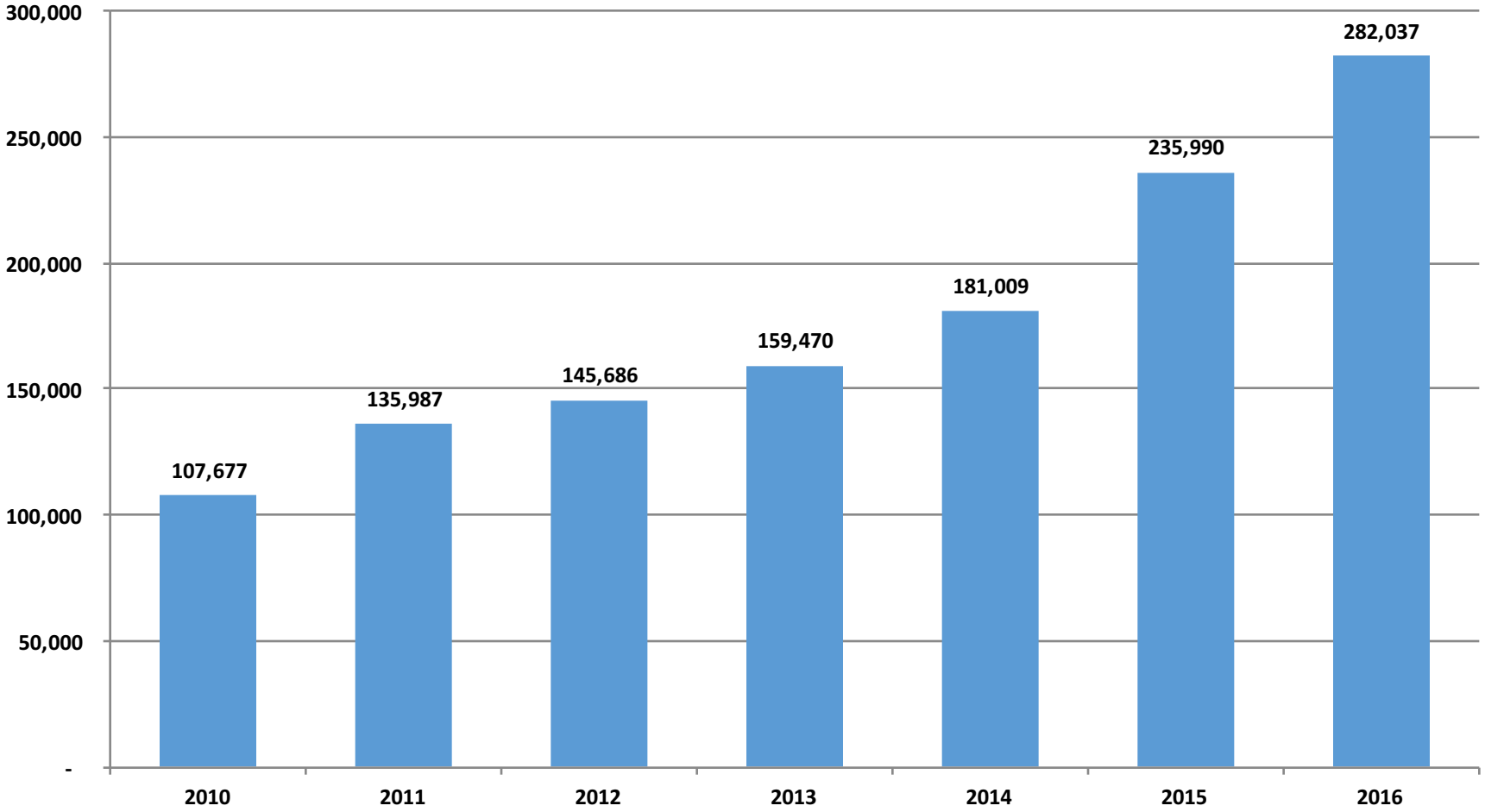
Update on Liverpool Drug Interaction Team Activities

