RESEARCH

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WHAT OUR READERS ARE SAYING

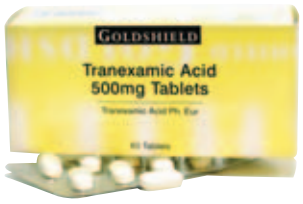
Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes

A couple of weeks ago we highlighted a rapid response to this cohort study (*BMJ* 2012;345:e5567). Our blogger Richard Lehman had some reservations about this:

"It's really weird that the *BMJ* flagged up and printed this rapid response because it is mistaken on almost every count. This is a database study of the blood pressure as measured by UK general practitioners in the first year of diagnosis of type 2 diabetes (from 1990 to 2005), and how it relates to mortality over that period. It tells us nothing about treatment effects. The reason that the glycaemic index of the patients is not reported is presumably because nobody wanted to eat them."

Effect of tranexamic acid on mortality in patients with traumatic bleeding

According to this prespecified analysis of data from a randomised controlled trial (p 16), tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding and should not be restricted to the most severely injured. A rapid respondent said this:



"Current practice is to infuse 1 g tranexamic instantaneously, followed by 1 g over 8 hours. Unfortunately, there is great inter-individual difference in triggering the contact phase of coagulation, which is why it is not easy to predict which dosage of contact trigger is exactly necessary for the individual patient. A fixed initial dosage could be given in the emergency room and the following appropriate dosage might be determined by performing differentiated ultra-specific, ultra-sensitive recalcified thrombin generation assays in the plasma of the individual patient. Instead of tranexamic acid another contact trigger such as hydroxyethyl starch could be given to stop severe bleeding. An alternative to infusion of a thrombin generating drug would be the application of ultrasound exactly at the position of the bleeding if known."

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RESEARCH ONLINE: see www.bmj.com/research

Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection

According to this cohort study of 2766 patients, treatment with diclofenac could result in an increased proportion of patients with anastomotic leakage after colorectal surgery. COX-2 selective NSAIDs should therefore be used with caution after colorectal resections with primary anastomosis, say the authors.

Clinicians' gut feeling about serious infections in children

In this observational study of 3369 children and young people assessed clinically as having a non-severe illness, six were subsequently admitted to hospital with a serious infection. A "gut feeling"—an intuition that something was wrong despite the clinical assessment of non-severe illness—substantially increased the risk of serious illness and acting on this gut feeling had the potential to prevent two of the six cases being missed, say the authors. The observed association between intuition and clinical markers of serious infection means that by reflecting on the genesis of their gut feeling, clinicians should be able to hone their clinical skills, say the authors.

Cardiovascular disease risk in healthy children and its association with body mass index

According to this meta-analysis of 63 studies of 49 220 children, having a body mass index outside the normal range worsens risk parameters for cardiovascular disease in school aged children. All parameters measured had similar increases, showing a gradient effect with lesser increases in overweight children compared with normal weight children. The authors conclude that being overweight or obese in childhood may have a larger effect on risk parameters for cardiovascular disease and on future health than previously thought.

Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis

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EDITORIAL by Olsen and Green
RESEARCH, p 15
PERSONAL VIEW, p 31

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bmj.com
Research: Sunbed use in children aged 11-17 in England (*BMJ* 2010;340:c877)

STUDY QUESTION

What is the estimated burden of melanoma resulting from sunbed use in western Europe?

SUMMARY ANSWER

Sunbed use is associated with a significant increase in the risk of melanoma, with risk increasing with number of sessions and if use starts at a young age (<35 years). The cancerous damage associated with sunbed use is substantial and accounted for about 3438 cases annually.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous studies reported an increased risk of cutaneous melanoma associated with sunbed use but no consistent dose-response relation. This meta-analysis confirms a doubling of the risk of melanoma when first sunbed use takes place at a young age, and there was evidence of a dose-response relation between amount of sunbed use and risk of melanoma. In Europe an estimated 3438 new cases of melanoma each year are associated with sunbed use.

Selection criteria for studies

Observational studies reporting a measure of risk for skin cancer (cutaneous melanoma, squamous cell carcinoma, basal cell carcinoma) associated with ever use of sunbeds. We searched PubMed, ISI Web of Science (Science Citation Index Expanded), Embase, Pascal, Cochrane Library, LILACS, and MedCarib, as well as published surveys reporting prevalence of sunbed use at national level in Europe.

