hypertension, and cigarette smoking [17]. In addition, HIV infection and ART have been found to be further independent risk factors for cardiovascular diseases and other age-related chronic conditions [18]. The ageing of the HIV epidemic will also have important consequences for the organization of HIV care and prevention. Treated HIV is a chronic condition interacting with and accelerating ageing. Comorbidities, interactions with other drugs, and drug toxicity complicate ART in the elderly, who often require individualized regimens and careful monitoring [18]. Furthermore, disease progression increases with age at acquiring HIV, and effectiveness of ART is lower in people initiated at an older age than at younger age [18].

The above-mentioned processes are not accounted for in the model; however, it is unlikely that they will severely affect our results. A reduced effectiveness of ART and thus increased transmission probability of HIV, coupled with the expected lower all-cause mortality [16], may result in an even more substantial increase in the number of HIV-infected elderly compared to our model predictions. On the contrary, our assumption that the full WHO treatment guidelines will be implemented in 2011 will result in a slight overestimation of the number of HIV-infected elderly since, under the current South African ART policy, only pregnant women and tuberculosis-infected patients are eligible for ART at 350 cells/μl or less, whereas, for others, the 200 cells/μl or less threshold remains for the time being. Furthermore, disease progression is generally faster in the elderly [18], but this is likely to have a limited impact on our predictions since these patients often die of other causes. Finally, we did not consider the impact of ART and HIV on the population growth in the area because long-term projections on population size and structure would require additional assumptions regarding future changes in fertility and background mortality rates which are not only influenced by HIV and ART, but also other processes such as economic growth, and political and economic stability.

We used a 92% reduction in infectivity due to ART and a factor of 3 increase in ART naive based on the best available estimates, but some argue that this might be overly optimistic [19]. If we assume an 80% reduction instead, HIV prevalence in the population aged over 50 years will increase even further to about 26% in 2040, and the total number of HIV-infected individuals aged over 50 years will have doubled by 2040 (results not shown). Also, increased survival benefits [20] will result in a further increase in the HIV prevalence (to 25% in 2040) and the total number of HIV-infected elderly (a 90% increase in 2040 compared to 2010). The proportion of HIV-infected patients aged over 50 years only changes slightly under these alternative assumptions (results not shown).

In conclusion, we show that the HIV epidemic in South Africa is at a critical turning point. Whereas the number of infections among young people will continue to

decline [6], the number of HIV infections in the elderly can be expected to increase by about 50% in the next 15 years. In the near future, this group will need to be an important focus of attention, and creative solutions need to be found to alleviate further stress placed on an already overburdened health system through the increased need for specialized care, and interacting with other public health problems of an ageing population.

Acknowledgements

J.A.C.H., M.N.L., and S.Jd.V. performed the main analysis, interpreted the results and drafted the manuscript. R.B. assisted in developing the model and interpreting the results. M.L.N., F.T., T.B., and R.B. assisted in interpreting the results and drafting the manuscript.

Conflicts of interest

This work is supported by the National Institute of Health (1R01MH083539–01 to Dr M. Lurie) and grants from the Wellcome Trust to the Africa Centre for Health and Population Studies, University of KwaZulu-Natal, South Africa 082384/Z/07/Z. The funding organizations had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review or approval of the manuscript. In addition, this study is made possible by the generous support of the American people through the US Agency for International Development (USAID) and the President's Emergency Plan (PEPFAR) under the terms of Award No. 674-A-00-08-0001-00 for the Hlabisa Treatment and Care Programme. The opinions expressed herein are those of the authors and do not necessarily reflect the views of USAID or the US Government.

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Received: 1 April 2011; revised: 24 May 2011; accepted: 3 June 2011.

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DOI:10.1097/QAD.0b013e32834982ea

Frequency of CXCR4-using viruses in primary HIV-1 infections using ultra-deep pyrosequencing

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We used ultra-deep pyrosequencing and the Toulouse Tropism Test phenotypic assay to determine the prevalence of CXCR4-using viruses in 21 patients with primary HIV-1 infections. We found X4-containing virus populations in 9% of patients by ultra-deep pyrosequencing using position-specific scoring matrices ($PSSM_{X4/R5}$) or geno2-$pheno_{5.75}$ and in 14% using the combined 11/25 and net charge rule. The phenotypic assay identified 9% of CXCR4-using viruses. This confirms that R5 viruses are predominant in primary HIV-1 infections.