David Back

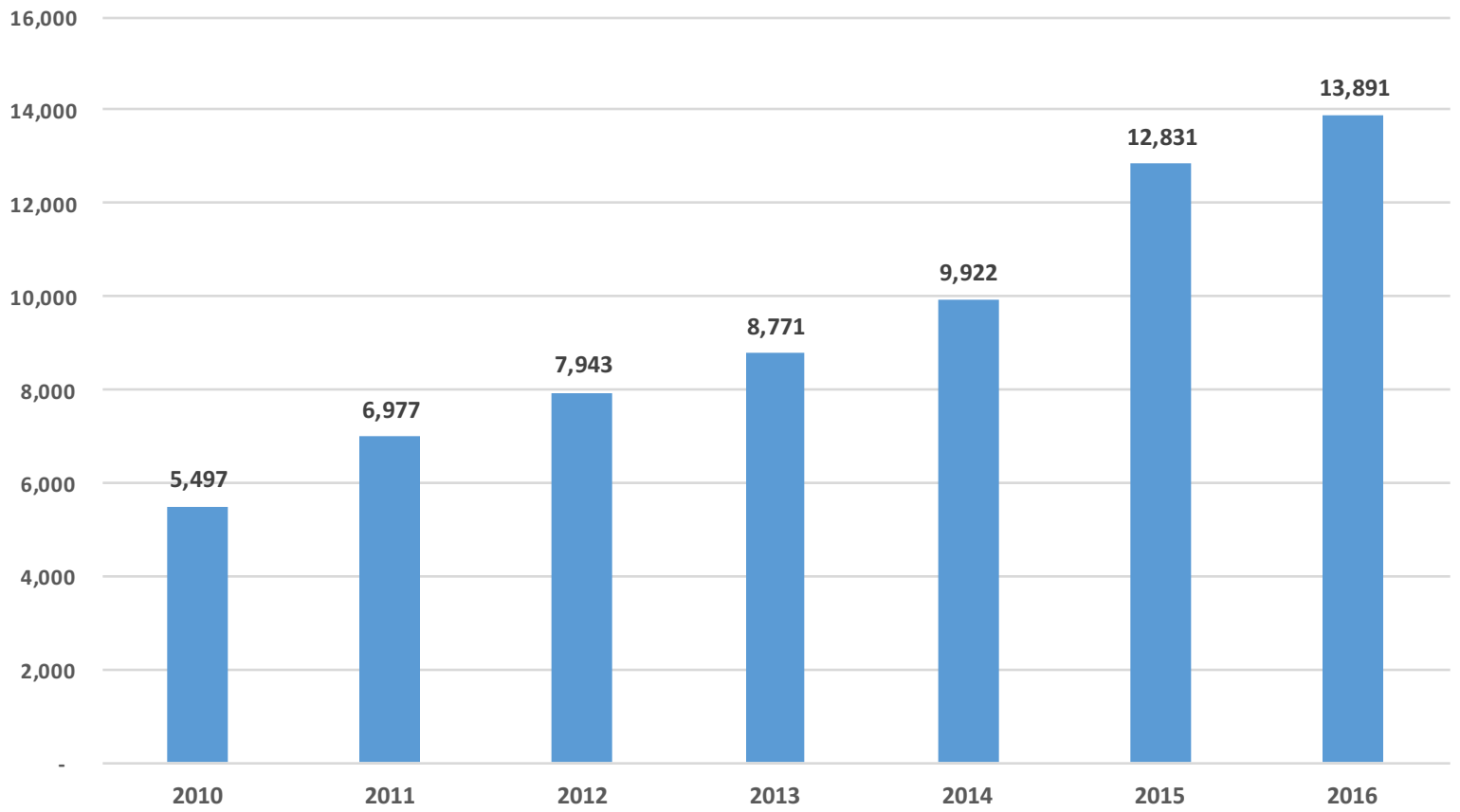
1. Analytics
2. Expansion of the Interaction Classification
3. Other ongoing projects.
4. New Drugs
5. New Site