Primary outcome

Risk of cutaneous melanoma associated with ever sunbed use.

Main results and role of chance

Based on 27 studies ever use of sunbeds was associated with a summary relative risk of 1.20 (95% confidence interval 1.08 to 1.34). Calculations for dose-response showed a 1.8% (95% confidence interval 0% to 3.8%) increase in risk of melanoma for each additional sunbed use per year. Based on 13 informative studies, first use of sunbeds before age 35 years was associated with a summary relative risk of 1.87 (1.41 to 2.48), with no indication of heterogeneity between studies. By using prevalence data from surveys and data from GLOBOCAN 2008, in 2008 in the 15 original member countries of the European Community plus three countries that were members of the European Free Trade Association, an estimated 3438 cases of melanoma could be attributable to sunbed use, most (n=2341) occurring among women.

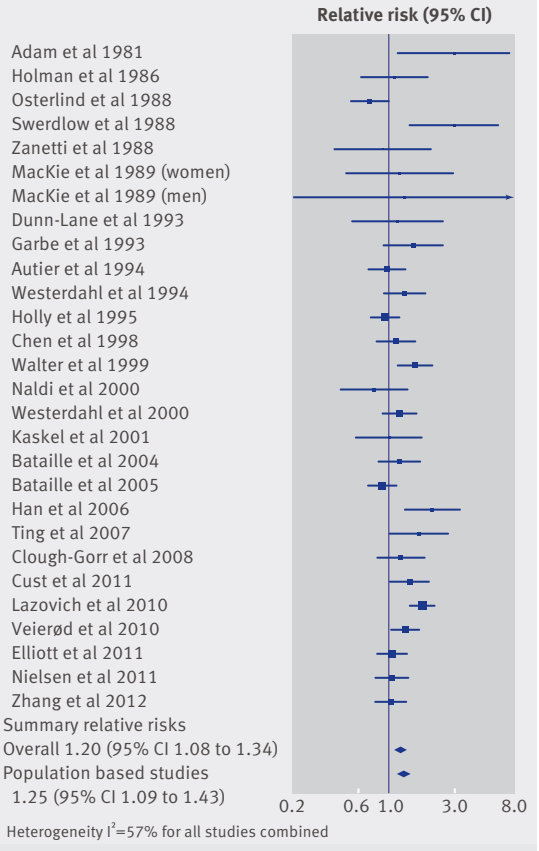
Bias, confounding, and other reasons for caution

We investigated sources of heterogeneity and bias. Publication bias was not evident in any of the analyses. The risk of melanoma associated with sunbed use was found in all white populations irrespective of individual sensitivity to sun. The computation of attributable cases is a first estimate and relies partly on the available surveys published at population level in Europe. Not all countries had estimated the prevalence of sunbed use.

Study funding/potential competing interests

This study did not receive funding. We have no competing interests.

Risk of melanoma associated with ever use of sunbeds



Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis

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EDITORIAL by Olsen and Green
RESEARCH, p 14
PERSONAL VIEW, p 31

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Melanoma—Part 1: epidemiology, risk factors, and prevention (*BMJ* 2008;337:a2249)

STUDY QUESTION

What is the association between indoor tanning and non-melanoma skin cancer?

SUMMARY ANSWER

People who reported ever using a tanning bed had a 67% higher risk of squamous cell carcinoma and a 29% higher risk of basal cell carcinoma.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Indoor tanning is a known carcinogen for malignant melanoma. Indoor tanning is also associated with non-melanoma skin cancer, especially when exposure occurs early in life.

Selection criteria for studies

We included all articles that reported an original effect statistic for indoor tanning and non-melanoma skin cancer or that reported measurement of or adjustment for indoor tanning that could be used to calculate an effect estimate. We excluded articles that presented no data, such as review articles and editorials, and articles in languages other than English.

Primary outcome

The main outcome was relative risk of basal cell carcinoma and squamous cell carcinoma.

