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ORIGINAL ARTICLE

Trends in antiretroviral use in pregnancy in the UK and Ireland, 2008–2018

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Abstract

Introduction: HIV treatment recommendations have evolved over time, reflecting both growing availability of new antiretrovirals and accumulating evidence on their safe and effective use. We analysed patterns of antiretroviral use among diagnosed pregnant women living with HIV delivering in the UK and Ireland between 2008 and 2018 using national surveillance data.

Methods: All singleton pregnancies with known outcomes and known timing of antiretroviral initiation reported to the National Surveillance of HIV in Pregnancy and Childhood were included. Every individual instance of specific antiretroviral use was the unit of analysis in generating a snapshot of antiretroviral use overall and over calendar time. The final analysis was restricted to the 14 most frequently prescribed antiretrovirals.

Results: There were 12 099 singleton pregnancies reported during 2008–2018 and a total of 38 214 individual uses of the 14 most commonly prescribed antiretrovirals, the majority of which were started before conception (70.9%). In 2008, 37.7% (482/1279) of pregnancies were conceived under treatment, reaching 80.9% (509/629) by 2018. Patterns of antiretroviral use have changed over time, particularly for third agents. Between 2008 and 2018 the most frequently used protease inhibitor shifted from lopinavir to darunavir, whereas use of integrase inhibitors increased steadily over time.

Conclusions: These national surveillance data enable investigation of the 'real-world' use of antiretrovirals in pregnancy on a population level. Findings demonstrate mixed responsiveness of antiretroviral prescription to changes in pregnancy guideline recommendations and may also reflect changes in commissioning and in the characteristics of pregnant women living with HIV.

KEYWORDS
antiretroviral, HIV, pregnant, treatment

INTRODUCTION

In 2019, a total of 98 552 people living with HIV were seen for care in the UK, of whom 30 388 were female [1]. The number of pregnancies in diagnosed women living with HIV in the UK peaked at just under 1450 in 2008 and has been around 900–1000 in recent years [2].

Key global milestones in treatment of HIV have included the World Health Organization (WHO) Consolidated Guidelines in 2013, which recommended starting antiretroviral therapy (ART) if CD4 count was < 500 cells/ μL (vs. 350 cells/ μL) and the introduction of Option B+ for pregnant and breastfeeding women (i.e. lifelong ART), followed by the 'treat all' WHO guidance in 2015 recommending ART initiation as soon as possible after diagnosis [3–5]. Thanks to this and other interventions, vertical transmission (VT) rates have declined in many European countries to < 1% [6–8]. Success in preventing VT requires prompt identification of undiagnosed pregnant women living with HIV, facilitated by high uptake of antenatal HIV screening (e.g. currently estimated at 99% of all pregnant women in the UK). Awareness of HIV status also enables prompt treatment initiation, with an increasing proportion of pregnant women with HIV conceiving while on ART worldwide. In the UK, this proportion increased from 20% in 2000–2004 to 76% in 2015–2019 [9], with the VT rate among diagnosed women declining from 2.10% in 2000–2001 to 0.22% in 2017–2018 [2].

The evolving HIV treatment recommendations on a global, regional and national level have reflected both the growing availability of new antiretrovirals and the accumulating evidence with respect to their safe and effective use in general [4,10–13]. In 2008, the first agent belonging to the new class of integrase strand transfer inhibitors (INSTIs), raltegravir (RAL), was authorized by the European Medicines Agency (EMA). In 2011 a new nonnucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine (RPV) was authorized, followed in 2014 by two more INSTIs, dolutegravir (DTG) and elvitegravir (EVG); 3 years later a new nucleoside reverse transcriptase inhibitors (NRTI), tenofovir-AF (TAF) was authorized. However, there is a long-standing knowledge gap with respect to the safety and effectiveness of antiretroviral drugs in pregnancy, particularly for newer drugs, including a lack of pharmacokinetic data to guide adequate dosing [5,14,15].