HIV annual site visits 2010-16



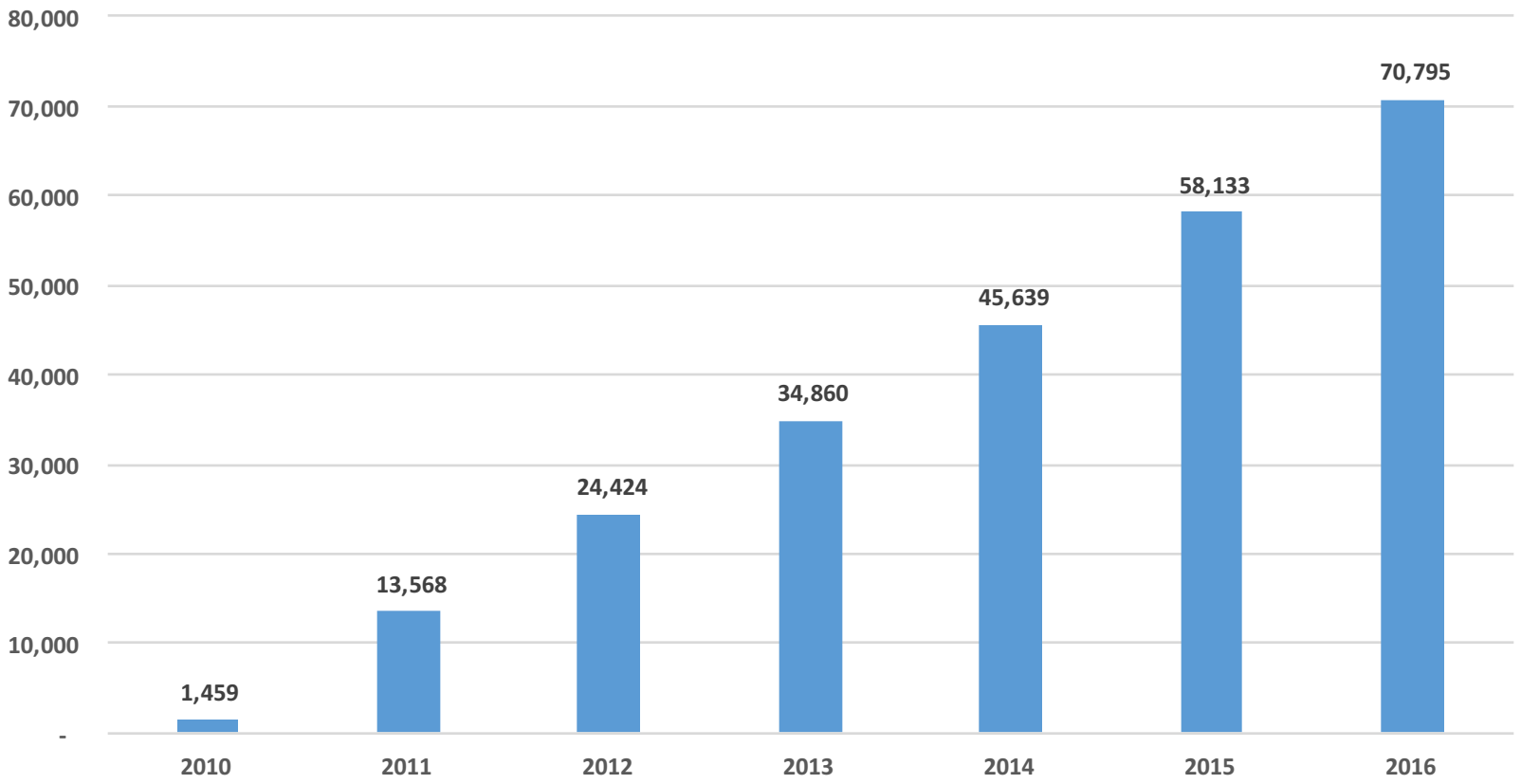
Google Analytics

HIV average monthly visitors 2010-16



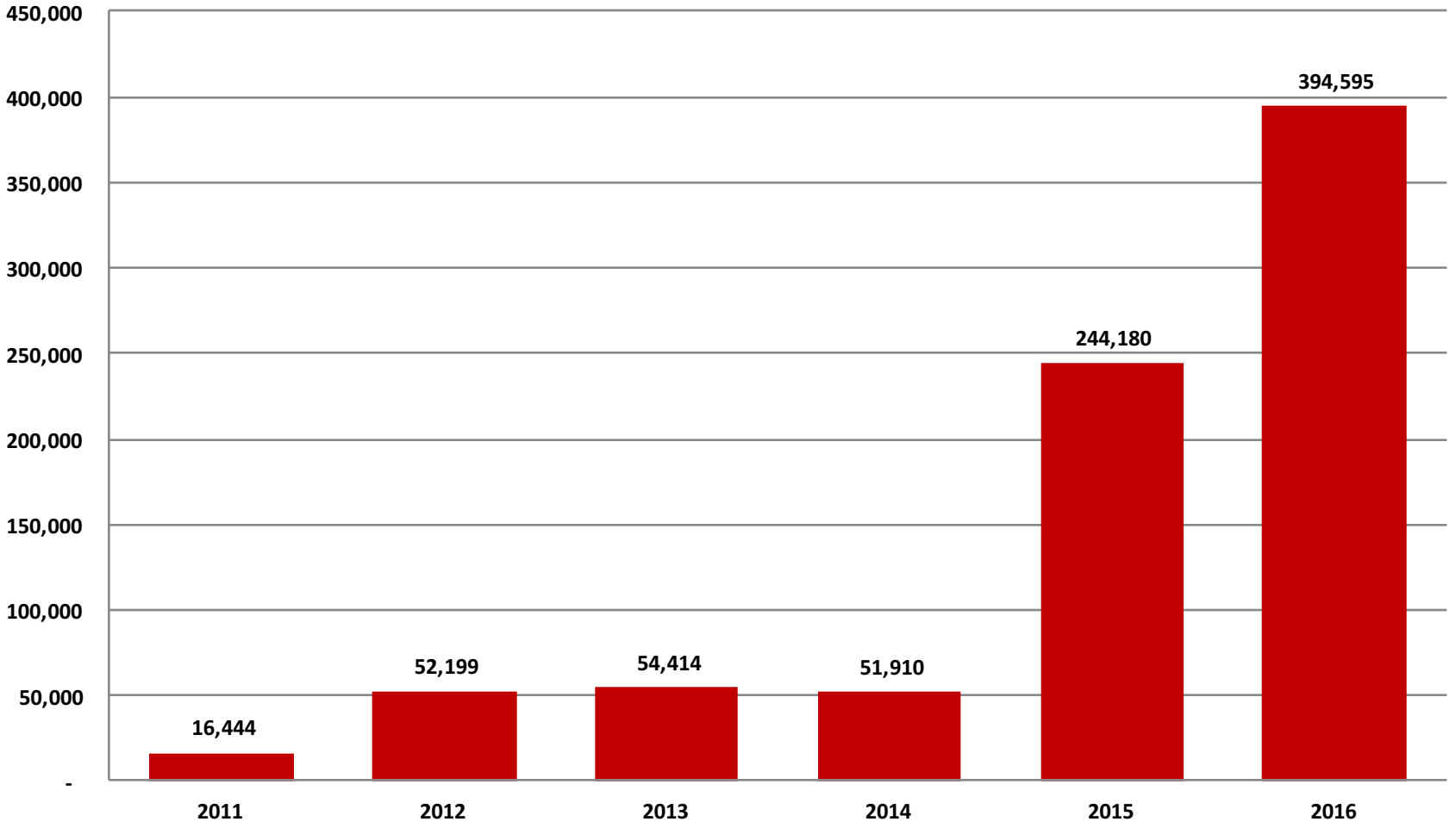
Google Analytics

HIV total app downloads 2010-16



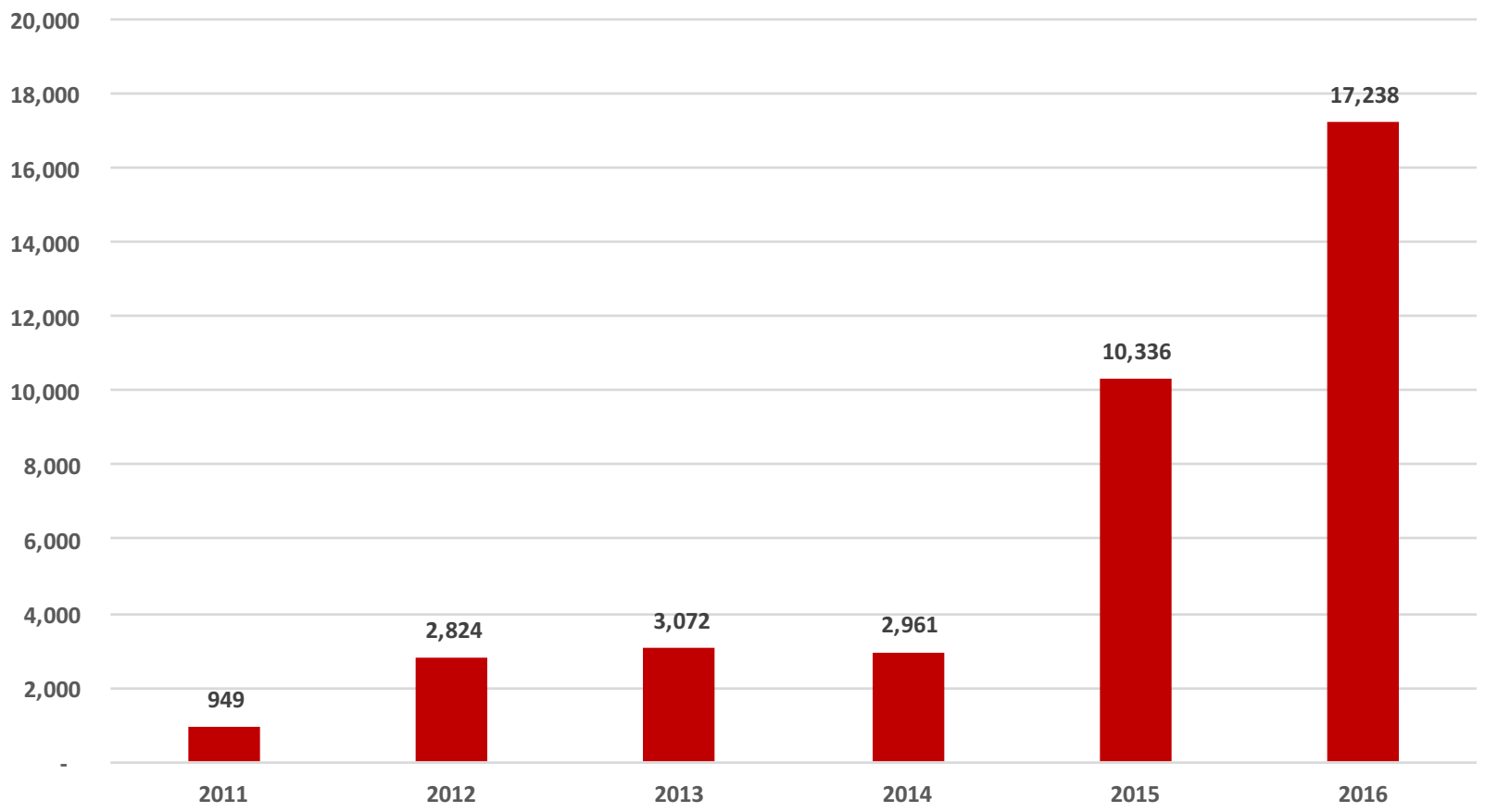
Google Analytics

HEP Annual site visits 2010-16



Google Analytics