Main results and role of chance

In our random effects meta-analysis of 12 studies that included 9328 cases of non-melanoma skin cancer, the summary relative risk for squamous cell carcinoma was 1.67 (95% confidence interval 1.29 to 2.17) and that for basal cell carcinoma was 1.29 (1.08 to 1.53) for participants who reported ever using indoor tanning compared with those who reported never using indoor tanning. We found no significant heterogeneity between studies. The population attributable risk fraction for the United States was estimated to be 8.2% for squamous cell carcinoma and 3.7% for basal cell carcinoma. This corresponds to more than 170 000 cases of non-melanoma skin cancer each year attributable to indoor tanning. Additionally, on the basis of data from three studies, use of indoor tanning before age 25 may be more strongly associated with both squamous cell carcinoma (relative risk 2.02, 0.70 to 5.86) and basal cell carcinoma (1.40, 1.29 to 1.52).

Bias, confounding, and other reasons for caution

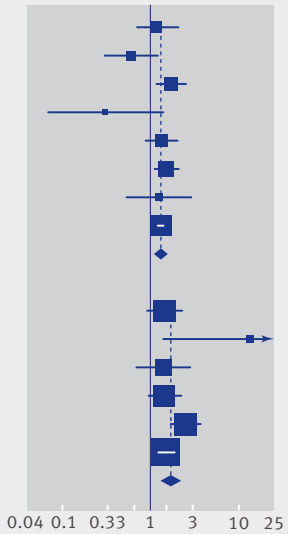
Publication bias and small study effects could have biased our results. However, funnel plots, Begg's rank correlation test, and Egger's weighted linear regression test all indicated that these were unlikely. Because most of the included studies were retrospective case-control studies, confounding is possible. However, most of the included studies adjusted for multiple confounders, and our results did not change appreciably in a sensitivity analysis excluding four studies that did not fully adjust for confounders.

Study funding/potential competing interests

This project was supported by award number KL2RR024130 from the National Center for Research Resources of the National Institutes of Health, and by award number K24 AR052667 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

Relative risk of non-melanoma skin cancer in participants ever exposed compared with never exposed to indoor tanning

Study	No exposed/No in group: Cases	No exposed/No in group: Controls	Odds ratio or hazard ratio (95% CI)
Basal cell carcinoma			
Bajdik 1996	23/226	33/404	1.20 (0.70 to 2.20)
Corona 2001	17/161	31/154	0.60 (0.30 to 1.20)
Ferrucci 2011	246/375	245/382	1.69 (1.15 to 2.48)
Gon and Minelli 2011	3/127	25/280	0.31 (0.07 to 1.35)
Han 2006	44/259	87/712	1.32 (0.87 to 2.03)
Karagas 2002	127/601	75/539	1.50 (1.10 to 2.10)
Rosso 1999	10/120	9/144	1.24 (0.53 to 2.88)
Zhang 2012	617/5494	–	1.29 (1.22 to 1.35)
Summary			1.29 (1.08 to 1.53)
Squamous cell carcinoma			
Asgari 2011	49/415	36/415	1.41 (0.90 to 2.22)
Aubrey and McGibbon 1985	4/92	1/174	13.42 (1.38 to 130.5)
Bajdik 1996	18/180	33/404	1.40 (0.70 to 2.70)
Han 2006	41/253	87/712	1.44 (0.93 to 2.24)
Karagas 2002	63/292	75/539	2.50 (1.70 to 3.80)
Zhang 2012	36/402	–	1.50 (1.20 to 1.78)
Summary			1.67 (1.29 to 2.17)



Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial

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STUDY QUESTION Does the effect of tranexamic acid on the risk of death and thrombotic events in patients with traumatic bleeding vary according to baseline risk of death?

SUMMARY ANSWER The beneficial effects of tranexamic acid in reducing all cause mortality and deaths from bleeding in patients with traumatic bleeding do not seem to vary significantly by risk of death at baseline.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Patients with traumatic bleeding who are given tranexamic acid within three hours of injury experience significantly reduced mortality with no apparent increase in adverse thrombotic events. This study showed these effects of tranexamic acid do not vary with baseline risk, suggesting that it can be administered safely to a wide spectrum of patients with traumatic bleeding and that its use should not be restricted to the most severe cases.

