Use of Hydrochlorothiazide in the United States Following Label Update About Skin Cancer Risk

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Disclosure

- **Conflict of Interest:** E.E. is currently an employee of IQVIA, a company that conducts research on behalf of pharmaceutical companies, including companies who develop products studied in this analysis. However, E.E. contributed to this work when she was employed by the U.S. FDA. The remaining authors report no conflict of interest.
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- **FDA Disclaimer:** The contents are those of the authors and do not necessarily represent the official views of, nor and endorsement, by FDA/HHS, or the U.S. Government.

Introduction

What is Hydrochlorothiazide (HCTZ)?

- **Class:** Thiazide diuretic
- **FDA approval**
  - First approved in September 1959
  - Indications[1]:
    - **Hypertension:** used alone or in combination with other antihypertensives
    - **Edema due to pathologic causes**: helps reduce fluid retention in conditions like congestive heart failure, liver cirrhosis, and kidney disorders

[1] FDA. Hydrochlorothiazide label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020504s026lbl.pdf

HCTZ in Hypertension Management

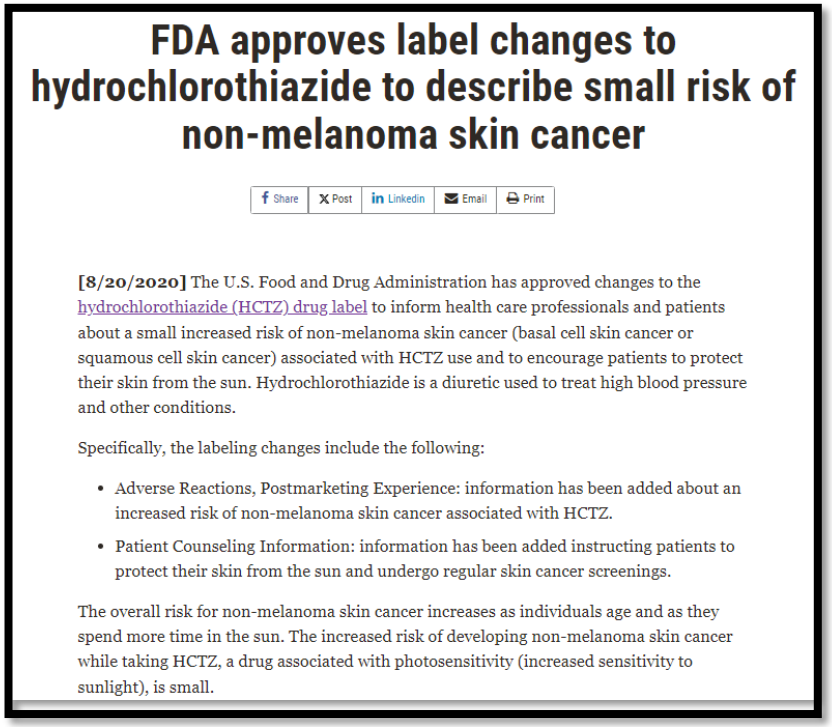
- Thiazide diuretics are recommended as **first-line** treatment for most patients[1,2]
  - Effective as monotherapy
  - Additive effect when used with other antihypertensives
  - Reduce hypertension-related morbidity and mortality

- HCTZ is the **most prescribed** thiazide diuretic in the U.S.[3]

[1] 2020 International Society of Hypertension Global Hypertension Practice Guidelines
[2] 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines
[3] Shah SJ et al. Am J Hypertens 2017.

FDA's Drug Safety Communication and Labeling Updates

- On 8/20/2020, FDA issued a Drug Safety Communication (DSC) with labeling updates to HCTZ
  - The increased risk of developing skin cancer while taking HCTZ is ***small*** (~ 1 additional case per 16,000 patients per year)
  - Treatment for non-melanoma skin cancer is typically local and successful, with ***very low rates of death***
  - Risk of uncontrolled blood pressure can be severe and include life-threatening heart attacks or stroke



FDA approves label changes to hydrochlorothiazide to describe small risk of non-melanoma skin cancer

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[8/20/2020] The U.S. Food and Drug Administration has approved changes to the hydrochlorothiazide (HCTZ) drug label to inform health care professionals and patients about a small increased risk of non-melanoma skin cancer (basal cell skin cancer or squamous cell skin cancer) associated with HCTZ use and to encourage patients to protect their skin from the sun. Hydrochlorothiazide is a diuretic used to treat high blood pressure and other conditions.

Specifically, the labeling changes include the following:

- Adverse Reactions, Postmarketing Experience: information has been added about an increased risk of non-melanoma skin cancer associated with HCTZ.
- Patient Counseling Information: information has been added instructing patients to protect their skin from the sun and undergo regular skin cancer screenings.

The overall risk for non-melanoma skin cancer increases as individuals age and as they spend more time in the sun. The increased risk of developing non-melanoma skin cancer while taking HCTZ, a drug associated with photosensitivity (increased sensitivity to sunlight), is small.

- DSC recommends patients
  - ***Continue*** HCTZ use unless otherwise instructed by healthcare providers
  - Adopt protective measures against skin cancer

Aim

- To evaluate the impact of the DSC and labeling updates on the dispensing patterns of HCTZ in the United States.

Methods

Study Design Overview

- Data sources (Jan 2017-Nov 2022):
  - Five Data Partners in Sentinel Distributed Database (SDD) – primary analyses
    - CVS Health (Aetna)
    - Carelon Research/Elevance Health
    - Duke - Center for Medicare and Medicaid Services - Medicare
    - Humana Healthcare Research
    - OptumInsight Life Sciences Inc.
  - Merative™ MarketScan® Research Databases – a secondary analysis

- Two cohorts
  1) Overall cohort: all patients with enrollment
  2) Skin cancer cohort: patients with a diagnosis of skin cancer

- Within each cohort, two analyses on monthly prevalence of HCTZ use
  1) Trend analysis
  2) Interrupted time series analysis

Trend Analysis on Monthly Prevalence

- Exposure of interest/Numerator
  - Use of any HCTZ-containing product
- Population/Denominator
  1) Limited denominator (primary): patients with active supply of any **thiazide diuretics**[1]
     - Evaluating within-class trends, i.e., from HCTZ - > non-HCTZ thiazides
  2) Full denominator (secondary): patients with active supply of any **antihypertensives**[2]
     - Evaluating between-class trends, i.e., from HCTZ - > non-thiazide antihypertensives
- Stratified analyses:
  - by HCTZ product type (monotherapy or combination therapy)
  - by patients' age group, sex, and race

[1] Thiazide diuretics include: HCTZ-containing product, chlorothiazide, bendroflumethiazide, and thiazide-like diuretics.
[2] Antihypertensives include: thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), Beta blocker, calcium channel blockers (CCB), loop diuretics, and potassium-sparing diuretics

Interrupted Time Series (ITS) Analysis

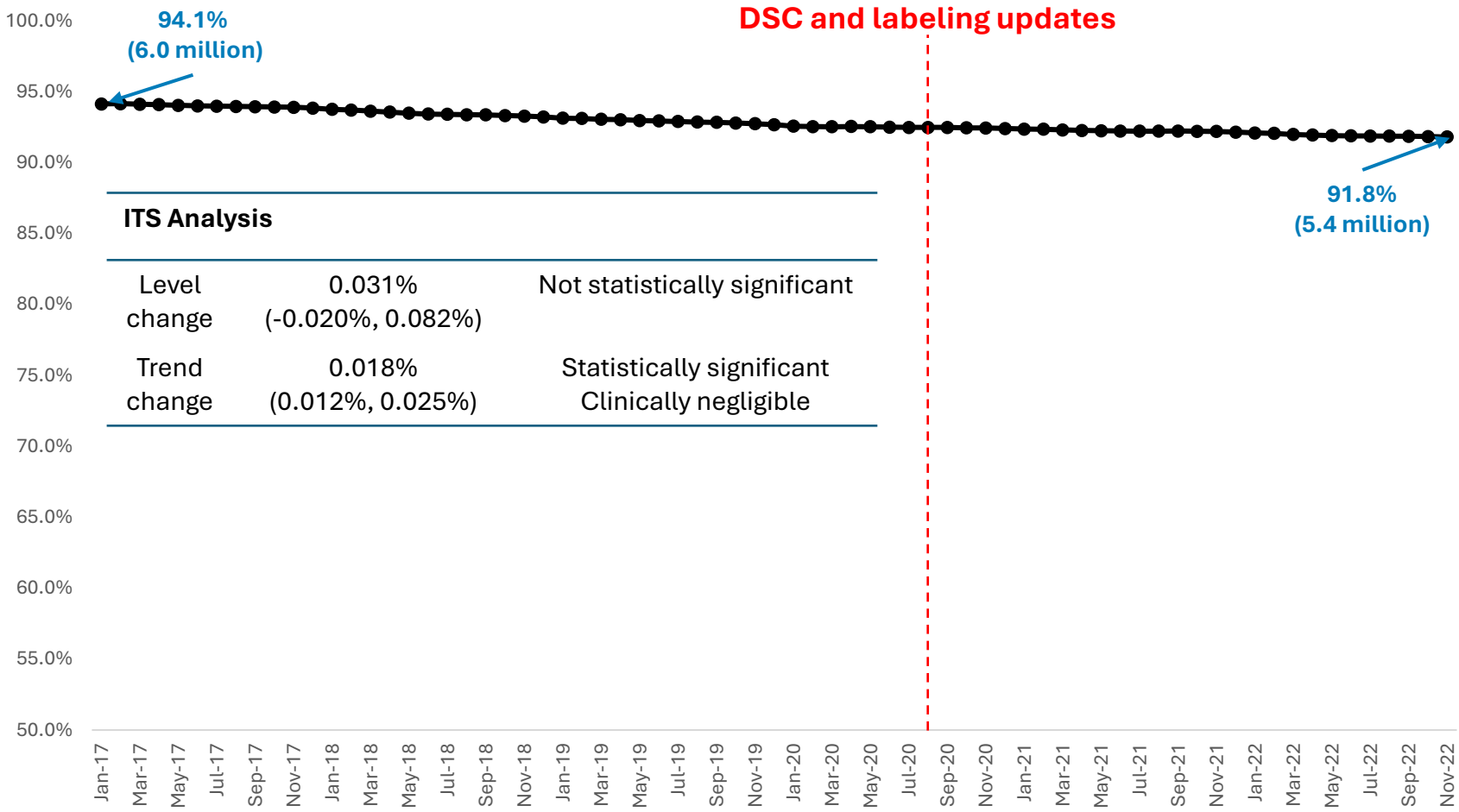
- Level change:
  - Prevalence change from Aug 2020 to Sept 2020
  - Indicates **immediate effect** of the DSC (issued on August 20,2020)

- Trend change:
  - Difference in the slopes of the trends before and after the DSC
  - Indicates **sustained effect** of the DSC