HEP average monthly visitors 2010-16



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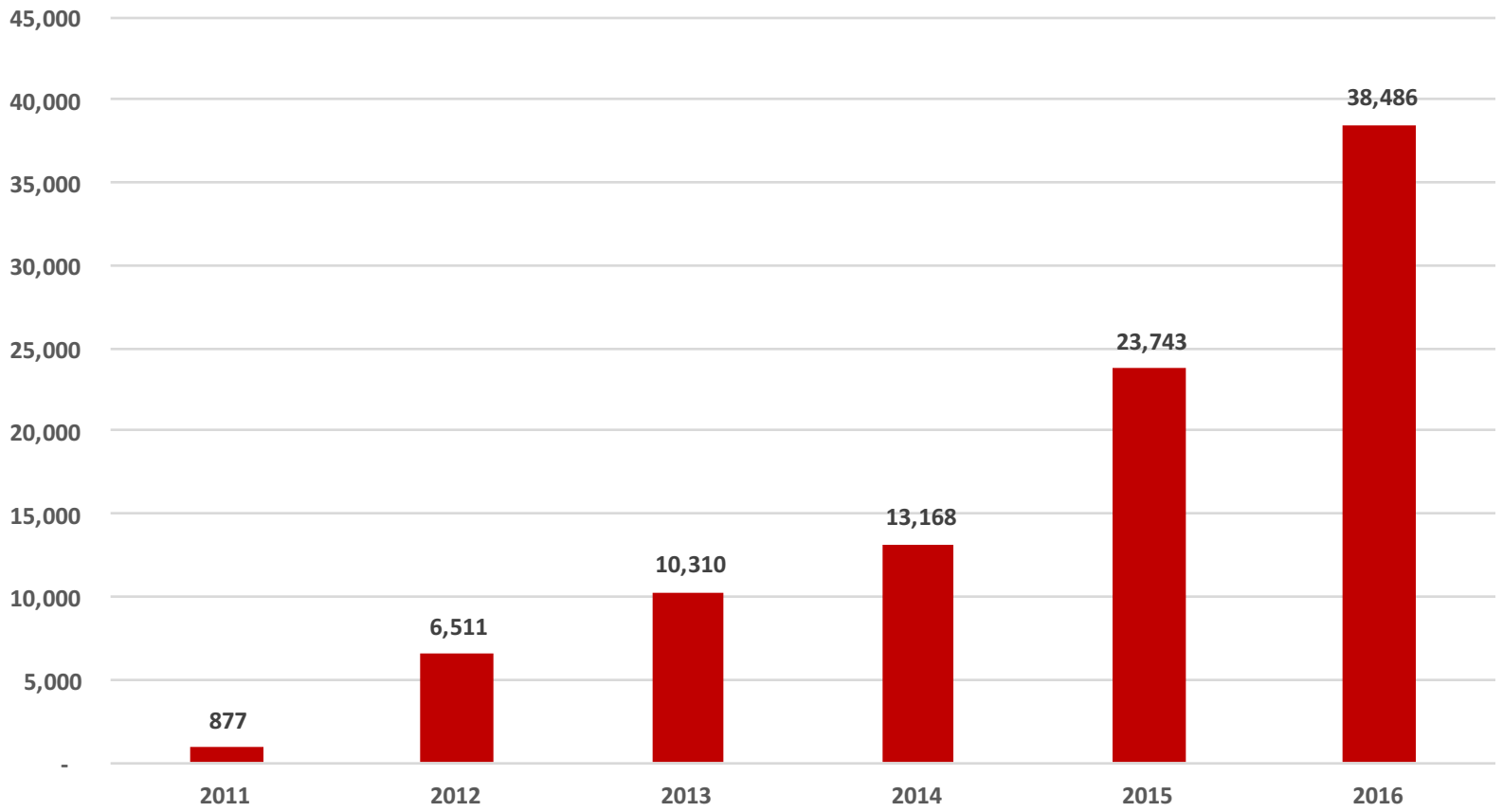
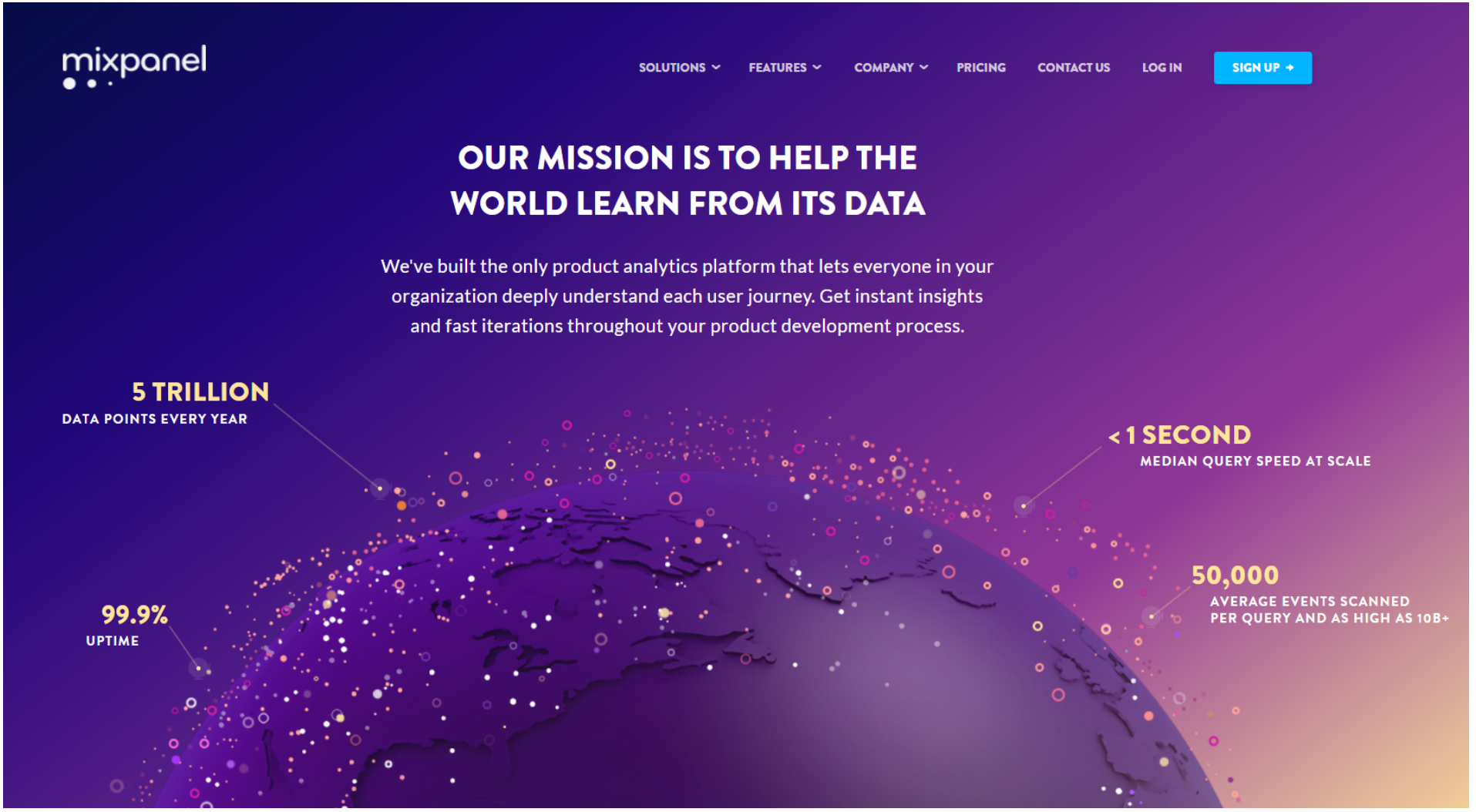
HEP total app downloads 2010-16



Google Analytics

Mixpanel


mixpanel
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OUR MISSION IS TO HELP THE WORLD LEARN FROM ITS DATA
We've built the only product analytics platform that lets everyone in your organization deeply understand each user journey. Get instant insights and fast iterations throughout your product development process.
5 TRILLION
DATA POINTS EVERY YEAR
< 1 SECOND
MEDIAN QUERY SPEED AT SCALE
99.9%
UPTIME
50,000
AVERAGE EVENTS SCANNED PER QUERY AND AS HIGH AS 10B+