This lack of robust and timely data was emphasized by the neural tube defect (NTD) safety signal associated with peri-conception DTG use reported from the Tsepamo Study in Botswana in 2018 [16]. Updated analyses from the study found no evidence of a statistically significant prevalence difference in NTD occurrence between DTG- and non-DGT-based exposure at conception, with one excess NTD/1000 births exposed to DTG from conception [17].

The objective of this study was to analyse patterns of antiretroviral use among diagnosed pregnant women living with HIV delivering their infants in the UK and Ireland between 2008 and 2018 using national surveillance data in order to produce a snapshot analysis of the use of antiretroviral agents in pregnancy.

METHODS

The National Surveillance of HIV in Pregnancy and Childhood (NSHPC) began in 1989 and has conducted comprehensive population-based active surveillance on all known cases of antenatal and perinatal exposure to HIV and paediatric HIV infections in the UK and Ireland. In 2018 the NSHPC became a part of the NHS Infectious Diseases in Pregnancy Screening Programme (IDPS) and became known as the Integrated Screening Outcomes Surveillance Service (ISOSS). National surveillance covers all women diagnosed with HIV prior to or during their current pregnancy and their infants, as well as all children aged < 16 years diagnosed with HIV in the UK (data collection from Ireland ceased in 2018). Maternity reports of all pregnancies in women living with HIV (regardless of outcome) and diagnosed by delivery are submitted by maternity units, and include data on socio-demographics, type and timing of ART, pregnancy management, delivery details and outcome. Paediatric reports of all HIV-exposed infants and children diagnosed with HIV are submitted by paediatric clinics, and data include *in utero* and perinatal exposure to ART. Reports are submitted by a named responder in each maternity or paediatric unit via a secure online portal. All data are collected without patient consent under Public Health England's Regulation 3 approval to do so [2,9].

Statistical analyses

The analysis included all singleton pregnancies with known outcomes and known timing of antiretroviral initiation, with estimated date of delivery (EDD) between January 2008 and December 2018. Pregnancy outcomes were classified as live birth, stillbirth, miscarriage and termination of pregnancy. As surveillance is based on maternity reporting, whereas late miscarriages are captured, there is likely to be an under-ascertainment of early miscarriages. Date of conception were estimated using gestational age at delivery (in weeks) for pregnancies ending in live births or stillbirths and EDD for other outcomes, in order to estimate timing of exposure to antiretroviral

agents (i.e. prior to or in pregnancy) and to calculate maternal age at conception.

Frequencies for all possible combinations of antiretroviral drugs were obtained. Data on maternal–fetal exposure to every component of each ART regimen used during pregnancy were analysed, i.e. every individual agent was the unit of analysis, even if included in a fixed-dose combination (FDC), except for ritonavir when used as booster. For example, for the combination of lamivudine/zidovudine (3TC/ZDV), this was considered as a total of two antiretroviral agents, the combination of efavirenz (EFV) + tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) was considered as three antiretroviral agents, and darunavir boosted with ritonavir (DRV/r) was considered as one antiretroviral. In this way, every antiretroviral agent received by a woman during her pregnancy was counted. The final analysis was restricted to the most frequently prescribed antiretroviral agents and included all singleton pregnancies ending in live births or stillbirths occurring between 2008 and 2018 in order to exclude drugs with very low usage. As we wanted to include some more recently authorized antiretroviral agents, we selected the top 14 most frequently prescribed agents for the final analysis, despite some accounting for a relatively small percentage of overall antiretroviral usage. These data were used to generate a snapshot of antiretroviral use overall and over calendar time. For the time trends analysis, the denominator was the total number of antiretroviral agents used in the total number of pregnancies delivering per calendar year. Trends were assessed using χ^2 tests. Data extraction from the NSHPC database was performed using SQL Management Studio (SSMS) 2018. Data were compiled and analysed using R version 4.0.2 (R Core Team 2020).