Design

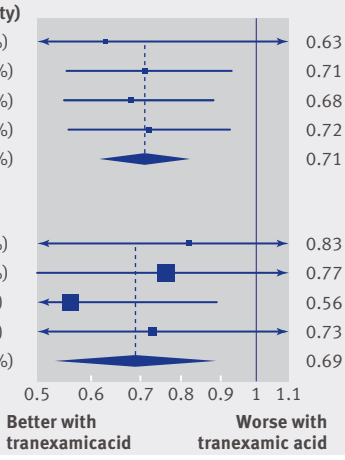
Prespecified stratified analysis of data from an international multicentre randomised controlled trial (the CRASH-2 trial) with an estimation of the proportion of premature deaths that could potentially be averted through the administration of tranexamic acid (1 g over 10 minutes followed by 1 g over eight hours).

Participants and setting

13 273 trauma patients in the CRASH-2 trial who were treated with tranexamic acid or placebo within three hours of injury, stratified by risk of death at baseline (<6%, 6-20%, 21-50%, >50%).

Risk of death from bleeding and risk of fatal and non-fatal thrombotic events in patients with traumatic bleeding according to treatment with tranexamic acid

Risk of death at baseline	No of patients (%): Tranexamic acid	No of patients (%): Placebo	Odds ratio (95% CI)
Death from bleeding (P=0.98 for heterogeneity)			
<6%	14/2487 (1%)	21/2353 (1%)	0.63 (0.32 to 1.24)
6-20%	96/2682 (4%)	134/2713 (5%)	0.71 (0.55 to 0.93)
21-50%	98/908 (11%)	142/940 (15%)	0.68 (0.53 to 0.88)
>50%	106/607 (17%)	132/583 (23%)	0.72 (0.56 to 0.93)
All	314/6684 (5%)	429/6589 (7%)	0.71 (0.61 to 0.82)
Fatal and non-fatal thrombotic events (P=0.74 for heterogeneity)			
<6%	14/2487 (1%)	16/2353 (1%)	0.83 (0.40 to 1.96)
6-20%	38/2682 (1%)	50/2713 (2%)	0.77 (0.50 to 1.17)
21-50%	29/908 (3%)	52/940 (6%)	0.56 (0.36 to 0.89)
>50%	17/607 (3%)	22/583 (4%)	0.73 (0.39 to 1.38)
All	98/6684 (1%)	140/6589 (2%)	0.69 (0.53 to 0.89)



Primary outcomes

Odds ratios and 95% confidence intervals for death in hospital within four weeks of injury, deaths from bleeding, and fatal and non-fatal thrombotic events associated with the use of tranexamic acid according to baseline risk of death.

Main results and the role of chance

Tranexamic acid was associated with a significant reduction in all cause mortality and deaths from bleeding. In each stratum of baseline risk, there were fewer deaths among patients treated with tranexamic acid. If the effect of tranexamic acid is assumed to be the same in all risk strata (<6%, 6-20%, 21-50%, >50% risk of death at baseline), the percentage of deaths that could be averted by administration of tranexamic acid within three hours of injury in each group is 17%, 36%, 30%, and 17%, respectively. There was no evidence of heterogeneity in the effect of tranexamic acid on all cause mortality (P=0.96 for interaction) or deaths from bleeding (P=0.98) by baseline risk of death. In those treated with tranexamic acid there was a significant reduction in the odds of fatal and non-fatal thrombotic events (odds ratio 0.69, 95% confidence interval 0.53 to 0.89; P=0.005) and a significant reduction in arterial thrombotic events (0.58, 0.40 to 0.83; P=0.003) but no significant reduction in venous thrombotic events (0.83, 0.59 to 1.17; P=0.295). There was no evidence of heterogeneity in the effect of tranexamic acid on the risk of thrombotic events (P=0.74).

Bias, confounding, and other reasons for caution

The data examined are a subset of the entire CRASH-2 trial. As most trauma protocols restrict use of tranexamic acid to patients who are within three hours of injury, we also restricted our analyses to these patients.

Generalisability to other populations

Given that our results are based on a subgroup analysis, they should be interpreted cautiously.

Study funding/potential competing interests

This study was funded by the UK Health Technology Assessment programme (09/22/165).

Trial registration number

The CRASH-2 trial is registered as ISRCTN86750102.

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- Effect of tranexamic acid on surgical bleeding (*BMJ* 2012;344:e3054)
- Intraoperative use of tranexamic acid to reduce transfusion rate in patients undergoing radical retropubic prostatectomy (*BMJ* 2011;343:d5701)
- Effect of tranexamic acid in traumatic brain injury (*BMJ* 2011;343:d3795)

Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies

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STUDY QUESTION To estimate the relative risks of death, myocardial infarction, stroke, and renal failure or dysfunction between antifibrinolytics and no treatment based on all available evidence, in light of aprotinin's recent reintroduction in Europe and Canada.