HIV-1 enters target cells by binding to the CD4 receptor and to one or both of the chemokine receptors CCR5 and CXCR4 [1–3]. CCR5-using clones are classified as R5 variants, CXCR4-using clones as X4 variants, and clones using both coreceptors as R5X4 or dual-tropic variants [4]. Virus populations that use both coreceptors are termed dual/mixed, as they may contain a mixture of the three variants. R5 viruses usually predominate early in an HIV-1 infection, whereas R5X4 or X4 viruses emerge later and are associated with the accelerated decline in $CD4^+$ T lymphocytes and progression to AIDS [5–8]. Previous studies estimated the prevalence of CXCR4-using viruses early in HIV infections at 3–17.2% by bulk genotyping or phenotyping [9–14]. The recent development of ultra-deep pyrosequencing can increase the sensitivity of genotypic assays for detecting CXCR4-using viruses. A recent study used ultra-deep pyrosequencing with the position-specific scoring matrices ($PSSM_{X4/R5}$) algorithm to estimate the prevalence of CXCR4-using viruses in 20 patients with primary HIV-1 infections (PHIs); they found the prevalence to be 50% [15]. This unexpectedly high rate of X4 viruses could impair the use of CCR5 antagonists to treat patients at the early stages of HIV infections. We therefore investigated the prevalence of CXCR4-using variants during PHI using ultra-deep pyrosequencing, taking into account the frequency of errors resulting from V3 amplification and pyrosequencing. We also determined the HIV-1 tropism using the highly sensitive Toulouse Tropism Test (TTT) that detects minor CXCR4-using variants down to 0.5% of the virus population [16,17].

We determined the HIV-1 coreceptor usage of viruses in 21 consecutive patients with PHI diagnosed at the Department of Infectious Diseases of Toulouse University Hospital, France. PHI was defined as a negative or indeterminate HIV serology result together with positive plasma HIV-1 RNA or an initially negative test for HIV antibodies followed by HIV-1 seropositivity within 6 months. The median age of the patients was 38 years [interquartile range (IQR) 29–50], their median $CD4^+$ T-cell count was 314 cells/μl (IQR 169.5–456), and their median plasma HIV-1 RNA viral load was 5.8 $\log_{10}$ copies/ml (IQR 5.6–6.5). Most (76%) of the patients were men, 19 were infected with subtype B HIV-1 and two with non-B subtypes (CRF02-AG and subtype C). All of them were treated with antiretrovirals within the first 6 months.

Ultra-deep pyrosequencing of the V3 env region was performed on a GS-FLX (Roche-454 Life Sciences, Branford, Connecticut, USA). HIV-1 RNA was extracted from 1 ml of plasma and underwent a single amplification in two steps. Two amplicons, V3-A (339 nucleotides) and V3-B (297 nucleotides), encompassing the V3 env region were generated by reverse transcription and PCR. The number of templates processed by ultra-deep sequencing ranged from 2406 to 390 000 DNA molecules (median 26 360 DNA molecules). The PCR products were clonally amplified in water-in-oil emulsion microreactors before being pyrosequenced in a GS-FLX Titanium PicoTiterPlate device. The sequence reads of the two amplicons of each patient were pooled and the V3 region analyzed. The sequence reads of the V3 region were quantified with GS AVA software Version 2.5p1 (Roche-454 Life Sciences), aligned with the BaL (GenBank AY426110) consensus sequence, and the alignments were manually edited to correct for insertions or deletions in homopolymeric regions that would result in a frameshift. The virus tropism of each clone was inferred from the V3 amino acid sequence by the $PSSM_{X4/R5}$ (http://www.fortinbras.us/cgi-bin/fssm/fssm.pl) [18], the geno2pheno tool with a false-positive rate of 5.75% (http://coreceptor.bioinf.mpi-sb.mpg.de/cgi-bin/coreceptor.pl), and the combined 11/25 and net charge rule [19–22]. The frequency of errors resulting from V3 amplification and pyrosequencing was assessed by analyzing the data from 10 plasmid clones of env previously sequenced by the Sanger method. The mean pyrosequencing error rate was 0.085% (99% confidence interval 0.03–0.14). The upper confidence limit of the error rate was used to calculate the sensitivity of pyrosequencing. We used the Poisson distribution to distinguish authentic variants from artefactual V3 sequences resulting from PCR amplification and ultra-deep pyrosequencing errors. $P < 0.001$ was considered statistically significant.