RESULTS

There were 12 099 singleton pregnancies with known pregnancy outcomes and known timing of ART initiation reported to the NSHPC between 2008 and 18; of these 11 197 (92.5%) resulted in live births, 99 (0.8%) in stillbirths, 656 (5.4%) in miscarriage and 147 (1.2%) in terminations. Almost three-quarters of women were of black African ethnicity and were born in sub-Saharan Africa (SSA); 61.7% of women were aged 30–40 years at time of conception (Table 1) and the median age at conception was 33.4 years (interquartile range: 29.4–37.2). Most women (89.4%) had acquired HIV heterosexually and for the vast majority (82.9%) of pregnancies, maternal HIV diagnosis had been established prior to conception (Table 1); the proportion of pregnancies where women knew their diagnosis before pregnancy increased from 69.0% (883/1279) in 2008 to 90.3% (568/629) in 2018 (test-for-trend $p < 0.001$).

TABLE 1 Maternal characteristics among the 12 099 pregnancies, 2008–18

	n	%
Ethnicity		
Black African	8934	73.8%
Black other	436	3.6%
White	2089	17.3%
Other	622	5.1%
Missing	18	0.1%
Region of birth		
Sub-Saharan Africa	8725	72.1%
UK and Ireland	1857	15.3%
Europe	672	5.5%
Elsewhere	674	5.6%
Missing	171	1.4%
Age at conception (years)		
< 25	816	6.7%
25–29	2175	17.9%
30–34	3802	31.4%
35–39	3665	30.3%
40–44	1505	12.4%
≥ 45	136	1.1%
HIV acquisition route		
Heterosexual	10 815	89.4%
Injecting drug use	168	1.4%
Vertical transmission	182	1.5%
Other	140	1.2%
Not known/missing	863	7.1%
Timing of HIV diagnosis		
Before pregnancy	10 039	82.9%
During pregnancy	2060	17.0%
ART initiation		
Before pregnancy	7249	59.9%
During pregnancy	4850	40.1%

Abbreviation: ART, antiretroviral therapy.

There was a total of 38 214 individual uses of the 14 most commonly prescribed antiretrovirals, which are presented in Table 2. The majority of these drugs (27 099, 70.9%) were started before conception. At the start of the study period, 37.7% (482/1,279) of pregnancies were conceived on treatment, and by 2018 this proportion had increased to 80.9% (509/629) (test-for-trend $p < 0.01$).

Over the study period, the patterns of antiretroviral usage have changed, and the trends of yearly proportions of antiretroviral use are shown in Figure 1, which also

TABLE 2 The 14 most frequently prescribed antiretroviral agents between 2008 and 2018: year of licensing and proportion of total antiretrovirals (ARVs) used

ARV agent	ARV class	Year of licensing	Proportion of all ARVs used[a]
Tenofovir disoproxil fumarate (TDF)	NRTI	2002	18.3%
Emtricitabine (FTC)	NRTI	2003	17.4%
Lamivudine (3TC)	NRTI	1996	14.5%
Zidovudine (ZDV)	NRTI	1987	8.6%
Lopinavir (LPV)	PI	2001	8.1%
Abacavir (ABC)	NRTI	1998	7.5%
Atazanavir (ATV)	PI	2004	6.1%
Efavirenz (EFV)	NNRTI	1999	5.2%
Darunavir (DRV)	PI	2007	5.1%
Nevirapine (NVP)	NNRTI	1998	3.6%
Raltegravir (RAL)	INSTI	2008	2.8%
Dolutegravir (DTG)	INSTI	2014	1.1%
Rilpivirine (RPV)	NNRTI	2011	1.1%
Elvitegravir (EVG)	INSTI	2014	0.2%

Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Note that these proportions add up to 99.4%; this is because other ARV agents contribute to 0.6% of the total prescriptions.