DSC=drug safety communication

Results 1: Overall Cohort

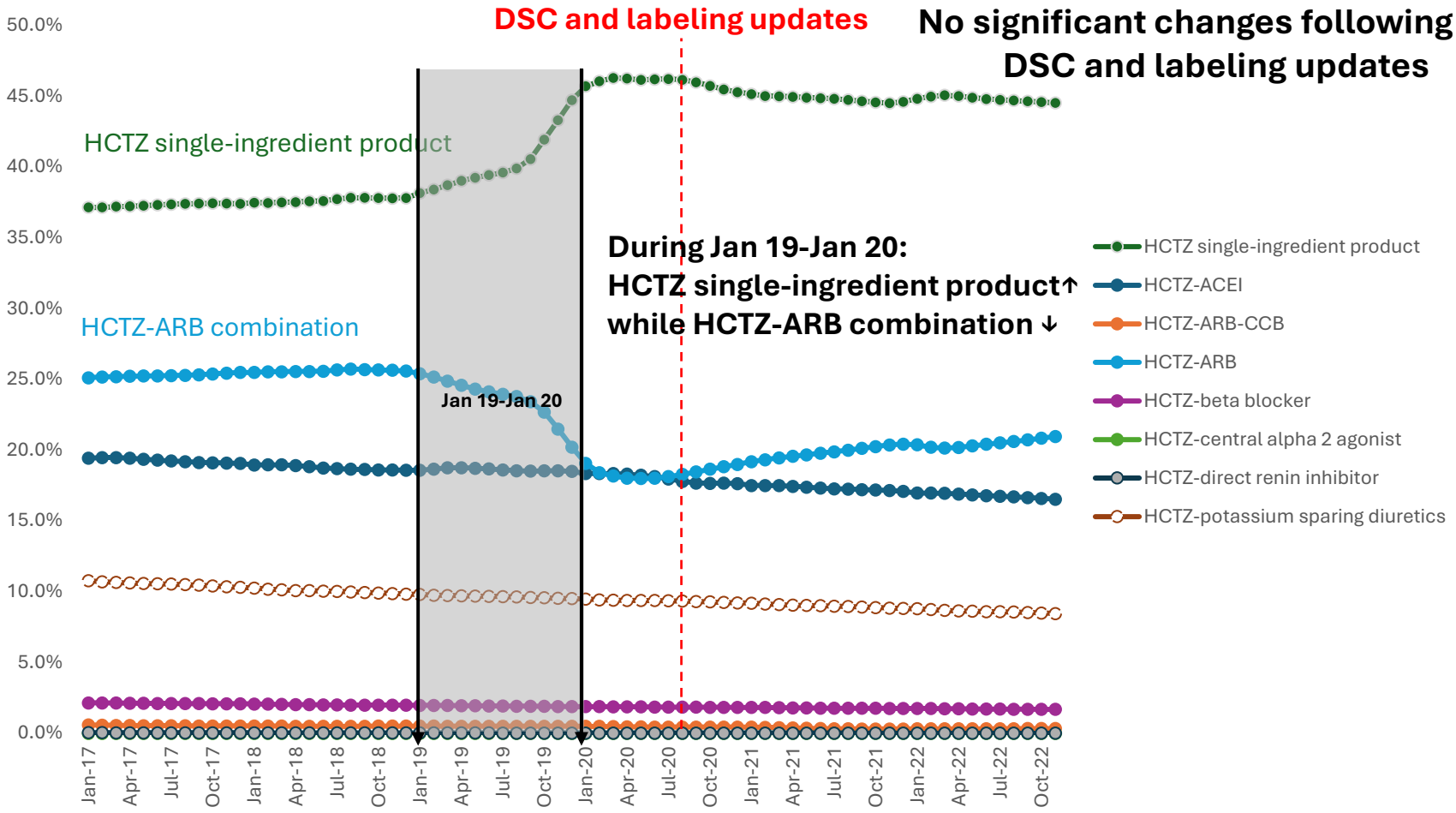
Trend of HCTZ Use Among Thiazide Users



ITS Analysis		
Level change	0.031% (-0.020%, 0.082%)	Not statistically significant
Trend change	0.018% (0.012%, 0.025%)	Statistically significant Clinically negligible

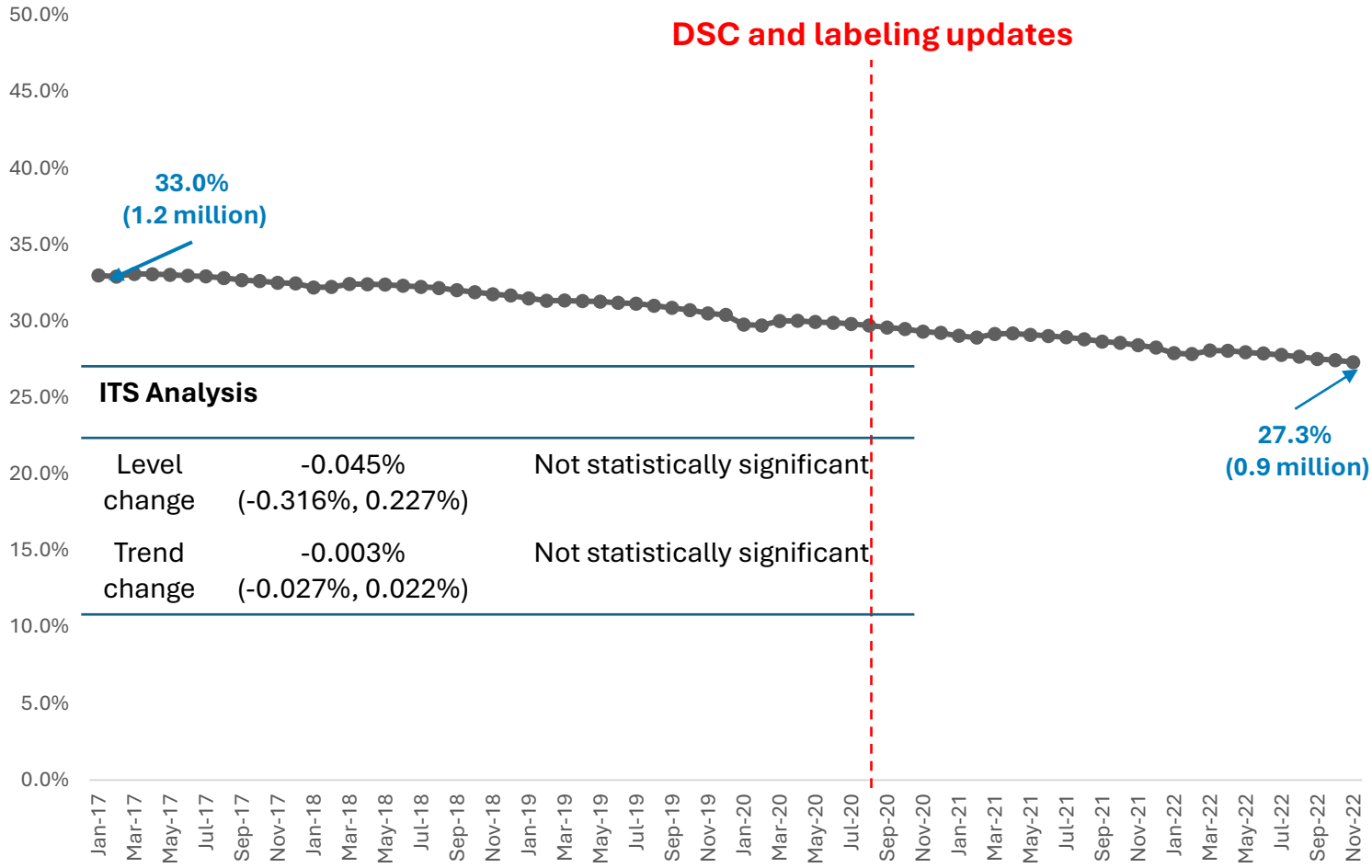
ITS=Interrupted times series; DSC=drug safety communication

Trend of HCTZ Use Among Thiazide Users, by HCTZ Product



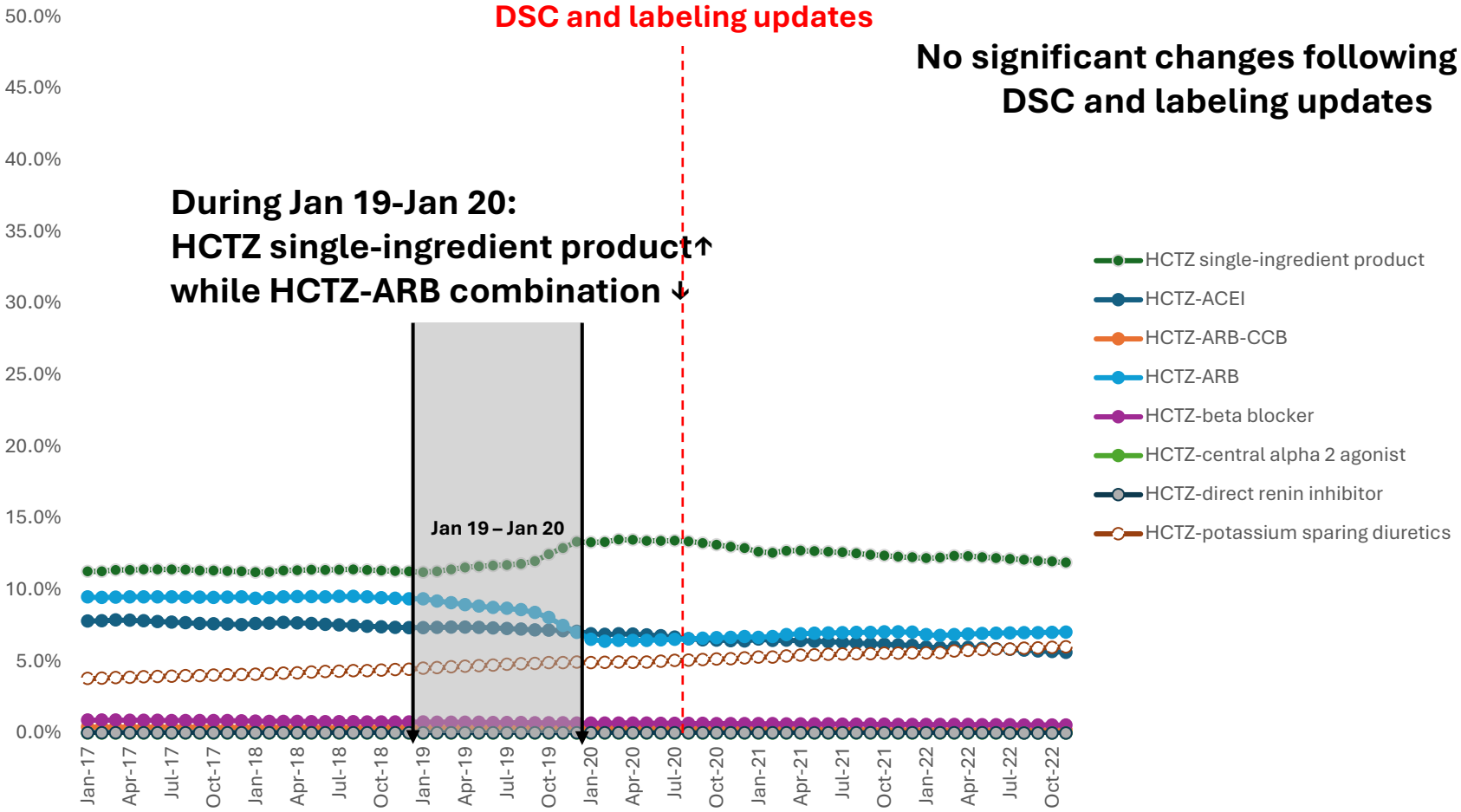
DSC=drug safety communication; ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin receptor blockers; CCB=calcium channel blockers.