MixPanel: Real Time View

Event	Time	Browser	City	Country	Distinct ID	Referring Domain
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Interaction	55 sec. ago	Chrome	Guadalajara	Mexico	15a80f15a460-04218ff00807ae-2...	—
Interaction	55 sec. ago	Chrome	Guadalajara	Mexico	15a80f15a460-04218ff00807ae-2...	—
Co-drug	58 sec. ago	Chrome	Guadalajara	Mexico	15a80f15a460-04218ff00807ae-2...	—
Co-drug	1 min. ago	Internet Explorer	Winnipeg	Canada	158405f26dd28d-0338e6e68c07b...	—
Interaction	1 min. ago	Internet Explorer	Winnipeg	Canada	158405f26dd28d-0338e6e68c07b...	—
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Co-drug	1 min. ago	Internet Explorer	Winnipeg	Canada	158405f26dd28d-0338e6e68c07b...	—
Interaction	1 min. ago	Internet Explorer	Odessa	United States	15632599b3b16-0058f6ccc3997e-...	hep-druginteractions.org
Interaction	24 sec. ago	Internet Explorer	Islington	United Kingdom	15b1089edac6a4-0abbe778ad2c9...	www.hiv-druginteractions.org
Interaction	24 sec. ago	Internet Explorer	Islington	United Kingdom	15b1089edac6a4-0abbe778ad2c9...	www.hiv-druginteractions.org
Co-drug	24 sec. ago	Internet Explorer	Islington	United Kingdom	15b1089edac6a4-0abbe778ad2c9...	www.hiv-druginteractions.org
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Interaction	52 sec. ago	Internet Explorer	Mexico City	Mexico	1540c5b33b92e1-0df552287ed96...	www.hiv-druginteractions.org
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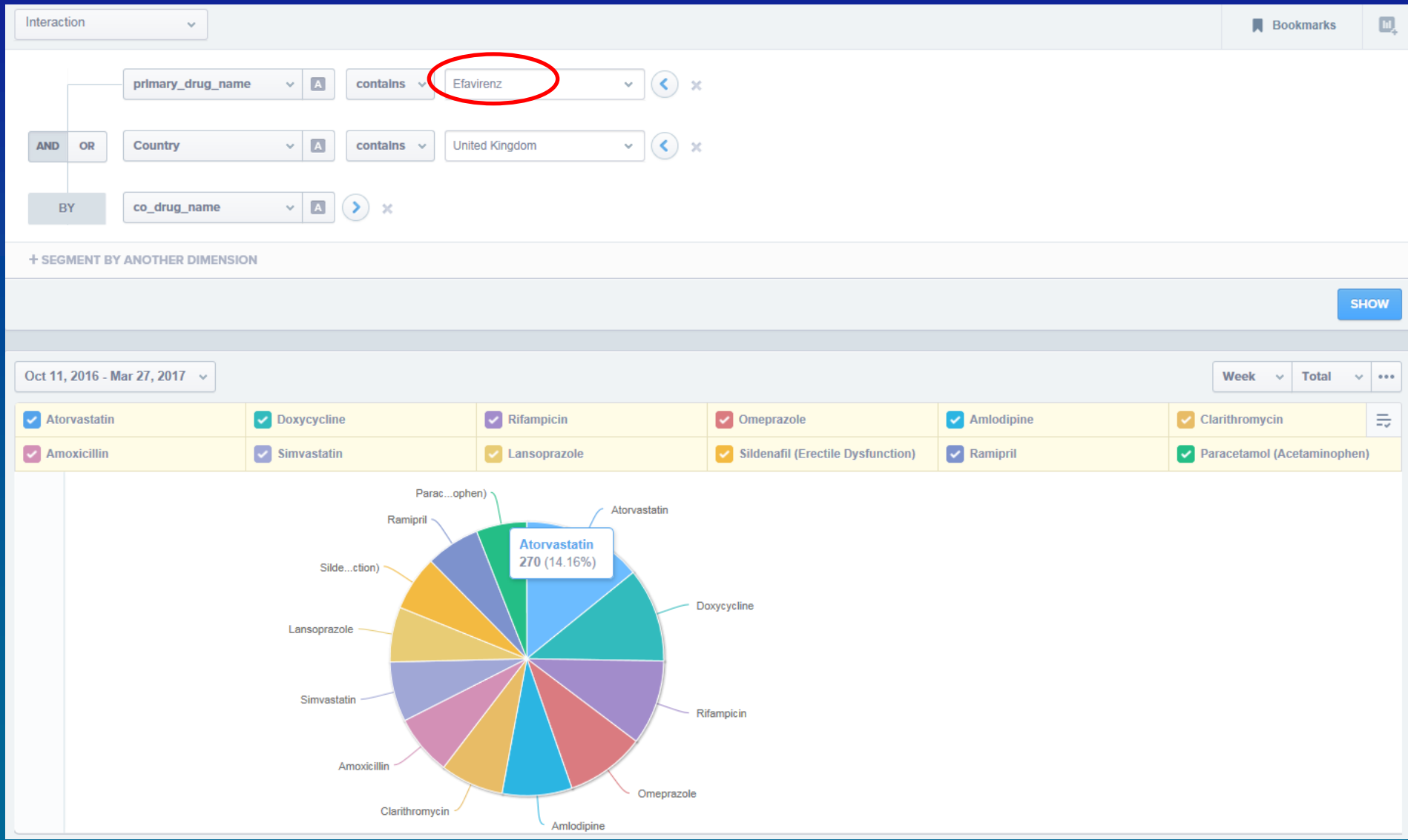
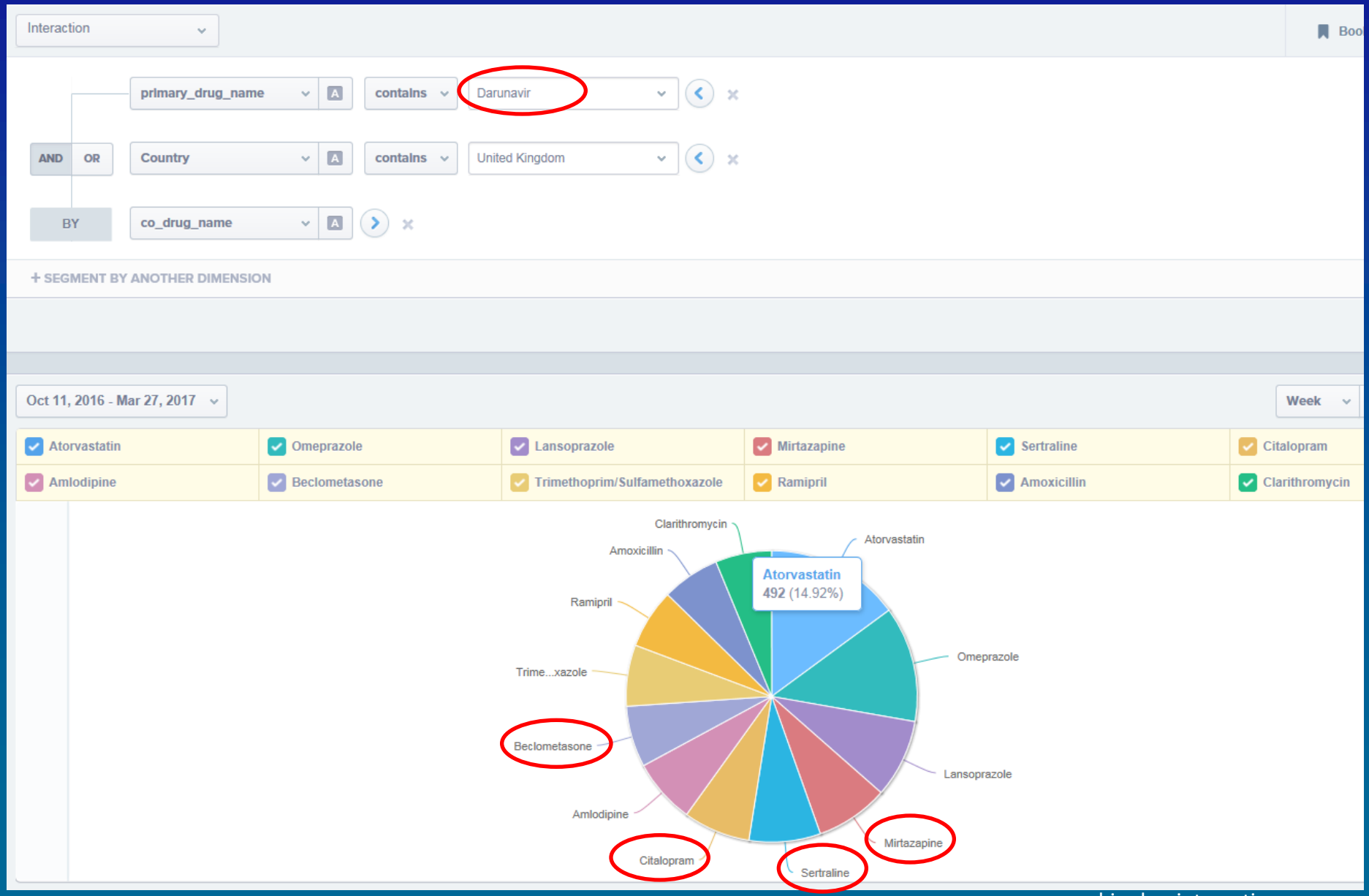
MixPanel: Top Co-Med Searches