SUMMARY ANSWER While meta-analyses of randomised controlled trials were largely inconclusive, addition of observational data suggested that concerns remain about the safety of aprotinin. Tranexamic acid and epsilon-aminocaproic acid are effective alternatives that may be safer for patients.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
After suspension from the market in 2008, aprotinin was reintroduced in Canada (2011) and Europe (2012). Important observational evidence about the safety of antifibrinolytics warrants consideration in syntheses of the evidence to study the safety of these drugs. In this review, evidence from randomised trials and observational studies was used in network meta-analyses to compare treatments, which showed that important risks may remain for some patients receiving aprotinin.

Summary of results from network meta-analysis

Outcomes by treatments compared with aprotinin (reference group)	Odds ratio (95% credible interval)	
	RCTs only	RCTs and observational studies
Death:		
No treatment	0.99 (0.72 to 1.36)	0.91 (0.71 to 1.16)
Tranexamic acid	0.64 (0.41 to 0.99)*	0.71 (0.50 to 0.98)*
Epsilon-aminocaproic acid	0.79 (0.47 to 1.55)	0.60 (0.43 to 0.87)*
Myocardial infarction:		
No treatment	1.14 (0.89 to 1.47)	0.98 (0.81 to 1.20)
Tranexamic acid	0.95 (0.66 to 1.44)	0.89 (0.73 to 1.11)
Epsilon-aminocaproic acid	0.79 (0.50 to 1.30)	0.78 (0.60 to 1.03)
Stroke:		
No treatment	1.05 (0.40 to 2.23)	1.14 (0.68 to 1.89)
Tranexamic acid	1.06 (0.33 to 2.63)	0.81 (0.48 to 1.40)
Epsilon-aminocaproic acid	0.72 (0.15 to 2.02)	0.89 (0.48 to 1.59)
Renal failure or dysfunction:		
No treatment	0.83 (0.50 to 1.37)	0.66 (0.45 to 0.88)*
Tranexamic acid	0.82 (0.31 to 1.68)	0.66 (0.48 to 0.91)*
Epsilon-aminocaproic acid	0.74 (0.23 to 1.43)	0.65 (0.45 to 0.88)*

RCT=randomised controlled trial. An odds ratio less than one suggests greater risk with aprotinin.
*Statistically significant.

Selection criteria for studies
We sought studies that enrolled patients undergoing cardiac surgery using cardiopulmonary bypass, with no restrictions for surgical history, urgency, or procedure. We included randomised controlled trials if at least two of the following were compared: aprotinin, tranexamic acid, epsilon-aminocaproic acid, or no treatment (including placebo), regardless of drug dose. Propensity matched and adjusted observational studies were also included. We retained studies reporting on death, myocardial infarction, stroke, or renal failure or dysfunction. Network meta-analysis was used to compare treatments for each outcome, and odds ratios with 95% credible intervals were estimated. Meta-analyses were carried out for randomised controlled trials alone and with observational studies.

Primary outcomes
Death, myocardial infarction, stroke, and renal failure or dysfunction.

Main results and role of chance
106 randomised controlled trials and 11 observational studies (43 270 patients) were included. Most estimates based on randomised controlled trials were inconclusive owing to wide credible intervals. When all information was synthesised, comparisons showed an increased risk of mortality on average with aprotinin compared with tranexamic acid and epsilon-aminocaproic acid, as well as increased risks of renal failure or dysfunction on average relative to all comparators.

Bias, confounding, and other reasons for caution
Observational studies increased our sample sizes and in some comparisons led to strong results; however, even propensity adjusted and matched studies may have residual confounding. Some of the observational research that was captured varied doses of the treatments studied.

Study funding/potential competing interests
This study received no funding.

Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: multicentre observational study

UK Collaborative Group on HIV Drug Resistance

EDITORIAL by Bertagnolio

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- Research: Impact of late diagnosis and treatment on life expectancy in people with HIV-1 (*BMJ* 2011;343:d6016)
- Research: Combined antiretroviral treatment and heterosexual transmission of HIV-1 (*BMJ* 2010;340:c2205)

STUDY QUESTION

Is resistance to antiretroviral therapy continuing to decline in transmitted HIV-1 infections probably acquired in the United Kingdom?