Trend of HCTZ Use Among Antihypertensive Users*



*Using Merative™ MarketScan® Research Databases only
ITS=Interrupted times series; DSC=drug safety communication

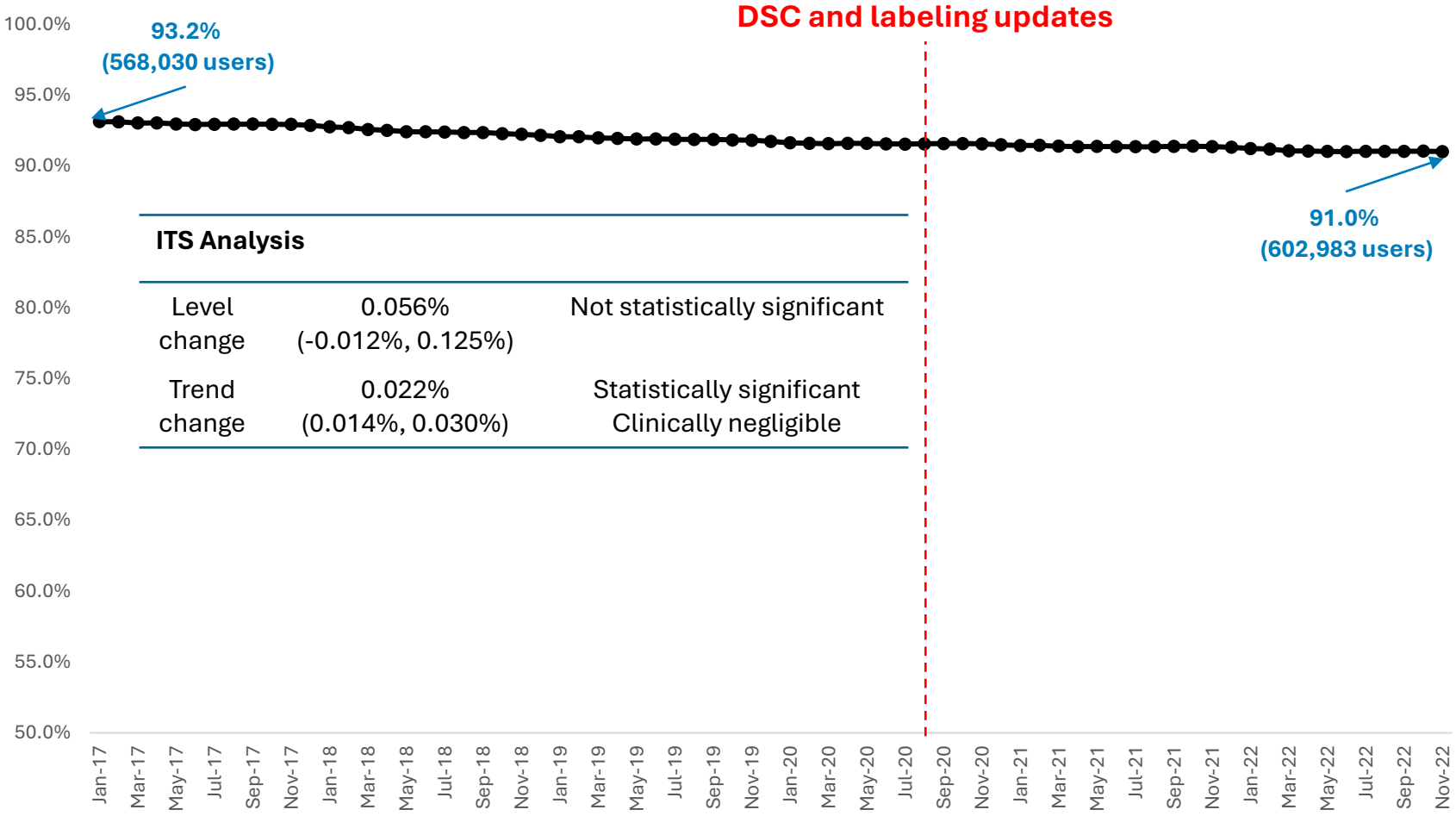
Trend of HCTZ Use Among Antihypertensive Users, by HCTZ Product



DSC=drug safety communication; ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin receptor blockers; CCB= calcium channel blockers.

Results 2: Skin Cancer Cohort

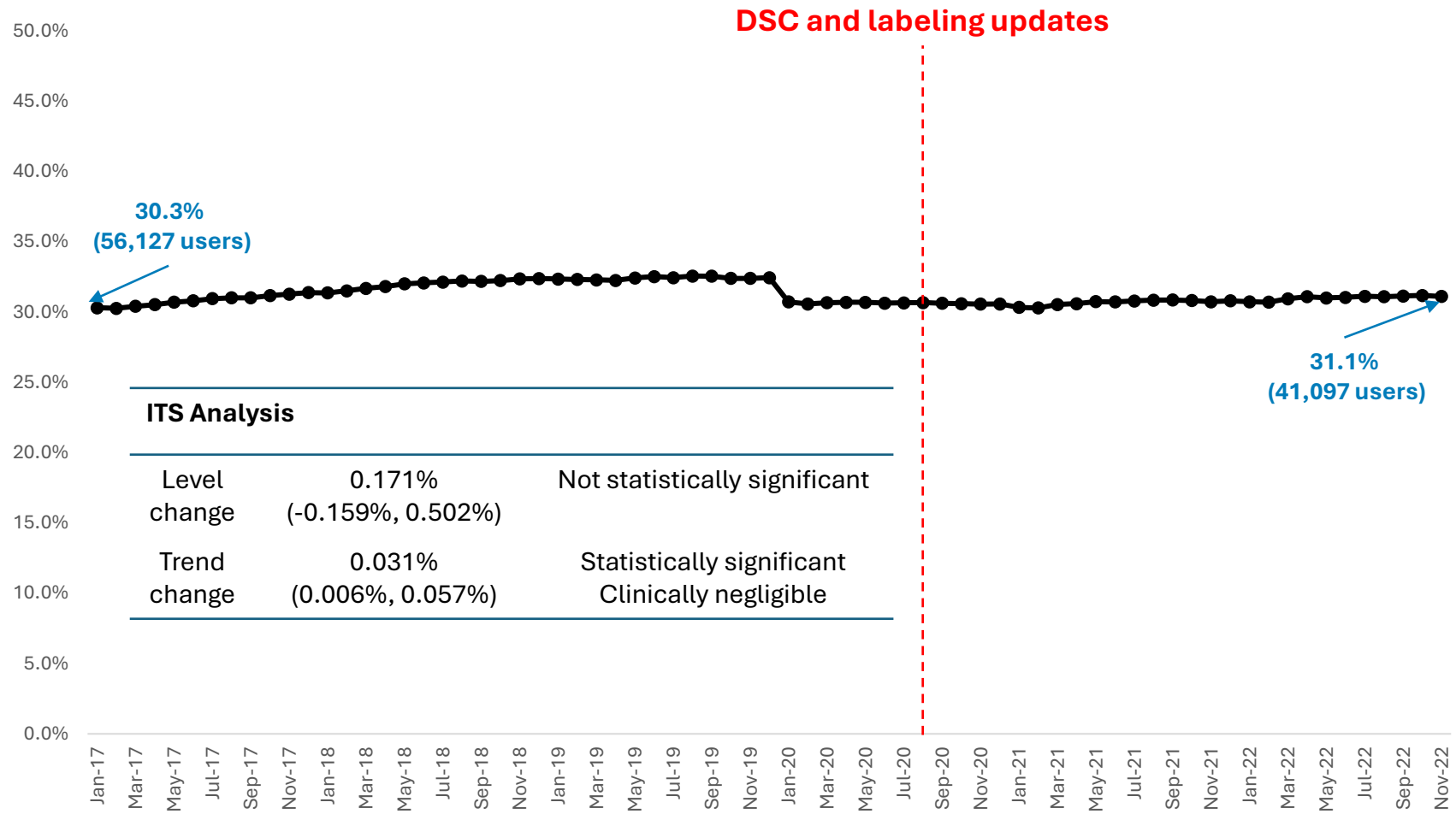
Trend of HCTZ Use Among Thiazide Users with Skin Cancer



ITS Analysis		
Level change	0.056% (-0.012%, 0.125%)	Not statistically significant
Trend change	0.022% (0.014%, 0.030%)	Statistically significant Clinically negligible

ITS=Interrupted times series; DSC=drug safety communication

Trend of HCTZ Use Among Antihypertensive Users with Skin Cancer*



*Using Merative™ MarketScan® Research Databases only
ITS=Interrupted times series; DSC=drug safety communication

Stratified Trends by Patient Demographics

- No significant change in HCTZ use following the DSC in any age, gender or race subgroups

Discussion

Main Findings

- We found NO clinically significant changes in HCTZ utilization following the DSC, among the overall population or those with a history of skin cancer.
  - Consistent across all HCTZ-containing products and across patients with various demographics
  - Expected and in line with the DSC recommendation on continuing HCTZ use

DSC=drug safety communication

Compared with Literature

ORIGINAL ARTICLE | Full Access

Use of hydrochlorothiazide in Denmark following publication of skin cancer risk findings

Anton Pottegård, Bodil Hammer Bech, Sidsel Arnspang Pedersen, Bo Christensen

First published: 26 August 2021 | https://doi.org/10.1002/pds.5350 | Citations: 4

- Danish study:[1] Prevalence of HCTZ use among antihypertensive users dropped from 12.7% in Jan 2017 to 7.2% in Sept 2020 (a relative drop of 43%)
  - likely due to dissemination of HCTZ's skin cancer risk findings from two Danish studies
- Our study: Prevalence of HCTZ use among antihypertensive users dropped slightly from 33.0% in Jan 2017 to 29.6% in Sept 2020 (a relative drop of 10%)
  - minimal impact of published studies on US dispensing patterns

[1] Pottegård et al. Pharmacoepidemiol Drug Saf. 2021

Compared with Literature CONT.