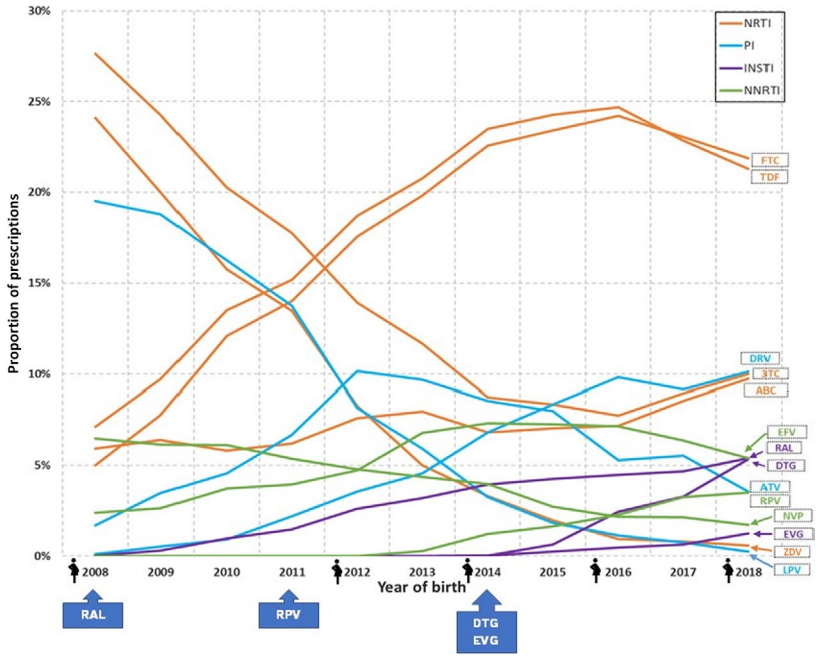

FIGURE 1 Trends of the most frequent antiretroviral agents used in the NSHPC, 2008–18. ATV, atazanavir; , BHIVA pregnancy guideline update; RAL, Year of licensing of named drug; 3TC, lamivudine; ABC, abacavir; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; LPV, lopinavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

includes information on the timing of updated British HIV Association (BHIVA) pregnancy guidelines and of new drug licensing; a summary of preferred and alternative regimens in the BHIVA guidelines is provided in Table S1. Looking at backbone NRTIs, in 2008 the most commonly used NRTI was ZDV, widely prescribed with 3TC as a FDC, consistent with BHIVA guidelines. Over time, use of ZDV and 3TC steadily declined, with ZDV

going from 24.1% (942/3909) of all antiretrovirals used in 2008 to 0.6% (12/2024) of those used in 2018, and use of 3TC decreased from 27.6% (1081/3909) of all antiretrovirals used in 2008 to 9.9% (202/2024) in 2018 (test-for-trend $p < 0.01$). Meanwhile, use of TDF and FTC concurrently increased, from 9.0% (278/3909) and 6.3% (196/3909) of all antiretrovirals used, respectively, in 2008 to a peak for both agents in 2016, with TDF accounting for 24.7% (811/3284) and FTC for 24.2% (795/3284) of all the agents used. TDF/FTC was first recommended as an alternative backbone in the BHIVA guidelines in 2012, and then as a preferred backbone in 2016. Despite this, the use of these two drugs had slightly decreased, to 21.2% (431/2024) and 21.8% (443/2024), respectively, in 2018, alongside a concurrent increase in use of 3TC and abacavir (ABC) (Figure 1).

Third agents have experienced the greates change in patterns of use in pregnancy over time. For example, among the protease inhibitors (PIs), atazanavir (ATV) use in 2008 accounted for only 1.6% (66/3909) of all the antiretroviral drugs used in pregnancies delivering that year, but its use then steadily increased, reaching a peak in 2012–2013 when it contributed approximately 10% (389/3830 in 2012 and 358/3701 in 2013, respectively). There was a subsequent decrease, with ATV use reaching its lowest level in 2018, accounting for 3.5% (70/2022) of all antiretrovirals used. Similarly, in 2008 DRV usage was extremely rare in pregnancy [0.1% (4/3909) of all antiretrovirals used that year]; however, it became increasingly used such that it accounted for 1 in 10 (205/2022) of all antiretrovirals prescribed in 2018. Lopinavir (LPV) started as one of the most used third agents [i.e. 19.5% (763/3909) of all antiretrovirals used in 2008] but became one of the least used in 2018 [just 0.2% (5/2024) of all drugs].