MixPanel: Top Co-Med Searches



MixPanel – Top Co-med Searches: UK

Amlodipine
Atorvastatin
Ramipril
Simvastatin
Sidenafil

Omeprazole
Lansoprazole

Doxycycline
Rifampicin
Amoxicillin
Clarithromycin

Mirtazipine
Sertraline
Citalopram

Expansion of the interaction classification to include "yellow".

Tuesday 28 February 2017

We have recently expanded our interaction classification to include a new 'yellow' classification. In contrast to the existing '**amber**' interactions, which are **'potentially clinically significant and likely to require additional monitoring, alteration of drug dosage or timing of administration'**, the new **yellow** classification is for **'potential interactions likely to be of weak intensity where additional action/monitoring or drug dosage adjustment is unlikely to be required**'.

Examples with 3D* Regimen

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected

	OBV/PTV/r + DSV
Codeine	⚠
Sertraline	⚠
Tramadol	⚠

*Ombitasvir/Paritaprevir/ritonavir + Dasabuvir

Other Ongoing Projects

1. Translation

2. Linking of DDI database to other platforms/ systems, ie electronic prescribing, patient-focussed apps etc

3. Charts and Educational Resources

Chelsea and Westminster Hospital NHS NHS Foundation Trust | University of Liverpool | Royal Free London NHS NHS Foundation Trust

Switching to Rezolsta®/Prezcobix® (darunavir+cobicistat) or Evotaz® (atazanavir+cobicistat)

- Rezolsta/Prezcobix and Evotaz are once daily fixed dose combinations (FDCs) of darunavir (DRV) 800 mg with cobicistat 150 mg, and atazanavir (ATV) 300 mg with cobicistat 150 mg respectively, and are indicated in combination with other antiretroviral medicinal products for the treatment HIV-1 infection in adults aged 18 years or older*.
- There are clinical differences between ritonavir (r) and cobicistat boosted protease inhibitors (PIs) which need to be considered prior to switch:
  - Cobicistat's drug interactions differ in that, unlike ritonavir, cobicistat does not induce glucuronidation (UGT1A1) or some CYP enzymes. Consequently, switching from PI/r to PI/cobicistat may increase levels of some drugs metabolised via these routes and require monitoring and/or dose modification (see table). Alternatively, consider remaining on ritonavir-boosted PI.
  - Cobicistat decreases estimated creatinine clearance by average 10 ml/min due to inhibition of tubular secretion of creatinine. This does not affect the actual glomerular filtration rate (GFR).
- Although bioequivalent to DRV+r 800+100 mg, DRV Cmin reduces by ~25-30% with cobicistat, but remains above the IC50 for DRV wild type virus. This may be relevant for some cohorts.
- The guidance below addresses key differences when switching from DRV+r or ATV+r to the FDCs and should be used in addition to the Product Labels and www.hiv-druginteractions.org.

Darunavir+ritonavir to Rezolsta/Prezcobix

Rezolsta/Prezcobix is NOT RECOMMENDED* if:

- Patient requires DRV 600 mg twice daily.
- Taking any of the following, which are not recommend with Rezolsta/Prezcobix but may be used with DRV+r (with dose adjustment to twice daily for some drugs):

ARVs:	Anti-convulsants:	Other:
Efavirenz	Carbamazepine	Bosentan
Etravirine	Phenobarbital	OBV/PTV/r ± DSV (AbbVie "2D/3D")*†
Nevirapine	Phenytoin	

- There are any DRV resistance associated mutations.
- eGFR <70 ml/min when co-administered with medicines that require dose adjustment based on renal function (e.g. tenofovir DF, lamivudine or emtricitabine).
- Patients aged <18 years where the safety and efficacy of Rezolsta/Prezcobix has not been established.