Ultra-deep pyrosequencing detected CXCR4-using variants in two of 21 samples (9%) using $PSSM_{X4/R5}$ or geno2$pheno_{5.75}$ and in three of 21 (14%) samples using the combined 11/25 and net charge rule (Table 1). The detection threshold of minor X4 variants has been indicated according to the number of reads of V3 for each sample. Analyses with the TTT detected R5X4 variants in two of 21 samples (9%). The genotypic prediction by ultra-deep pyrosequencing and geno2$pheno_{5.75}$ was in

Table 1. Ultra-deep pyrosequencing and Toulouse Tropism Test phenotypic assay of samples from 21 patients with primary HIV-1 infections.

				Ultra-deep pyrosequencing of the env V3 region					
					$PSSM_{X4/R5}$		Geno2pheno$_{5.75}$		Combined 11/25 and net charge rule	
Patient	Plasma HIV-1 RNA (log_{10} copies/ml)	HIV-1 subtype	TTT phenotypic assay	Number of reads	% of CXCR4-using clones	Tropism	% of CXCR4-using clones	Tropism	% of CXCR4-using clones	Tropism
10	5.9	B	R5X4	905	<0.66	R5	100	X4	100	X4
14	5.6	B	R5X4	1751	<0.5	R5	24.84	X4-containing	<0.5	R5
4	5.8	B	R5	1383	3.25	X4-containing	<0.53	R5	6.87	X4-containing
16	7	B	R5	2369	9.58	X4-containing	<042	R5	9.58	X4-containing
1	6	B	R5	2370	<0.42	R5	<0.42	R5	<0.42	R5
2	6.5	B	R5	1191	<0.59	R5	<0.59	R5	<0.59	R5
3	6.7	B	R5	2632	<0.4	R5	<0.4	R5	<0.4	R5
5	5.6	B	R5	1553	<0.52	R5	<0.52	R5	<0.52	R5
6	4.9	B	R5	1886	<0.48	R5	<0.48	R5	<0.48	R5
7	5	B	R5	2386	<0.42	R5	<0.42	R5	<0.42	R5
8	5.8	B	R5	1822	<0.49	R5	<0.49	R5	<0.49	R5
9	6	B	R5	1719	<0.5	R5	<0.5	R5	<0.5	R5
11	5.8	CRF02	R5	824	<0.71	R5	<0.71	R5	<0.71	R5
12	7	B	R5	1317	<0.53	R5	<0.53	R5	<0.53	R5
13	4.8	B	R5	2442	<0.41	R5	<0.41	R5	<0.41	R5
15	5.3	B	R5	2748	<0.4	R5	<0.4	R5	<0.4	R5
17	5.7	B	R5	2921	<0.4	R5	<0.4	R5	<0.4	R5
18	5.1	C	R5	1907	<0.47	R5	<0.47	R5	<0.47	R5
19	7	B	R5	1371	<0.53	R5	<0.53	R5	<0.53	R5
20	6.5	B	R5	2777	<0.4	R5	<0.4	R5	<0.4	R5
21	6.7	B	R5	2503	<0.4	R5	<0.4	R5	<0.4	R5

$PSSM_{X4/R5}$, position-specific scoring matrices; TTT, Toulouse Tropism Test.

perfect agreement with the TTT (Table 1). The concordance between the phenotype and tropism inferred from the ultra-deep pyrosequencing data was 81% when interpreting V3 sequences with the $PSSM_{X4/R5}$ algorithm and 86% when using the combined 11/25 and net charge rule. The genotypic score distributions of the samples containing X4 variants are provided in the Supplementary Table 1 (http://links.lww.com/QAD/A151). Despite good correlations between genotypic algorithms [21,23], some discrepancies are observed and may be because of differences in the criteria or the database used for predicting HIV-1 CXCR4 usage.