	Our Study	Danish Study
Intervention of interest	FDA's DSC and labeling updates	Dissemination of HCTZ's skin cancer risks findings
Potential reason 1 for difference	The DSC explicitly recommended against discontinuing HCTZ solely due to its skin cancer risk	HCTZ's skin cancer risks findings received considerable lay media attention - > surge in patient consultations with prescribers
Potential reason 2 for difference	In U.S., thiazide users predominantly used HCTZ	In Europe, bendroflumethiazide was more commonly used,[1] offering a compelling alternative to HCTZ

[1] McNally et al. Br J Clin Pharmacol. 2019

Other Findings

- Trend shift from HCTZ-ARB combination products to single-ingredient HCTZ in Jan 2019-Jan 2020
  - Partially coincided with multiple recalls of ARB-containing products including HCTZ-ARB combinations during Jul 2018-Nov 2019
  - The recall was due to impurities in these products

ARB=Angiotensin receptor blockers

Limitations

- Potential misclassification of medication use
  - Missing out-of-pocket purchase
  - Unable to verify adherence

- Potential misclassification of skin cancer patients
  - Potential underdiagnosis of skin cancer
  - Potential under-capture of skin cancer diagnoses through diagnosis codes

Acknowledgement

Many thanks are due to those who participated in this project and Sentinel Data Partners who provided data used in the analysis:

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- Carelon Research/Elevance Health, Wilmington, DE
- Duke University School of Medicine, Department of Population Health Sciences, Durham, NC, through the Centers for Medicare and Medicaid Services which provided data
- Humana Healthcare Research Inc., Louisville, KY
- OptumInsight Life Sciences Inc., Boston, MA

Conclusion

- We did NOT observe any clinically significant change in HCTZ use following the DSC and labeling updates regarding its skin cancer risk, both among the overall cohort and those with a history of skin cancer, in a U.S. population.
- Our findings were in line with the DSC recommendation.

DSC=drug safety communication

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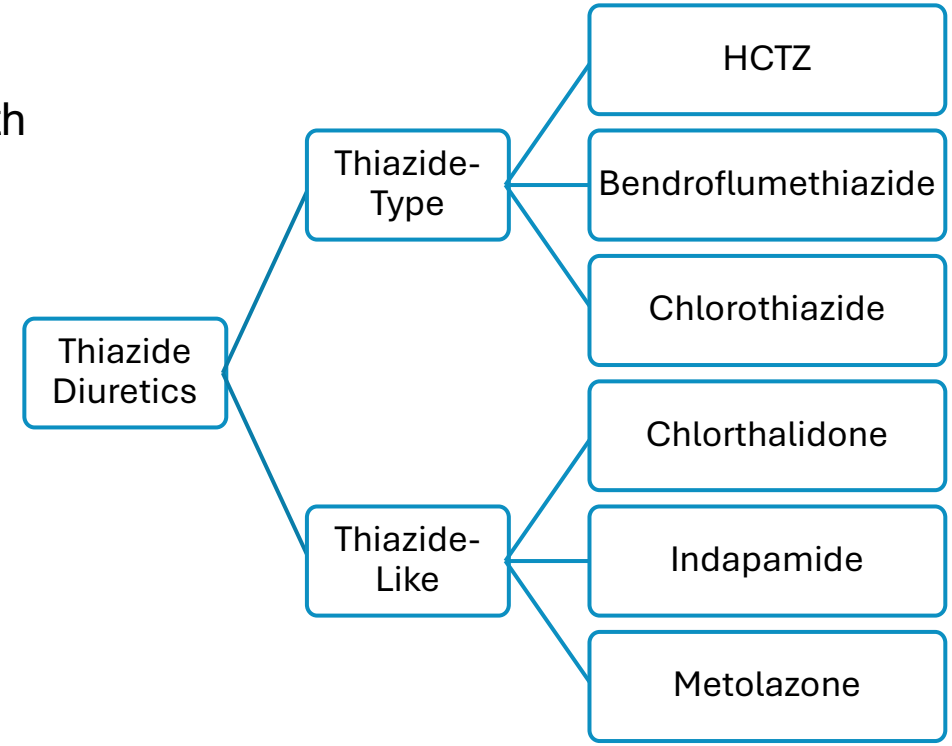
Q & A

Backup Slides

Thiazide Diuretics in Hypertension Management

- Recommended as first-line treatment for most patients[1,2]
  - Effective as monotherapy
  - Additive effect when used with other antihypertensives
  - Reduce hypertension-related morbidity and mortality
- HCTZ is the most prescribed thiazide diuretics in the U.S.[3]

Fig. Thiazide diuretics currently available in the U.S.



[1] 2020 International Society of Hypertension Global Hypertension Practice Guidelines
[2] 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines
[3] Shah SJ et al. Am J Hypertens 2017.

HCTZ and Skin Cancer Risk

- **Biologic mechanism:** HCTZ enhances DNA damage induced by UV radiation - > increases the risk of skin cancer
- **Evidence in literature:**
  - In three case-control studies using Danish registries[1-3]
    - HCTZ use was associated with increased risk of squamous cell carcinoma (SCC) of the lip, SCC and basal cell carcinoma of the skin, and potentially certain melanoma subtypes.
    - No increased risk with other diuretics or antihypertensive medications
  - In a Sentinel study[4]
    - HCTZ use was associated with 1.04-fold increased risk of SCC in the overall population

    - > approximately 1 additional case per 16,000 patients per year

[1] Pottegård et al. J Intern Med. 2017
[2] Pedersen et al. J Am Acad Dermatol. 2018
[3] Pottegård et al. JAMA Intern Med. 2018
[4] Eworuke et al. JNCI Cancer Spectr. 2021

Interrupted Time Series (ITS) Analysis

$$Monthly\ HCTZ\ prevalence = b_0 + b_1T + b_2D + b_3P + E$$

- T is the number of months since the study start in Jan 2017
- D is a dummy variable indicating observation collected before or after the DSC
  - $D = 0$ for months before and in Aug 2020, $D = 1$ for months after Aug 2020
- P is the number of months since the DSC in Aug 2020
  - $P = 0$ for months before and in Aug 2020

Parameters of interest	Name	Interpretation
b_2	Level change	The prevalence change from Aug 2020 to Sept 2020; Indicates **immediate effect** occurred after the DSC
b_3	Trend change	Difference between the slopes of the trend before and after the DSC; indicates **sustained effect** of the DSC

- Significance level: two-sided P<0.05

DSC=drug safety communication

Sensitivity Analysis on ITS

- Including an anticipatory period for DSC and labeling updates to take effect
  - Anticipatory period: from 2 months before through 2 months after Aug 2020
- Only conducted for Limited Denominator analysis
- The results were consistent with the primary analysis without anticipatory period

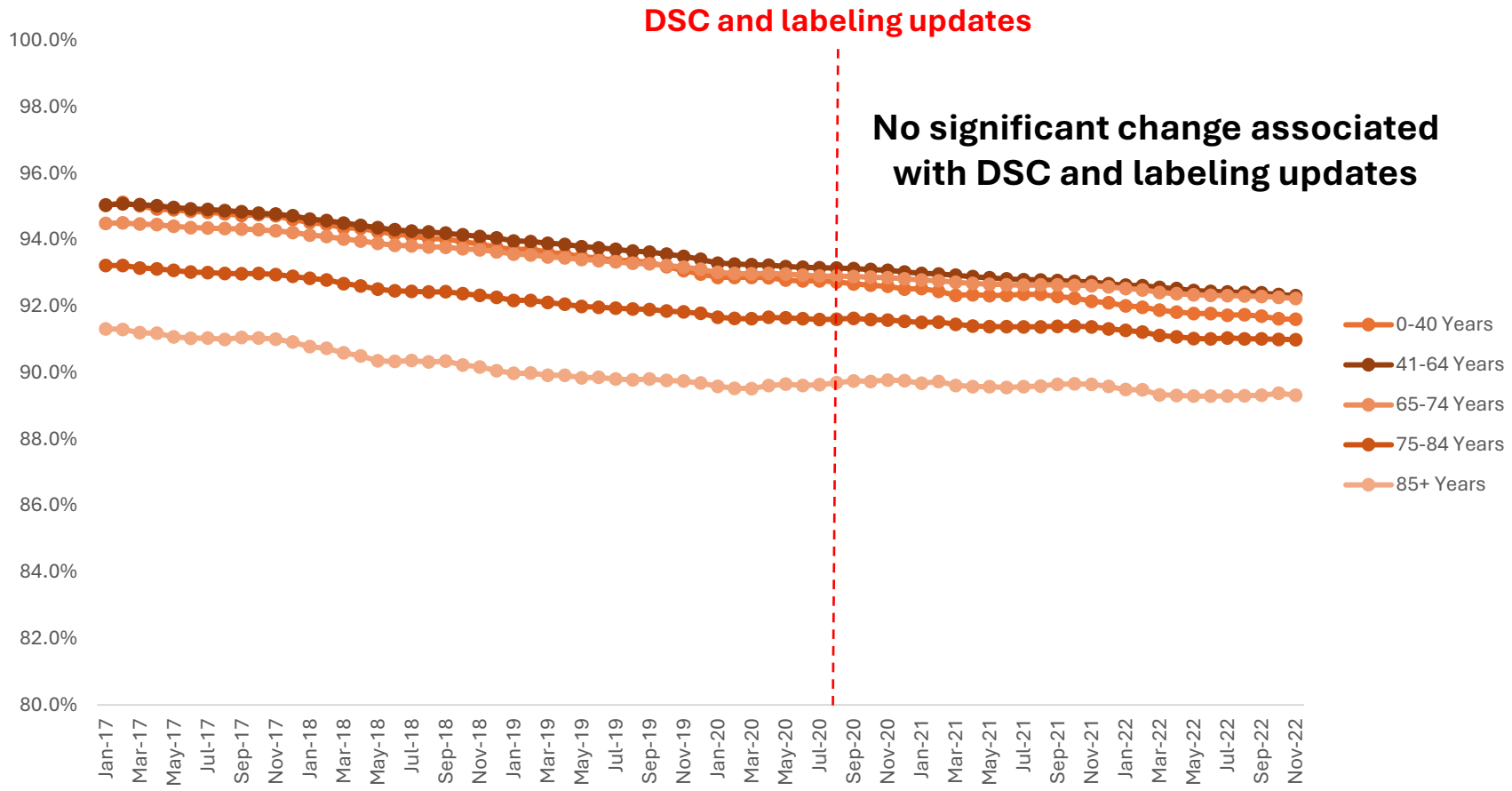
Sample Sizes Across the Years

Cohort	Denominator type	Data	# of enrollees in the cohort	#of patients in the denominator
Overall	Limited	SDD	144 million[a]	18 million[a]
Overall	Full	MarketScan	55 million[b]	10 million[b]
Skin Cancer	Limited	SDD	8 million[a]	1.8 million[a]
Skin Cancer	Full	MarketScan	1.1 million[b]	0.4 million[b]

[a] These numbers reflected the sample size using data from Jan 2017 to Apr 2023. We right truncated the data to Nov 2022 in the analyses due to potential incompleteness of data in the right tail.
[b] These numbers reflected the sample size using data from Jan 2017 to Dec 2022. We right truncated the data to Nov 2022 in the analyses due to potential incompleteness of data in the right tail.