Rezolsta should be used with CAUTION* when:

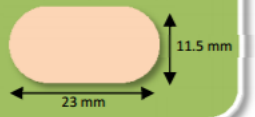
- There are concerns about lower DRV exposure (compared to DRV+r) such as:
  - Protease inhibitor monotherapy.
  - Pregnancy, including if actively planning to conceive.
  - Where DRV is part of a regimen for patients with HIV encephalopathy or in patients with CSF HIV RNA escape.
- Taking any other medicines, particularly those listed in the table. Conduct full medicines review.
- Any combinations other than 2 NRTIs + Rezolsta/Prezcobix as these have not been studied.

Specific counselling points for Rezolsta/Prezcobix:

- The recommended dosing regimen is one tablet of Rezolsta/Prezcobix taken once daily with food.
- Use up all Prezista (DRV) and ritonavir prior to switch to Rezolsta.
- There may be a requirement to switch away from the fixed dose combination when a generic darunavir become available.

Patient factors for Rezolsta/Prezcobix:

- The Rezolsta/Prezcobix tablet is larger than other ARVs and may not be acceptable to some. Ensure the patient has seen the tablet prior to leaving clinic.



Atazanavir+ritonavir to Evotaz

Evotaz is NOT RECOMMENDED* if:

- Patient requires ATV 400 mg daily, with or without pharmacokinetic booster.
- Taking hormonal contraceptives, including those containing 30 µg of ethinylestradiol due to potential increase in estrogen exposure. Alternative forms of contraception (non-hormonal) should be considered.
- Taking any of the following, which are not recommend with Evotaz but may be used with ATV+r:

ARVs:	Anti-convulsants:	Other:
Efavirenz	Carbamazepine	Bosentan
Etravirine	Phenobarbital	Hormonal contraceptives
	Phenytoin	OBV/PTV/r ± DSV (AbbVie "2D/3D")*†

- There are any ATV resistance associated mutations.
- eGFR <70 ml/min when co-administered with medicines that require dose adjustment based on renal function (e.g. tenofovir DF, lamivudine or emtricitabine).
- Patients aged <18 years of age where the safety and efficacy of Evotaz has not been established.

Evotaz should be used with CAUTION* when:

- Pregnant, including if actively planning to conceive due to a lack of data.
- Taking any other medicines, particularly those listed in the table. Conduct full medicines review.
- Any combinations other than 2 NRTIs + Evotaz as these have not been studied.

Specific counselling points for Evotaz:

- The recommended dosing regimen is one tablet of Evotaz taken once daily with food.
- Use up all Reyataz (ATV) and ritonavir prior to switch to Evotaz.
- There may be a requirement to switch away from the fixed dose combination when a generic atazanavir becomes available.

*Consult Product Label for country-specific full indications, cautions, and contraindications.

† 2D = OBV/PTV/r (Viekirax®, Technivie®); 3D = OBV/PTV/r + DSV (Viekirax® + Exviera®, Holkira®, Viekira Pak®, Viekira XR®). Note, OBV/PTV/r ± DSV can be administered with DRV or ATV alone (i.e. without cobicistat or additional ritonavir).

Monitoring considerations for both Rezolsta/Prezcobix and Evotaz:

- Consider additional monitoring post switch for those with identified "cautions" or other clinical indications.
- Serum creatinine is expected to increase with a resulting reduction in eGFR of ~10 ml/min. Typically this plateaus after 4 weeks of cobicistat-based ART. If a further change in eGFR is observed, or other renal markers change, this should prompt review.

Educational Resources

- 3 modules (each of 10, 15 min lectures) on

  - Basic Drug Disposition and Pharmacokinetics
  - Pharmacology of Antiretrovirals
  - Pharmacology in Special Populations

Saye Khoo, David Back, Andrew Owen, Marco Siccardi, Marta Boffito, Catia Marzolini, David Burger

New Drugs 2017-

- ❑ Bictegravir (Ph 3)
- ❑ Cabotegravir (Ph 3)
- ❑ Doravarine (Ph 3)

- ❑ Glecaprevir/pibrentasvir (Ph 3)
- ❑ Voxilaprevir (Ph 3)
- ❑ Grazoprevir/ruzasvir/ uprifosbuvir (Ph2)

www.cancer-druginteractions.org

UNIVERSITY OF LIVERPOOL Radboudumc

Under Development

Combining the internationally recognised drug-drug interactions expertise of the University of Liverpool (UK) with the clinical pharmacology in oncology expertise of Radboud University Nijmegen (the Netherlands), the site will provide a world-leading DDI resource which will inform clinicians, pharmacists and patients about the potential for DDIs with anti-cancer agents.

Both an educational resource and a tool to support better prescribing, the website will improve quality of care and patient outcomes.

Interactions will be described using a simple “traffic light” classification

	Dasatinib	Erlotinib	Gefitinib	Imatinib	Lapatinib	Nilotinib	Pazopanib	Sunitinib
Dolutegravir	◆	◆	◆	◆	◆	◆	◆	◆
E/C/F/TAF	■	■	■	■	■	■	■	■
E/C/F/TDF	■	■	■	■	■	■	■	■
Maraviroc	■	◆	◆	■	■	■	■	◆
Raltegravir	◆	◆	◆	◆	◆	◆	◆	◆

The University of Liverpool has been providing drug-drug interaction information since 1999 and the format of this new site will be based on the existing websites for HIV and Hepatitis.

HIV Drug Interactions

HEP Drug Interactions

Email k.mcallister@liv.ac.uk to register interest in supporting or sponsoring the site today.

Google Images