Although the geno2pheno tool performed excellently on this dataset that comprised 90% of HIV-1 subtype B samples, the combined 11/25 and net charge rule could be useful for predicting coreceptor usage by non-B subtypes of HIV-1, such as CRF02-AG [20]. Ultra-deep sequencing can be very sensitive when a sufficient number of reads is analyzed, but this technique is also prone to artefactual errors. This is why we calculated the limit of detection of minor CXCR4-using variants for each sample (median 0.48%, range 0.4–0.71%) after having determined the mean error rate of pyrosequencing of the V3 region. The slightly lower threshold in the study by Abbate *et al.* [15] (0.3%) does not explain the observed discrepancies because the frequencies of X4 variants were greater than 0.48% for all but one of the X4-infected patients, ranging from 0.9% to 56.3%. In addition, setting the threshold at 0.3% does not alter the prevalence of X4-infected patients in our study.

Our data show that R5 viruses were predominant during PHI, even when ultrasensitive genotypic or phenotypic techniques were used to determine HIV-1 tropism. The percentage of CXCR4-using viruses was lower (9%) than the rate reported by Abbate *et al.* [15] using ultra-deep sequencing and the $PSSM_{X4/R5}$ tool (60% in patients treated during PHI and 40% in the group free of therapy). The discrepancies between the two studies were explained neither by the virus subtype nor by the antiretroviral treatment. The prevalence of X4-infected patients in our study was two of 19 (10.5%) for HIV-1 subtype B. In addition, all the patients were treated during PHI. Our results are in agreement with prior studies that estimated the prevalence of X4 variants during PHI at between 3% and 4% using phenotypic assays [10,11,24]. We previously identified eight R5X4 virus infections in 124 patients during PHI (6.4%) using the highly sensitive TTT [14].

Ultra-deep pyrosequencing is very useful for improving the sensitivity of genotypic predictions of HIV-1 tropism. However, the specificity is also important and HIV-1 coreceptor usage must be predicted accurately in order

to identify patients eligible for treatment with CCR5 antagonists and to carry out pathophysiological studies.

Acknowledgements

S.R., F.N., P.D. and J.I. designed the study and wrote the manuscript. A.S and F.N. analyzed the data. F.N., M.D. and M.C. performed the experiments. B.M. and P.M. contributed substantially to study conception and provided clinical samples. K.S.-S. performed the statistical analysis.

The English text was checked by Owen Parkes.

Conflicts of interest

Financial support for this work was provided by INSERM U1043. The authors declare that they have no competing interests.

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Received: 19 April 2011; revised: 23 May 2011; accepted: 3 June 2011.

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DOI:10.1097/QAD.0b013e3283498305

Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir

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There have been no data presented on the relative rates of the development of renal stones in those receiving ritonavir-boosted atazanavir (ATZ/r) when compared with other commonly used antiretrovirals (ARVs). We compared the rate of development of renal stones in a cohort of HIV-infected individuals attending the Chelsea and Westminster Hospital Foundation Trust exposed to ATZ/r with those exposed to efavirenz (EFV)/ritonavir-boosted lopinavir (LPV/r) and ritonavir-boosted darunavir (DRV/r) over a 45-month study period. The rate of development of renal stones in the ATZ/r group ($n = 1206$) compared with the EFV/LPV/r/DRV/r combined group ($n = 4449$) was 7.3 [95% confidence interval (CI) 4.7–10.8] per 1000 patient-years and 1.9 (95% CI 1.2–2.8) per 1000 patient-years ($P < 0.001$), respectively. The renal stones rate remained significantly higher in the ATZ/r group after adjusting for prior ATZ/r/indinavir (IND) exposure. When choosing a boosted protease inhibitor, ATZ/r renal stones should be considered as a potential comorbidity.