SDD=Sentinel Distributed Database

Trend of HCTZ Use Among Thiazide Users, by Age Groups



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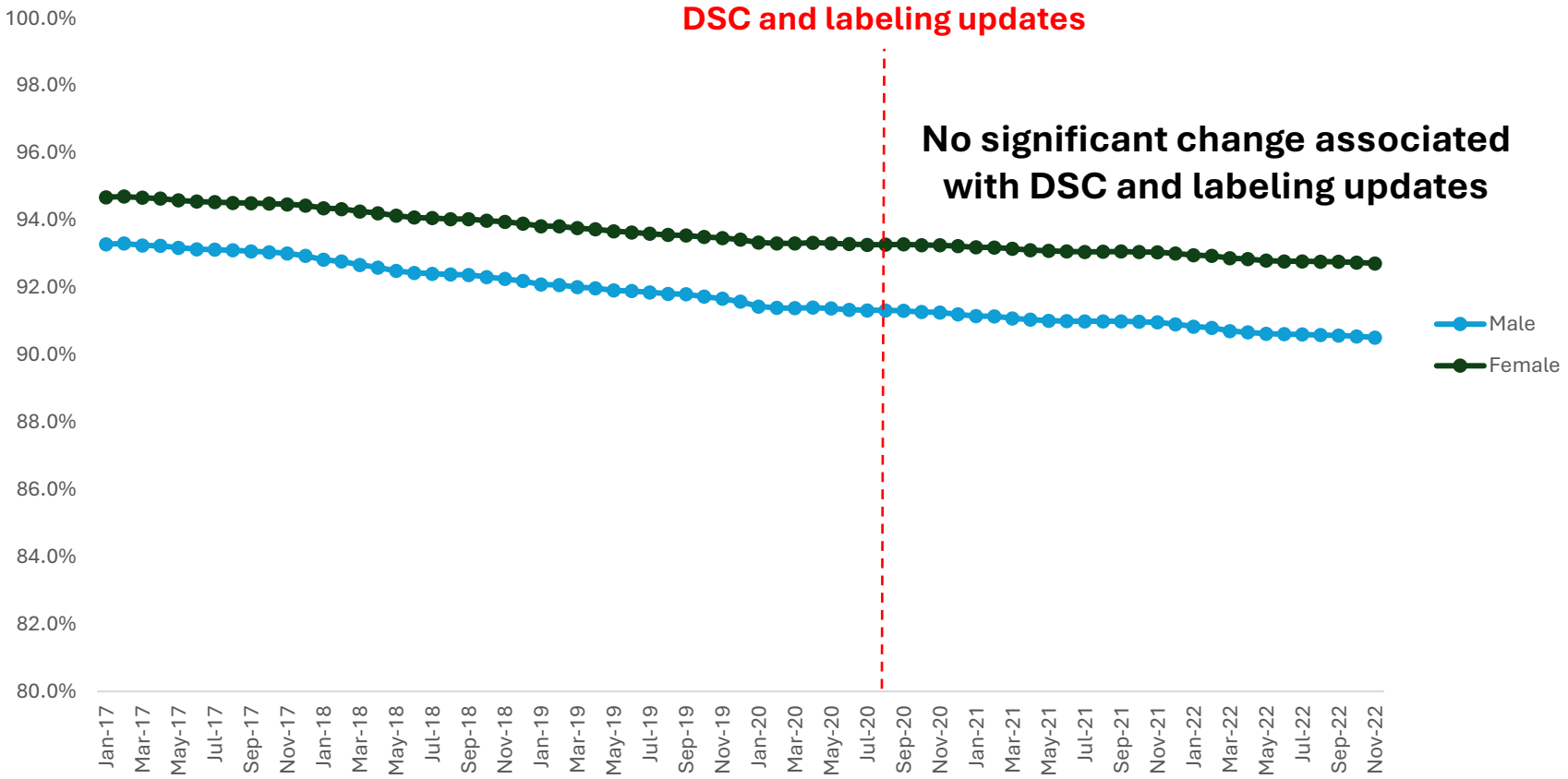
Trend of HCTZ Use Among Thiazide Users, by Sex



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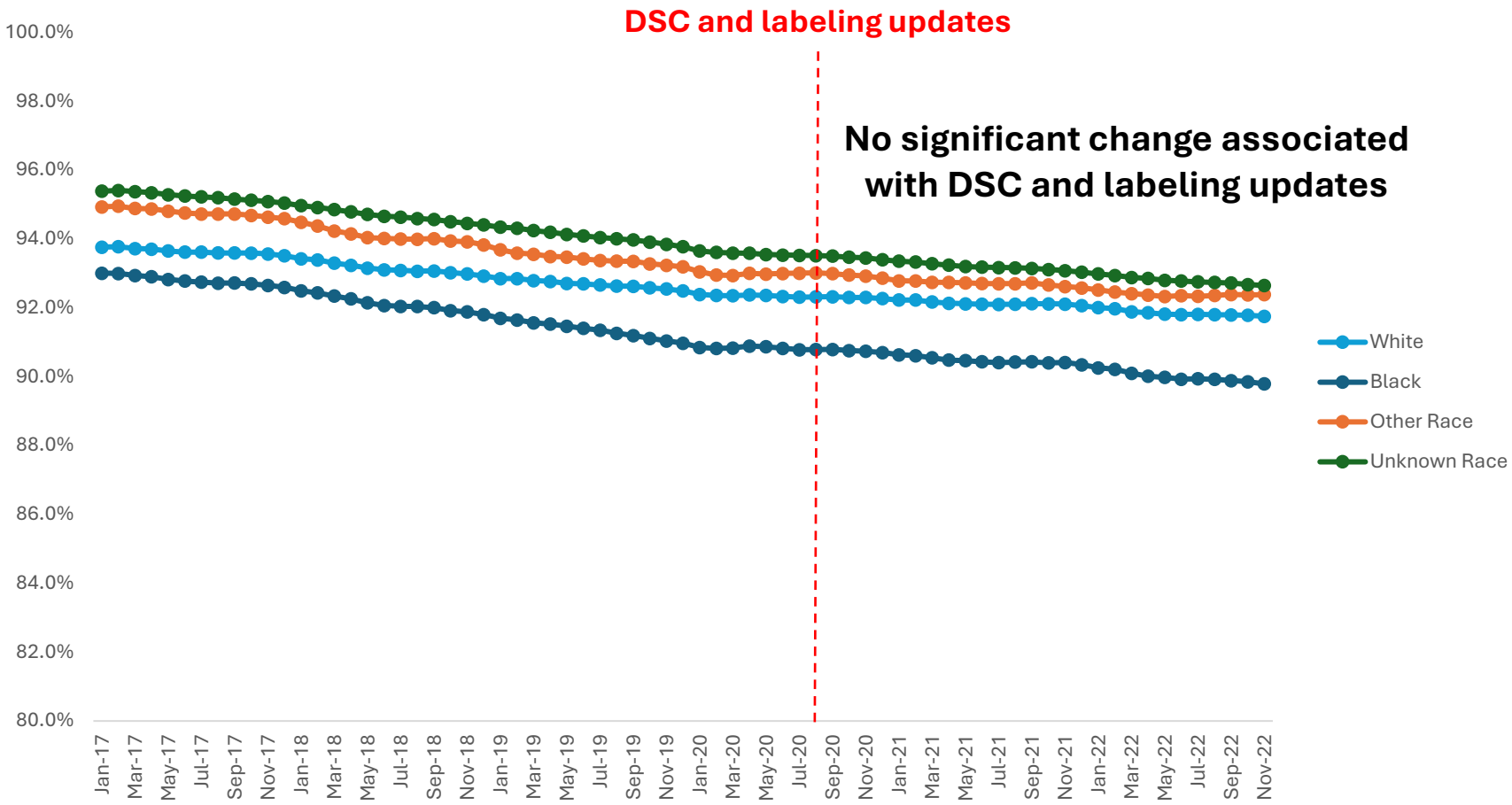
Trend of HCTZ Use Among Thiazide Users, by Race



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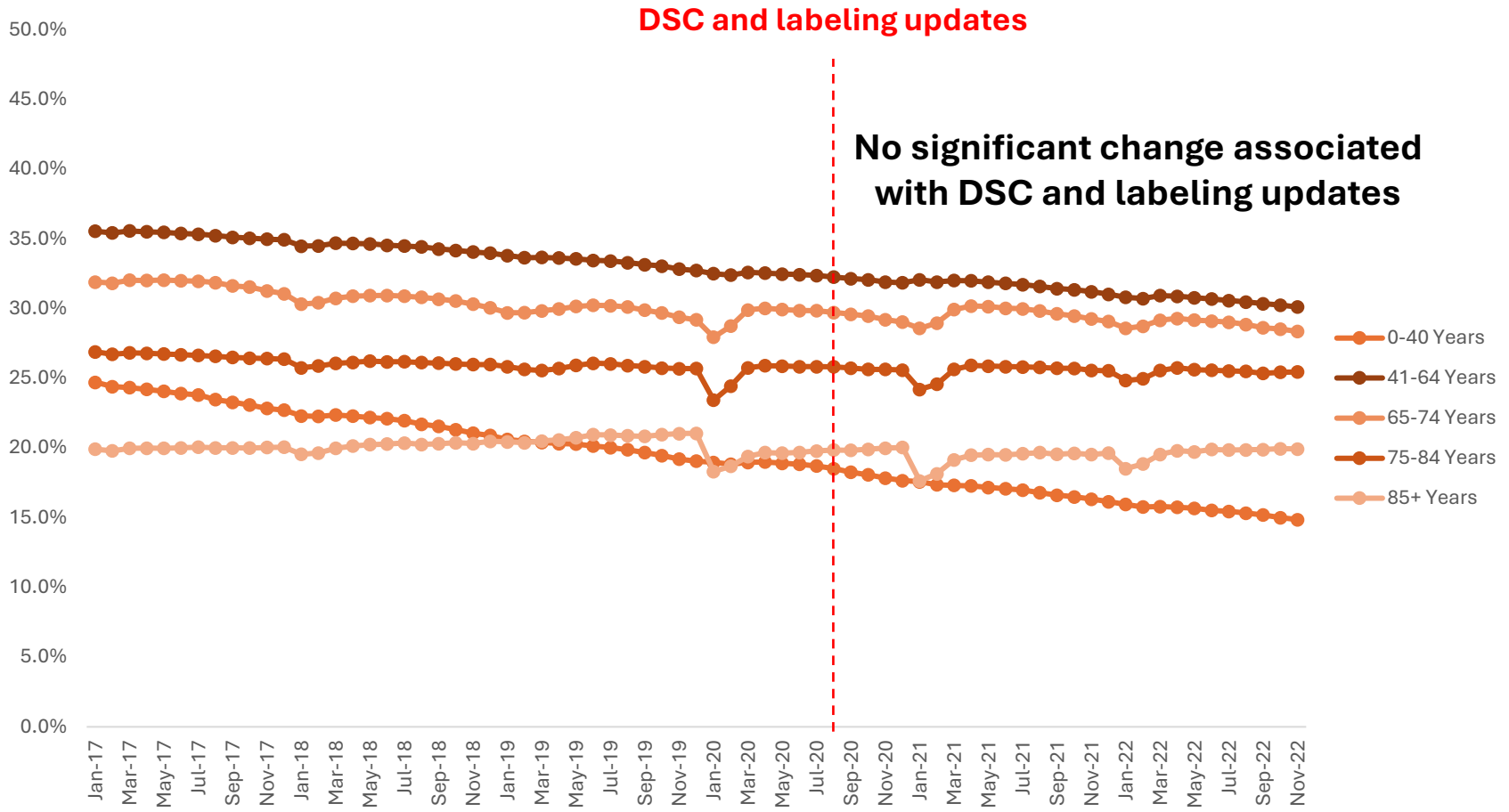
Trend of HCTZ Use Among Antihypertensive Users, by Age Groups