SUMMARY ANSWER

The decline in HIV-1 transmitted drug resistance seems to have stabilised, and the continued high prevalence of thymidine analogue mutations suggests that a source of this resistance may be increasingly from patients who are antiretroviral therapy naive and who harbour the resistant virus.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Transmitted drug resistance in HIV-1 strains has been on the decline in the UK since 2002. This paper shows that such a decline no longer exists, and points to a sustained epidemic that is resistant to nucleos(t)ide reverse transcriptase inhibitors, irrespective of previous antiretroviral therapy use within the UK.

Participants and setting

We used records from the UK HIV Drug Resistance Database, which collects the majority of genotypic resistance tests undertaken in the UK as part of routine clinical care. We analysed the first resistance test from adults infected with HIV-1 subtype B virus and who had not yet undergone antiretroviral therapy.

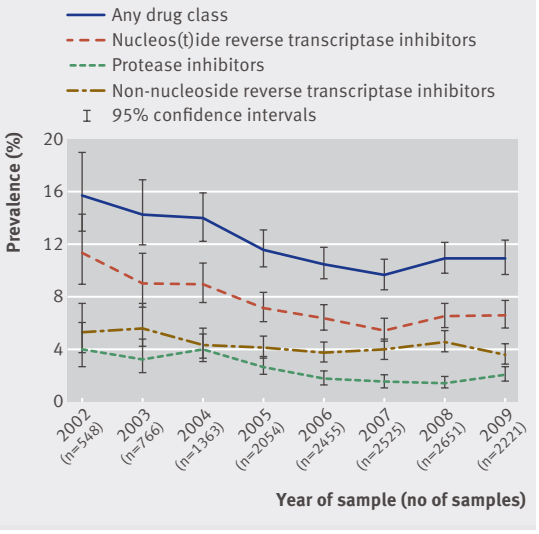
Design, size, and duration

We did a multicentre observational study of 14 583 adults. We defined transmitted HIV-1 drug resistance as one or more mutations from the surveillance list recommended by the World Health Organization. Trends over time (between January 2002 and December 2009) were analysed using piecewise linear logistic regression with a flexible choice of a single inflexion point.

Main results and the role of chance

Samples from 11.3% (n=1654; 95% confidence interval 10.8% to 11.9%) of patients had mutations associated with transmitted HIV-1 drug resistance. In total, 6.9% (n=1009; 6.5% to 7.3%), 4.1% (n=604; 3.8% to 4.5%), and 2.2% (n=319; 2.0% to 2.4%) of patients had one or more mutations associated with nucleos(t)ide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors, respectively. The prevalence of resistance associated with any drug class was observed to decline until around January 2007, but between 2007 and 2009, we saw a non-significant increase in prevalence from 9.6% to 10.9%. Mutations associated with nucleos(t)ide reverse transcriptase inhibitors and protease inhibitors have also non-significantly increased since 2007 and 2008, respectively. The prevalence of mutations associated with non-nucleoside reverse transcriptase inhibitors remained stable at around 3.6%, with no evidence of an increase in recent years. The trends in resistance associated with nucleos(t)-ide reverse transcriptase inhibitors largely reflected the high prevalence of thymidine analogue mutations. The prevalence of these mutations to thymidine analogues levelled off over time, which is paradoxical in the light of the reduction in use of antiretroviral drugs that typically lead to their development.

Prevalence of transmitted drug resistance over time



Bias, confounding, and other reasons for caution

Between infection and the drug resistance test, viral quasi-species harbouring resistance mutations may be overgrown by viruses without resistance mutations. Therefore, the true level of transmitted HIV-1 drug resistance may have been underestimated.

Generalisability to other populations

Our analysis deliberately focused on subtype B infections to give insights on viral transmission dynamics in the UK only. However, the main conclusion that resistant lineages have become fixed in the circulating pool should apply widely, including in countries where thymidine analogues of reverse transcriptase inhibitors are used in first line regimens.

Study funding/potential competing interests

This work was supported by the UK Medical Research Council (grant G0900274) and the European Community's 7th Framework programme (FP7/2007-2013) under the Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN; 223131). The authors declare no competing interests.