Although there have been case reports of the development of nephrolithiasis in individuals receiving antiretroviral (ARV) therapy including ritonavir-boosted atazanavir (ATZ/r) [1–5], there have been no data presented on the relative rates of the development of renal stones in those receiving ATZ when compared with other commonly used ARVs. Although primarily metabolized by the liver, approximately 7% of an ATZ/r dose is excreted unchanged in the urine and its solubility decreases with an increased alkalinity of urine [6]. When renal calculi do develop, they have been reported to contain 40–100% of ATZ by weight [3,4].

The mechanism of development of ATZ-associated renal stones is unknown, although there have been reports of ATZ intratubular crystal precipitation which have been confirmed by renal biopsy [4].

ATZ-associated renal stones may lead to obstructive uropathy and acute renal failure needing interventional management. Prior case series have suggested an association with viral hepatitis co-infection, prior renal stones and baseline chronic renal impairment [1,4,5,7]. We retrospectively compared the rate of development of renal stones in a large cohort of HIV-infected individuals exposed to ARV regimens containing ATZ/r with a second group exposed to efavirenz (EFV), ritonavir-boosted lopinavir (LPV/r) and ritonavir-boosted darunavir (DRV/r) over a 45-month study period from May 2006 to February 2010.

The departmental computer database, which holds data on clinical, therapeutic and investigations of all those attending the HIV unit, was used to identify individuals who developed renal stones. To ensure full case ascertainment, this was cross-checked with a separate database held in the radiology department of all individuals who had undergone an abdominal radiograph, a renal ultrasound scan, a computed scan of the abdomen or a pelvis or intravenous urogram at the Chelsea and Westminster Hospital. Diagnosis of renal stones was made only on a radiological basis. As ARV-associated renal stones are often radiolucent, abnormalities in the collecting systems compatible with obstruction or dilatation secondary to a recently passed stone were included as evidence of stones, but only in the context of an appropriate clinical history.

Rate of renal stones for each ARV studied was calculated using Poisson regression model in which total duration on each individual ARV was used as a denominator. In order to keep the coefficient of the denominator constant, this was $\log_e$-transformed and used as an offset in the Poisson model. The data were analysed using the Genmod procedure in SAS, version 9.1 (SAS Institute, Cary, North Carolina, USA) with $\log_e$ link and Poisson error distributions. This fits generalized linear models allowing time-dependent measures of probability. Data are presented as renal stone rate per 1000 patient-years with 95% confidence interval (CI) and statistical significance was evaluated by comparing the ATZ/r group with those receiving combined EFV/LPV/r/DRV/r. A subanalysis was performed, excluding individuals who developed renal stones during the study period with previous ritonavir-boosted IND (IND/r) or ATZ/r exposure.

The total number of individuals in the cohort was 5655. The rate of nephrolithiasis in the ATZ/r group ($n = 1206$) compared with the EFV/LPV/r/DRV/r combined group ($n = 4449$) was 7.3 (95% CI 4.7–10.8] per 1000 patient-years and 1.9 (95% CI 1.2–2.8] per 1000 patient-years ($P < 0.001$), respectively. After adjusting for previous IND/r exposure in the ATZ/r group, and previous ATZ/r/IND/r exposure in the EFV/LPV/r/DRV/r combined group, the renal stone rate was in the ATZ/r group ($n = 1000$) compared with the EFV/LPV/r/DRV/r group cohort ($n = 3293$) was 5.67 (95% CI 3.6–9.36) per 1000 patient-years and 1.51 (95% CI 0.85–2.4) per 1000 patient-years ($P < 0.001$) (Table 1), respectively.

The median bilirubin at renal stones diagnosis in the ATZ/r group, compared with the recent bilirubin measurement in all remaining patients on ATZ/r who attended during the study period and who had at the time not developed renal stones, was 50.5 [interquartile range

Table 1. Comparison of prevalence and rate of renal stones in the ritonavir-boosted atazanavir vs. combined efavirenz/ritonavir-boosted darunavir/ritonavir-boosted lopinavir group from May 2006 to February 2010.