Three drugs from the NNRTI class were examined, with nevirapine (NVP) use having the most noticeable change, with a gradual decrease over time to 1.7% (35/2024) by 2018. Use of EFV stayed at a relatively low rate, despite it being the preferred third agent recommended by BHIVA in 2012. Its use peaked between 2014 and 2015 at around 7% of all antiretrovirals used and, after plateauing until 2016, it declined further, although it remained a preferred third agent. No reports of RPV use in pregnancy were apparent until a year after its licensing (Figure 1), and although usage increased more than 10-fold after 2013 [with only 10 usages reported that year: 0.3% (10/3701) of total usage], by 2018 it still only contributed 3.5% (71/2024) of all antiretrovirals prescribed (Figure 1).

Turning to the class of INSTIs, in the year that RAL was licensed by the EMA (2008) it accounted for < 1% (0.02%, 1/3909) of all antiretrovirals reported to the NSHPC with a steady and gradual increase in use over the next 10 years reaching 5.4% (109/2024) of all agents used in 2018. It was first recommended by BHIVA (as a preferred agent for newly diagnosed women) in 2014 (Table S1). With respect to DTG and EVG, both licensed in 2014, the former showed a more rapid increase in use compared with the latter, being reported for the first time in 2015 and accounting for 5.3% (108/2204) of all antiretrovirals used in 2018, compared with 1.2% (25/22 024) for EVG (Figure 1).

DISCUSSION

This analysis provides a population-level picture of the use of specific antiretroviral agents in pregnancy in the UK and Ireland, with every reported instance of antiretroviral use in diagnosed pregnant women captured through our national surveillance system. We showed that 14 agents accounted for > 99% of all antiretroviral drugs prescribed in pregnancy during our study period (2008–2018), and we focused our calendar time trends analysis on these.

This snapshot included women starting on ART for the first time while pregnant (usually following antenatal HIV diagnosis) as well as those with established HIV diagnoses, some of whom may have been on ART for many years, including some women who were themselves vertically infected [18]. The total number of antiretrovirals included any additional drugs used as a result of switching regimens during pregnancy. Although the vast majority of women on ART at conception in the UK and Ireland are on suppressive regimens (e.g. 86% in 2009–2014 [19]), switching drugs or regimens in pregnancy may occur for various clinical reasons (e.g. tolerability or safety issues).

Over the past decade, the demographics and health status of pregnant women living with HIV in the UK and Ireland have changed considerably. We report that the proportion of pregnancies where maternal HIV status was established before conception increased from two-thirds to 90% between 2008 and 2018, with a consequent increase in the proportion of pregnancies conceived on ART to 81% in 2018. The high proportion of women on ART throughout pregnancy is reflected in the 92% of women delivering in 2019 with a viral load (VL) < 50 copies/mL [2], whilst over the study period, the VT rate declined from 0.60% in 2008–2009 to 0.46% in 2010–2011, 0.27% in 2012–2014, 0.28% in 2015–2016 and 0.22% in 2017–2018 [2].

The antiretroviral drugs that women are taking when they conceive in the most recent period thus largely reflects prescribing patterns in the general population living with HIV. A small proportion of women in our study (< 5%) migrate to the UK whilst pregnant (mostly from SSA), of whom nearly 30% are already on ART [20] and thus the regimens they receive will largely reflect WHO guidelines. Patterns of HIV drug prescription in pregnancy not only depend on the underlying characteristics of the women becoming pregnant (particularly in terms of

timing of diagnosis and treatment status at conception), but also reflect decision-making by the patient and their physician, recommendations from BHIVA guidelines and clinical commissioning policies for new HIV treatments.

In the UK, HIV prescribing and pricing structures for commissioning HIV drugs are organized regionally, although national guidance on best practice is provided by the National Health Service HIV Clinical Reference Group (CRG) [21]. Key principles include access to effective treatment for all people living with HIV, informed choice and shared decision-making around prescribing. A further principle is to use the lowest-cost treatment option first where clinical efficacy is equivalent, including replacement of branded drugs by the generic equivalent. The CRG recommends that prescribing decisions for ART initiation, use of new agents and specific switches (e.g. for tolerability, toxicity, resistance or virological failure) are reviewed by a multidisciplinary team. There is no specific mention of pregnancy in this national guidance, but reference is made to BHIVA guidelines.