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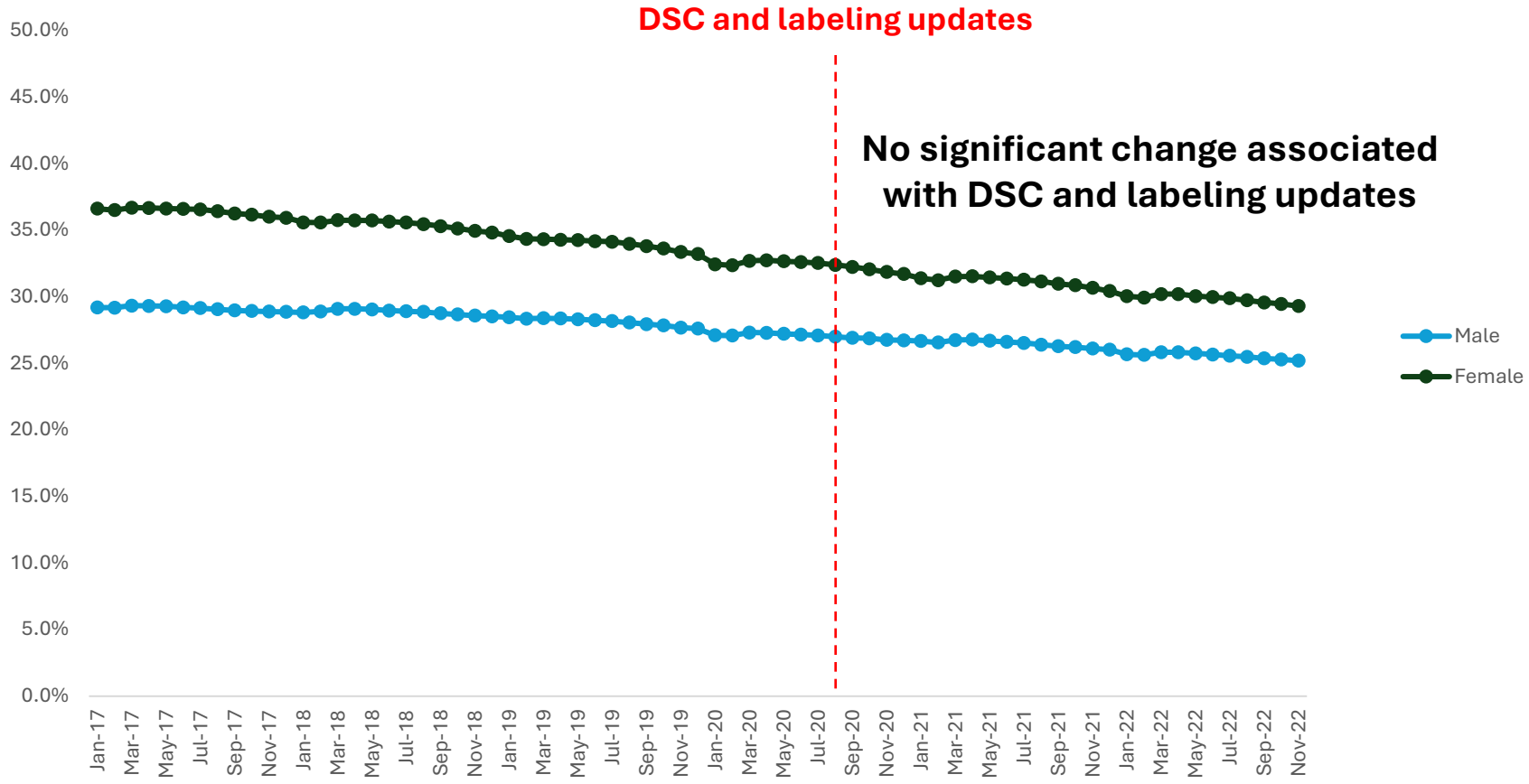
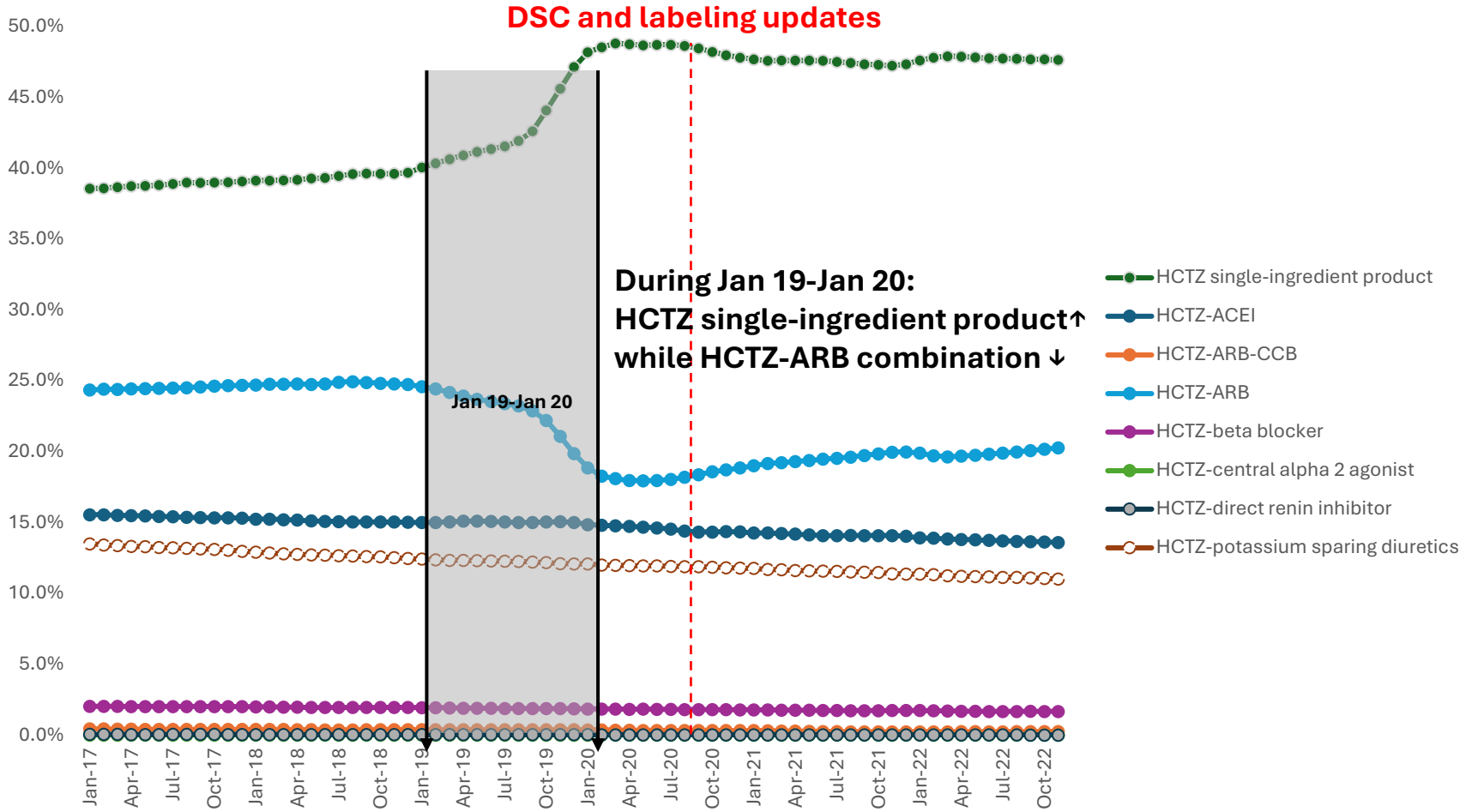