	Analysis of entire cohort			IND/r/ATZ/r exclusion subanalysis		
	ATZ/r ($n=1206$)	EFV/DRV/r/LPV/r ($n=4449$)	P value	ATZ/r ($n=1000$)	EFV/DRV/r/LPV/r ($n=3293$)	P value
Number of patients with RS	24	24		15	15	
Prevalence of RS: per 1000 patients (95% CI)	20 (13–30)	5.4 (3.2–7.6)	<0.001	15 (8.4–24.6)	4.6 (2.5–7.5)	<0.001
Rate per 1000 patient-years of ARV exposure (95% CI)	7.3 (4.7–10.8)	1.9 (1.2–2.8)	<0.001	5.67 (3.18–9.36)	1.51 (0.85–2.49)	<0.001

IND/r/ATZ/r exclusion subanalysis compares prevalence and rate of RSs in the ATZ/r vs. combined EFV/DRV/r/LPV/r group during the same study period after exclusion of individuals with prior IND/r exposure in the ATZ/r group and prior IND/r with or without ATZ/r exposure in the EFV/DRV/r/LPV/r group. ARV, antiretroviral; ATZ/r, ritonavir-boosted atazanavir; CI, confidence interval; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; IND/r, ritonavir-boosted indinavir; LPV/r, ritonavir-boosted lopinavir; RS, renal stone.

(IQR) 32–65] and 23 μmol/l (IQR 9–44) ($P<0.001$), respectively.

In our study, 42% of cases of ATZ/r-associated renal stones had baseline chronic renal impairment with an estimated glomerular filtration rate of less than 60 ml/min per 1.73 m^2 at the start of the study period. This was significantly higher than that in 4.5% of cases with baseline chronic renal impairment, as defined above in those on ATZ/r who did not develop clinical evidence of renal stones ($P<0.001$). Forty percent of cases of ATZ/r-associated renal stones with chronic baseline renal impairment had a history of renal stones prior to the beginning of the study period. The proportion of ATZ/r-associated stone formers with chronic viral hepatitis B or C co-infection was 8% and did not significantly differ from rates of 4.2% in those on ATZ/r who did not form stones.

In the 24 individuals who developed renal stones while receiving ATZ/r, the median time from commencement of ATZ/r to developing a renal stone was 30 months (IQR 13–49). Twenty-one (87.5%) of the 24 individuals were switched from ATZ to an alternative protease inhibitor, six of whom had a further episode associated with nephrolithiasis. One individual who developed renal stones on DRV/r with a previous history of ATZ/r exposure had evidence of ATZ/r on stone analysis 21 months after stopping ATZ/r. Eight individuals with ATZ/r-associated renal stones required interventional management with stenting or nephrostomy insertion.

Our data have shown that the incidence of renal stones in those exposed to ATZ/r is greater than that with other commonly utilized ARV regimens, with and without adjusting for prior ATZ/r and IND/r exposure. The significantly higher median bilirubin in the group of ATZ/r-associated renal stone formers suggests that individuals with a pharmacogenetic predisposition to slower metabolization of ATZ/r may have an increased risk of stone formation due to associated higher levels of ATZ/r.

There are limitations to our study, including its retrospective nature. Although the rate of ATZ/r-associated renal stones was found to be 7.3 per 1000 patient-years, this is likely to be an underestimation of the true incidence of ATZ/r-associated renal stones, as we utilized a radiological diagnosis within our own hospital to calculate rates. Clearly, individuals may have presented to other hospitals for investigation. Only 13% of individuals with confirmed renal stones had stone composition analysis with infrared sphectrophotometry; thus, we cannot confirm that those developing renal stones on ATZ were indeed related to this therapy.

ATZ/r-associated renal stones should, thus, be considered as a potential comorbidity when making the choice of a suitable protease inhibitor for individual patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Received: 25 May 2011; accepted: 21 June 2011.

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DOI:10.1097/QAD.0b013e32834a1cd6