BHIVA regularly updates its guidelines for the clinical management of pregnant women, with six updates during the study period (i.e. approximately every 2 years [22–27], with guideline development using a modified GRADE system. In 2008, BHIVA recommended ZDV monotherapy as preferred treatment in pregnancy, with ZDV/3TC plus any PI/r as an alternative option [23], which is consistent with ZDV and 3TC accounting jointly for more than half of all prescribed antiretroviral drugs in the NSHPC in the same year. However, the rapid decline in use of ZDV and 3TC preceded the recommendation of this NRTI backbone as the 'preferred' option in 2012, whilst FTC/TDF use had started to increase well before its recommendation within a preferred regimen in 2014. An Italian study evaluating women who conceived on antiretrovirals between 2001 and 2011 showed similar trends with respect to NRTI backbones [28]. BHIVA started to recommend 3TC with ABC as a 'preferred' backbone option in 2016 [27], which might explain the contrasting trends of ZDV and 3TC use we show, with the former linearly decreasing over the whole study period, and the latter, having decreased alongside ZDV, starting to increase from 2016. Prescription of the FDC of 3TC/ABC/DTG from 2017 may also have driven the increasing use of ABC, supported by the parallel slopes in 2017–2018 in Figure 1. These changing patterns of use of NRTI backbones provide an insight into the complex relationship between 'real world' and guidelines.

During the study period, four new antiretroviral drugs were licensed – RAL, RPV, DTG and EVG – all third agents, and three from the INSTI class. Raltegravir was the first INSTI licensed and the first to have been recommended by BHIVA guidelines in 2014 for newly diagnosed patients [25], with this class characterized by rapid viral suppression, antiviral activity against strains of virus resistant to other drug classes and a strong transplacental transfer [29,30]. This is why initial clinical recommendations of RAL use were mostly intended for women presenting late to antenatal care and/or with high VL in late pregnancy [5,31]. In a previous NSHPC analysis of pregnancies with RAL use, RAL was started in the second or third trimester in 69%, and 35% of women had a detectable VL at delivery (considerably more than in the study as a whole), consistent with use of RAL in higher-risk pregnancies [32].

Dolutegravir was licensed in 2014, showing a high tolerability and lower reports of discontinuation due to adverse events compared with other third agents (such as DRV/r [33] or EFV [34], and it was therefore a much-awaited new drug to include in the existing arsenal of antiretrovirals. Although our data show that DTG started to be used from 2015, it only started to be recommended as an alternative third agent in the 2018 BHIVA guidelines. Our study period finished in 2018, the year that the DTG safety signal emerged, and thus it does not capture the impact of the resulting transient guideline changes [13,26,35,36]. With respect to third agents, NVP and EFV switching places as the most commonly used NNRTI in 2012 is consistent with the 2012 BHIVA pregnancy guidelines, which recommended EFV as the preferred third agent, with NVP or any PI/r as alternatives [24].

Turning to PIs, in 2008 LPV was the most commonly used third agent, accounting for nearly a fifth of all antiretrovirals prescribed in pregnancy. On a pregnancy level, around 60% of all pregnant women delivering in 2008 were receiving LPV, with this decreasing to $< 10\%$ by 2015 [37]. The rapid decline in LPV usage following a peak in 2009 partly reflected some changes in commissioning: a new tendering approach resulted in atazanavir (ATV) becoming cost-saving compared with other PIs, resulting in its increased use in patients starting PI therapy, as well as some switching of patients already on PI therapy to ATV [38]. The concurrent decline in LPV and increase in ATV is apparent in our snapshot. Some years later, in 2018, we reported an increased risk of preterm delivery associated with LPV/r use starting before conception [37], consistent with some (but not all) studies also finding associations between LPV/r specifically, or boosted PIs generally, and preterm delivery [39–43]. This not only underscores the fact that timely pregnancy safety data on specific drugs are often lacking, but also illustrates the complexities of interpreting patterns of use of antiretrovirals in pregnancy and their drivers.