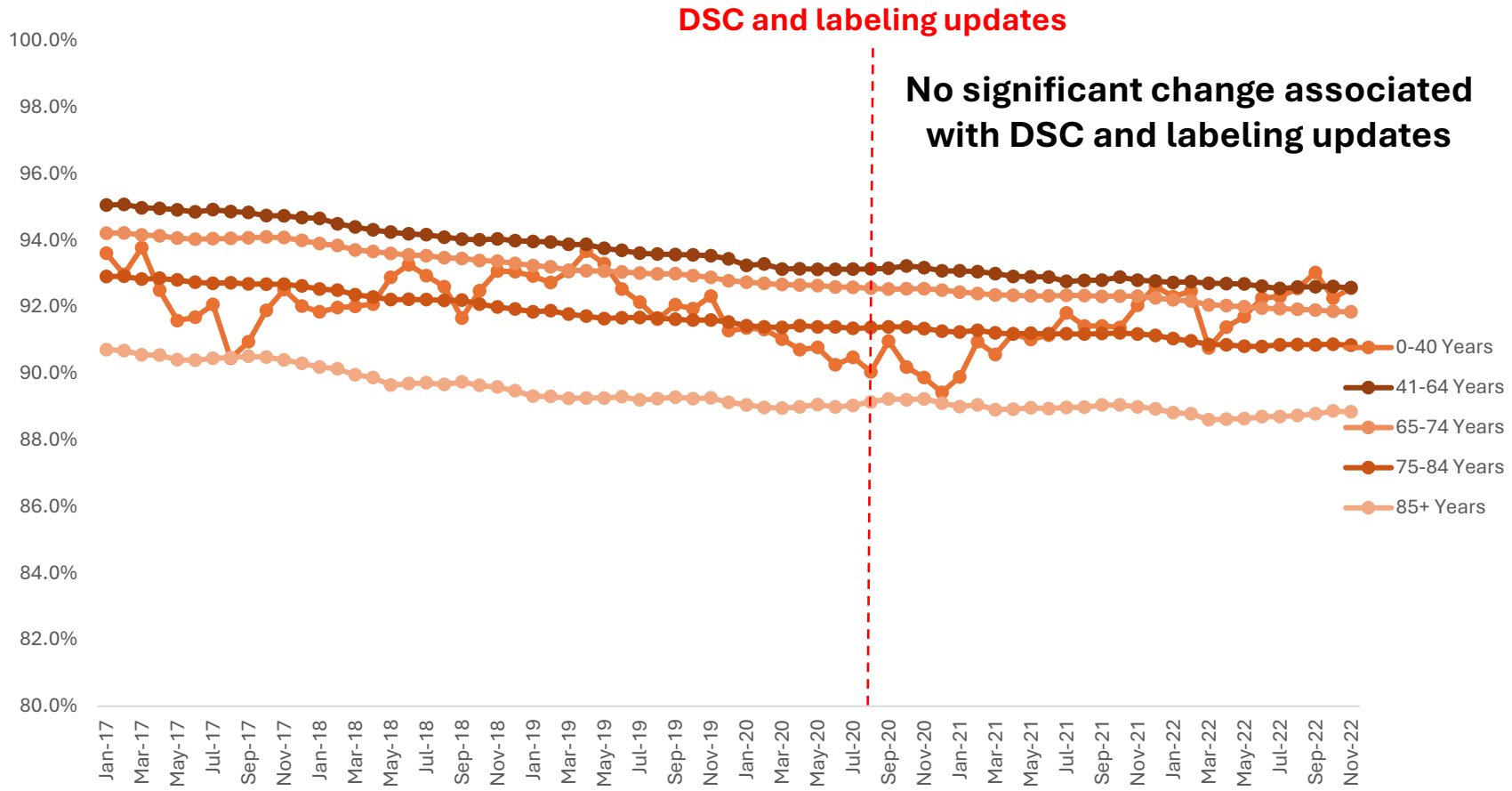
DSC=drug safety communication

Trend of HCTZ Use Among Thiazide Users with Skin Cancer, by HCTZ Product



DSC=drug safety communication; ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin receptor blockers; CCB=calcium channel blockers.

Trend of HCTZ Use Among Thiazide Users with Skin Cancer, by Age Groups



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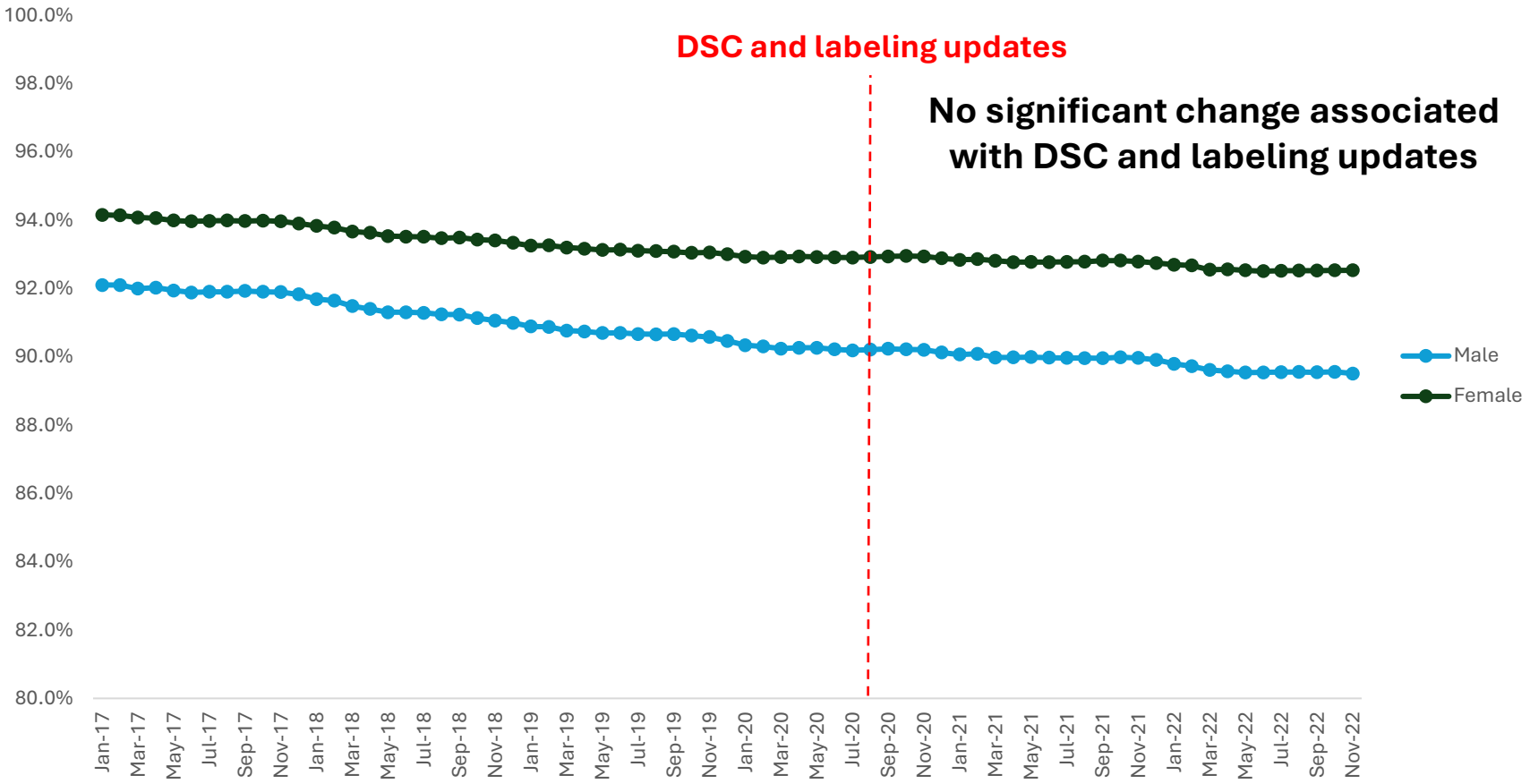
Trend of HCTZ Use Among Thiazide Users with Skin Cancer, by Sex



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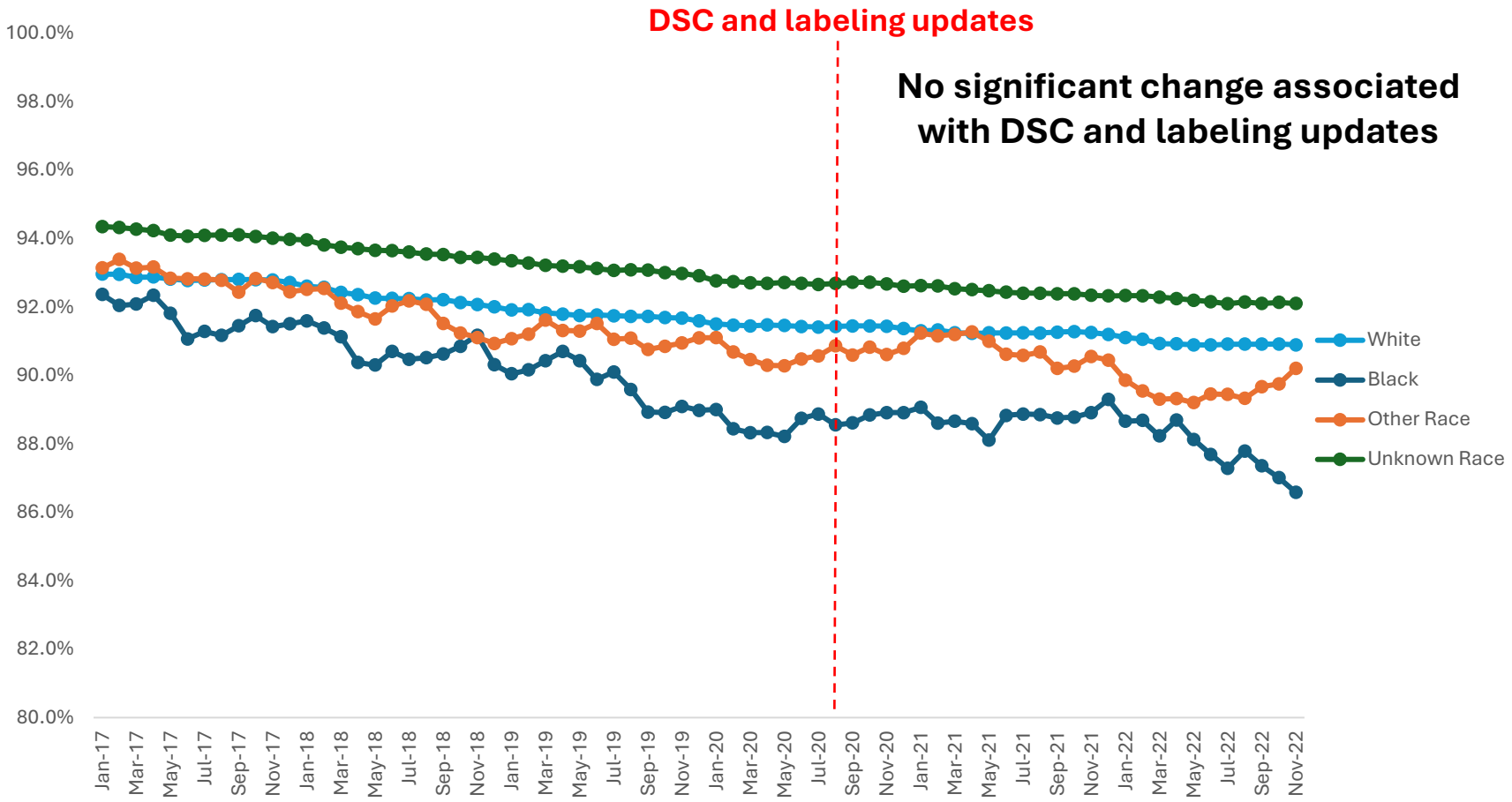
Trend of HCTZ Use Among Thiazide Users with Skin Cancer, by Race



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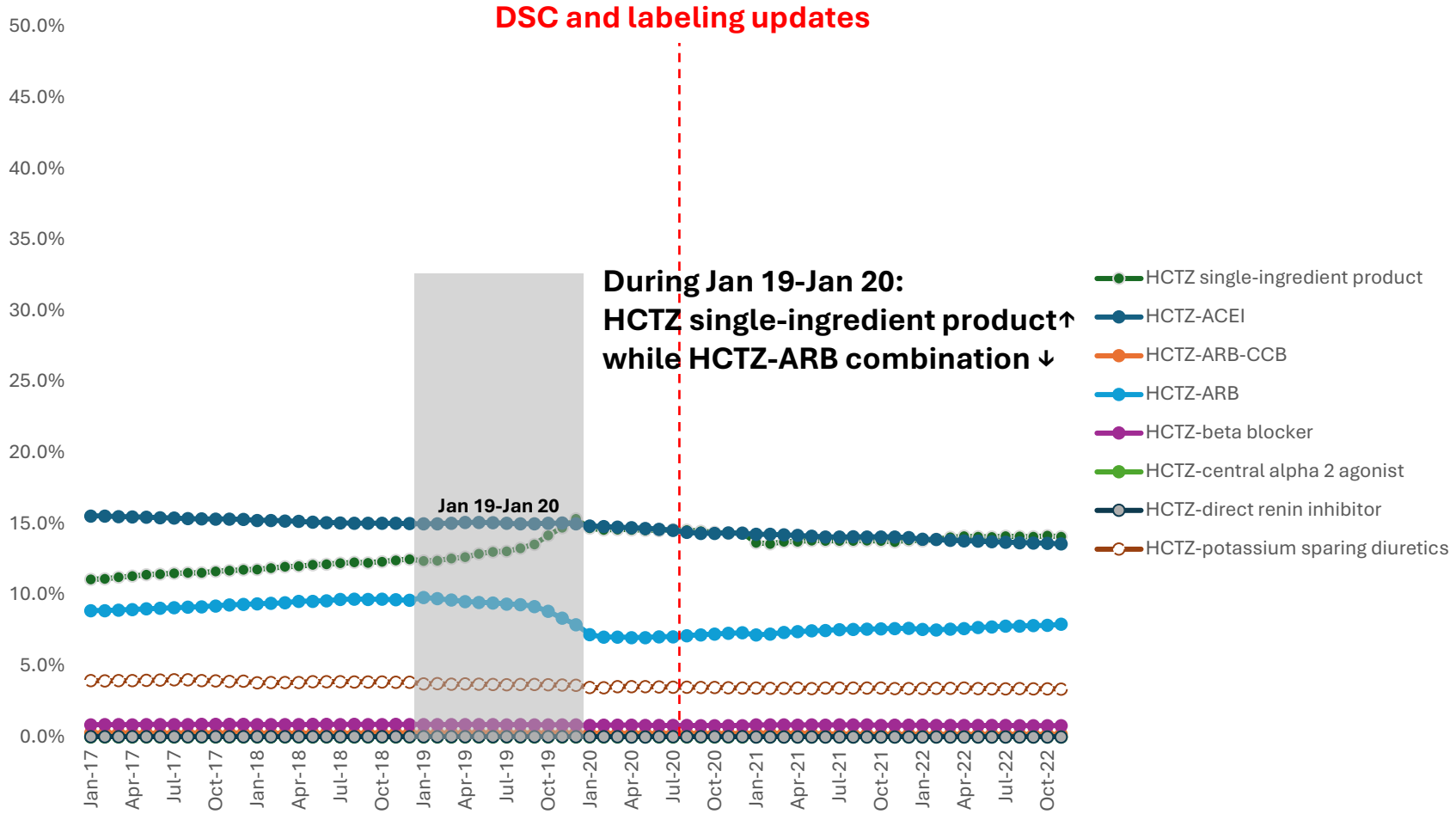
Trend of HCTZ Use Among Antihypertensive Users with Skin Cancer, by HCTZ Product



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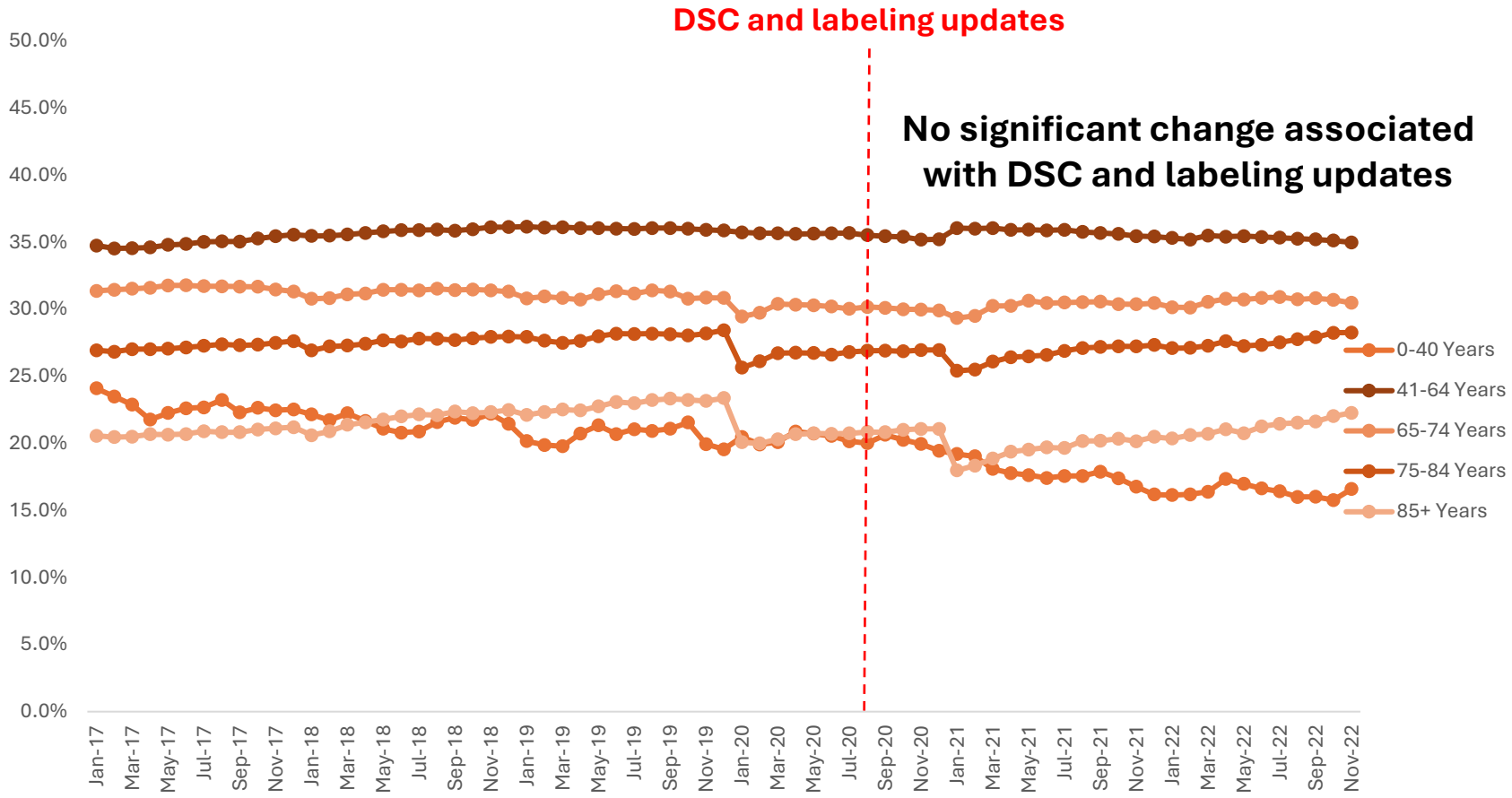
Trend of HCTZ Use Among Antihypertensive Users with Skin Cancer, by Age Groups



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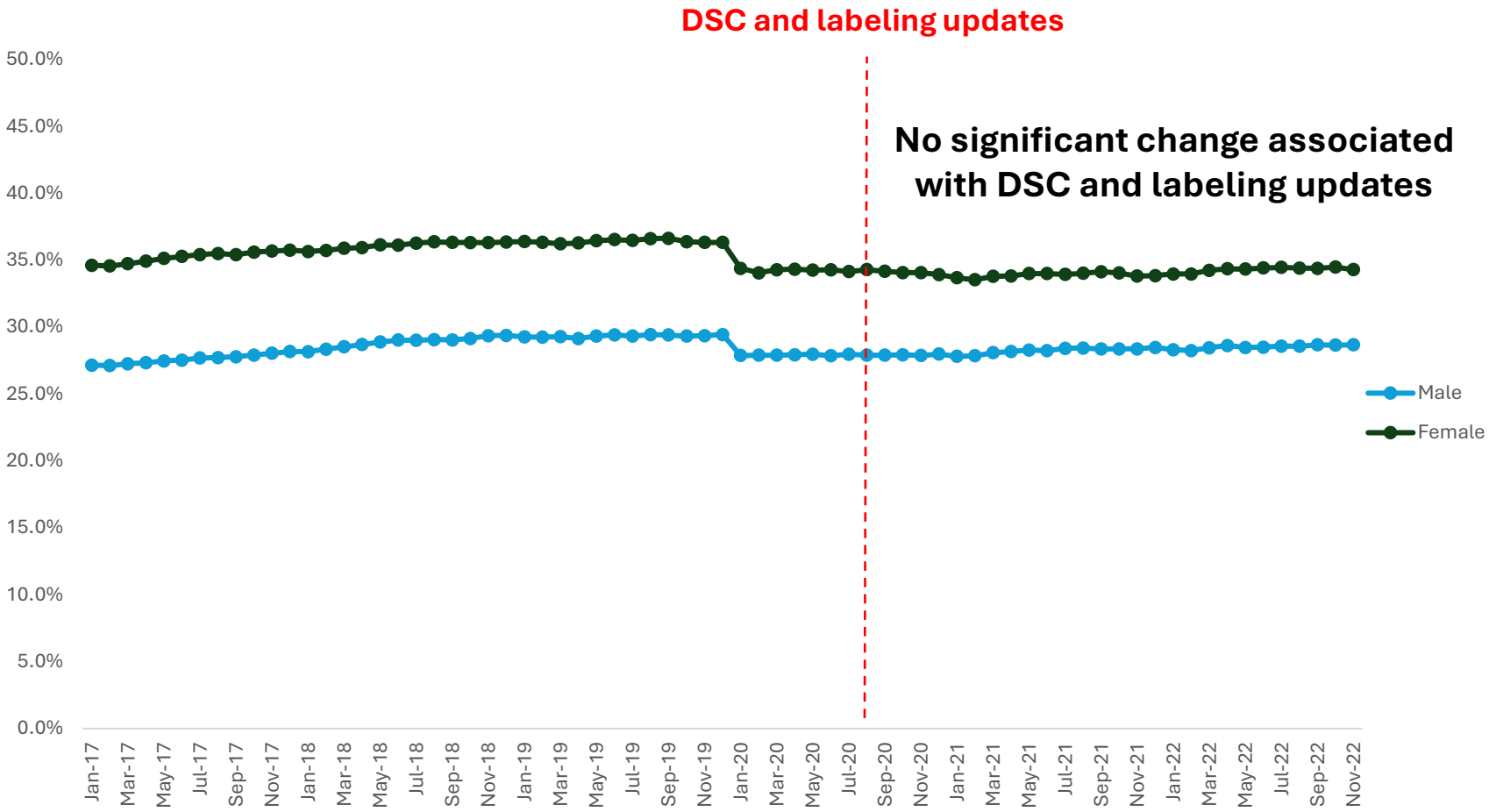

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