The analysis focused on the 14 most frequently used antiretroviral drugs during the study period, and thus drugs potentially used in third-line regimens and 'older' drugs such as indinavir or saquinavir are not included.

For example, by 2018 the most frequently used PI was DRV, while use of ATV, the 'preferred' PI in the BHIVA guidelines at the time, had declined from an earlier peak 5 years before. This most likely reflects the increasing ART experience of women becoming pregnant in later years.

Analyses exploring the changing use of antiretroviral drugs in pregnancy over time have been conducted in the US and Italy. One of two studies in the US evaluated data on all women enrolled in Medicaid between 2000 and 2007 and another used data from the Surveillance Monitoring for ART Toxicities (SMARTT) study; both showed temporal changes in prescription patterns consistent with changes over time in the US perinatal guidelines [44,45]. Floridia and colleagues, in their Italian study focused on ART at conception in 2001–2011, commented that most women in the latter period were conceiving on drugs that were not considered 'preferred' by the contemporary pregnancy guidelines [28]. Our findings suggest that changes in NRTI usage often precede guideline recommendations, while increased use of specific third agents appear to be accelerated by specific recommendations. Furthermore, the snapshot analysis improves knowledge of patterns of *in utero* exposure to antiretroviral agents. This is important in light of concerns around potential toxic effects and teratogenic effects of such exposures on the developing embryo/foetus, particularly as most women are on ART from before conception [5,46]. The literature on children who are HIV-exposed and uninfected (CHEU) reports differences in their health compared with unexposed children, including metabolic, mitochondrial, immunological, developmental and haematological differences [47–49]. Furthermore, CHEU are being increasingly exposed to newly approved antiretroviral agents for which information about both short- and long-term safety is limited. Work is ongoing in the UK to explore long-term outcomes of *in utero* and perinatal exposure to antiretrovirals through electronic record linkage [50].

Although a strength of this analysis is the use of NSHPC data, which has national coverage with a very high rate of reporting by healthcare respondents within routine clinical care, it has some limitations. By design, we opted for a 'snapshot' approach focused on the utilization of antiretroviral agents over a restricted and prespecified period of time, with the total instances of use of antiretrovirals as denominator rather than pregnancies. It is therefore not appropriate to extrapolate findings to women or pregnancies *per se*. Furthermore, our approach precluded assessment of factors (e.g. relating to maternal clinical or socio-demographic characteristics) potentially associated with type of ART and/or with probability of switching drugs or regimens while pregnant. Future research using ISOSS data is needed to provide an in-depth understanding of such factors. A further limitation was that, to simplify our snapshot approach, we focused on the 14 most frequently used regimens, and thus exclude some drugs from the analysis, albeit those with very low usage levels as a proportion of total drugs used.

In conclusion, our national surveillance data enabled investigation of the 'real-world' use of antiretrovirals by pregnant women living with HIV in the UK and Ireland on a population level. We show that patterns of use of specific antiretrovirals have changed over this period when not only new agents and new combinations became available, but also a new class. Our findings demonstrate mixed responsiveness of antiretroviral prescription, both before and during pregnancy, to changes in clinical guideline recommendations. The trends described also reflect changes in commissioning and in the characteristics of pregnant women living with HIV nationally. The increasing proportion of women starting ART before becoming pregnant, coupled with the growing use of newer drugs with limited pregnancy safety data, underscores the need for the current WHO-led call for action to accelerate the study of new drugs in pregnancy and for ongoing evaluation of the patterns of antiretroviral use [51].

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AUTHOR CONTRIBUTIONS

VR, MCB and CT conceived this study. VR wrote the original draft. VR and MCB planned and performed the statistical analyses. HP, KF, LB and RS were responsible for data acquisition, processing and verification. All authors contributed to interpreting the results and reviewing the article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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